INTERDISCIPLINARY RESEARCH TO IMPROVE DIAGNOSIS AND TREATMENTS IN PSYCHIATRY

EDITED BY: Jolanta Kucharska-Mazur, Hanna Karakula-Juchnowicz and Geert Dom
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INTERDISCIPLINARY RESEARCH TO IMPROVE DIAGNOSIS AND TREATMENTS IN PSYCHIATRY

Topic Editors:
Jolanta Kucharska-Mazur, Pomorski Uniwersytet Medyczny, Poland
Hanna Karakula-Juchnowicz, Medical University of Lublin, Poland
Geert Dom, University of Antwerp, Belgium

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Adverse Childhood Experiences and Neurocognition in Schizophrenia Spectrum Disorders: Age at First Exposure and Multiplicity Matter

*Justyna Kasznia[1], Aleksandra Pytel[2], Bartłomiej Stańczykiewicz[2], Jerzy Samochowiec[3], Joanna Preś[3], Karolina Rachubińska[4] and Błażej Misiak[5]**

[1] Inpatient Psychiatric Unit, Municipal General Hospital, Ostrów Wielkopolski, Poland, [2] Department of Nervous System Diseases, Wroclaw Medical University, Wroclaw, Poland, [3] Department of Psychiatry, Pomeranian Medical University, Szczecin, Poland, [4] Institute of Psychology, University of Szczecin, Szczecin, Poland, [5] Division of Consultation Psychiatry and Neuroscience, Department of Psychiatry, Wroclaw Medical University, Wroclaw, Poland

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Edited by:
Hanna Karakula-Juchnowicz, Medical University of Lublin, Poland

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***Correspondence:**
Błażej Misiak
blazej.misiak@umed.wroc.pl;
bartlomiej.stanczykiewicz@gmail.com

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Adverse childhood experiences (ACEs) might be related to cognitive impairments observed in schizophrenia spectrum disorders (SSD). However, it remains unknown what aspects of ACEs are associated with cognitive impairments in SSD. Therefore, we aimed to investigate the association between various characteristics of ACEs (age at first exposure, severity, and multiplicity) and cognition in SSD and healthy controls (HCs). We enrolled 127 individuals with SSD and 56 HCs. Cognitive performance was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The Childhood Experience of Care and Abuse Questionnaire was administered to record a history of ACEs. The following characteristics of ACEs were analyzed: multiplicity, severity, and age at first exposure. Individuals with SSD had significantly lower scores on all RBANS domains. Multiplicity and severity of ACEs were significantly higher in patients with SSD compared to HCs. In both groups, greater multiplicity of ACEs was associated with lower scores of global cognition and delayed memory. Additionally, in subjects with SSD, greater multiplicity and younger age at first exposure were associated with lower scores of attention. The present findings indicate that greater multiplicity and younger age at first exposure are the most important aspects of ACEs contributing to cognitive impairments observed in SSD. Moreover, ACEs might exert differential impact on cognition in SSD and HCs.

Keywords: stress, psychosis, childhood trauma, brain development, childhood maltreatment

INTRODUCTION

Convincing evidence indicates that a history of adverse childhood experiences (ACEs), such as emotional abuse or neglect, physical and sexual abuse, increase a risk of schizophrenia spectrum disorders (SSD) (1). It has been estimated that about one third of individuals with psychosis report childhood physical, sexual or emotional abuse (2). Various psychological processes have been recognized to mediate the association between ACEs and psychosis risk, including dissociation, post-traumatic stress disorder symptoms, emotional dysregulation, and negative schemas (3). Moreover, ACEs have been associated with a number of stress-related biological alterations in psychosis (4).

It has been shown that ACEs can also impact clinical expression of SSD. For instance, a recent meta-analysis revealed that ACEs are mainly related to higher severity of hallucinations and delusions (5). Only childhood neglect was found to be correlated with negative symptoms. Additionally, ACEs might be related to unfavorable clinical and functional outcomes of psychosis (6, 7). Another meta-analysis demonstrated that ACEs are associated with worse general cognition and working memory impairments in this clinical population (8). Vargas et al. (8) also tested a number of potential moderators, including age, gender, the use of first-episode psychosis populations and covariates (age, gender, and premorbid IQ). However, none of them was found to correlate with effect size estimates. Moreover, this meta-analysis did not include a number of moderators that were not recorded by eligible studies, including timing, severity and multiplicity of exposure.

Cognitive impairments represent core clinical characteristics of SSD that appear in the premorbid phase and are present in the majority of patients (9, 10). These impairments include deficits across a number of cognitive domains, such as current IQ, category fluency, verbal and working memory, attention and response inhibition (10). Cognitive impairments in SSD can be attributed to various neuroanatomical and electrophysiological alterations, of which, volume deficits in the medial temporal lobe, including the hippocampus, and the prefrontal cortex have been widely reported (11). According to neurodevelopmental considerations, the onset of SSD together with their core clinical characteristics represent the final consequence of various genetic and environmental insults that affect the brain development at different stages (12). However, the consequences of these insults can be deleterious when they act at "critical windows" of the brain development (13).

In light of the neurodevelopmental theory of SSD, considering the effects of ACEs on cognition as a dichotomous insult without detailed recognition of their characteristics might be insufficient to understand the impact of early-life stress. Therefore, in the present study, we investigated whether the extent of cognitive impairments in SSD is associated with such characteristics of ACEs as age at first exposure, multiplicity, and severity. Furthermore, we tested the hypothesis that the impact of these characteristics might be different in subjects with SSD compared to healthy controls.

METHOD

Participants

Inpatients with SSD were recruited at two university hospitals (Department and Clinic of Psychiatry at Wroclaw Medical University, Wroclaw, Poland; Department and Clinic of Psychiatry at Pomeranian Medical University, Szczecin, Poland) and one general hospital (Inpatient Psychiatric Unit, Municipal General Hospital, Ostrów Wielkopolski, Poland) in the years 2016 – 2020 ($n = 127$). Among them, there were 42 inpatients admitted for the first time. This subgroup of participants met the criteria of schizophrenia, schizoaffective disorder, schizophreniform disorder and brief psychotic disorder. In patients who were not admitted for the first time were diagnosed with schizophrenia or schizoaffective disorder. A diagnosis of SSD was based on the DSM-IV criteria, using the Operational Criteria for Psychotic Illness (OPCRIT) checklist (14). A severity of clinical manifestation was recorded using the Positive and Negative Syndrome Scale (PANSS) (15). The majority of them ($n = 125$) were receiving antipsychotic treatment with mean chlorpromazine equivalent dosage (CPZeq) of 357.7 mg/day (SD = 388.7 mg/day).

Healthy controls ($n = 56$) were recruited at Wroclaw Medical University (Wroclaw, Poland) through advertisements. They had absent family history of mood and psychotic disorders in first- and second-degree relatives. The protocol of this study was approved by the Ethics Committee at Wroclaw Medical University, Wroclaw, Poland. All participants provided written informed consent.

Assessment of Cognitive Performance

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to examine cognitive performance (16). The RBANS consists of 12 cognitive tasks grouped into five indexes: (1) immediate memory (list learning and story memory); (2) visuospatial/constructional abilities (figure copy and line orientation); (3) language (picture naming and semantic fluency); (4) attention (digit span and coding) and (5) delayed memory (list recall, list recognition, story memory, and figure recall). Higher scores indicate better cognitive performance.

Assessment of ACEs

The Childhood Experience of Care and Abuse Questionnaire (CECA.Q) was administered to obtain data on a history of ACEs (17). The CECA.Q is a self-report that records a history of the following ACEs before the age of 17 years: (1) parental loss; (2) mother antipathy; (3) mother neglect; (4) mother psychological abuse; (5) father antipathy; (6) father neglect; (7) father psychological abuse; (8) role reversal; (9) physical abuse and (10) sexual abuse. The subscales for parental psychological abuse and role reversal were not validated against interview, and thus they were excluded from data analysis in the present study.

In our study, three measures of ACEs were analyzed: (1) age at first exposure; (2) multiplicity and (3) severity. Age at first exposure was defined as the age when the first stressful experience appeared. Multiplicity was included as the number of ACEs reported by each participant (range: 0–7). In turn, severity was calculated for all ACEs together, except for parental loss, as the CECA.Q does not include the severity score for this category of ACEs. More specifically, we divided reported severity of exposure by the maximum severity score that can be obtained for specific category of ACEs. Next, all severity scores were summarized and divided by a number of ACEs categories ($n = 6$).

Data Analysis

Data analyses were carried out using the Statistical Package for Social Sciences, version 20 (SPSS Inc., Chicago, Illinois, USA). Normality of data distribution was assessed using the Kolmogorov-Smirnov test. Bivariate comparisons were performed using the χ^2 test or the Mann-Whitney U-test, where

TABLE 1 | General characteristics of the sample.

	SSD, $n = 127$	Controls, $n = 56$	Statistics
Age, years	39.1 ± 13.8	38.3 ± 6.8	$U = 3{,}366.5$, $p = 0.566$
Gender, males (%)	61 (48.0)	24 (42.8)	$\chi^2 = 0.4$, $p = 0.518$
Education, years	13.2 ± 2.8	16.0 ± 2.4	**$U = 889.5$, $p < 0.001$**
CECA.Q—age at first exposure	9.5 ± 4.6	9.0 ± 4.6	$U = 1{,}037.5$, $p = 0.616$
CECA.Q—multiplicity	2.3 ± 1.8	1.1 ± 1.3	**$U = 4{,}940.5$, $p < 0.001$**
CECA.Q—severity	0.45 ± 0.28	0.34 ± 0.36	**$U = 4{,}965.5$, $p < 0.001$**
CECA.Q—multiplicity > 0, *n* (%)	101 (79.5)	32 (57.1)	**$\chi^2 = 10.4$, $p = 0.001$**
CECA.Q—parental loss, *n* (%)	38 (29.9)	12 (21.4)	$\chi^2 = 1.5$, $p = 0.223$
CECA.Q—mother antipathy, *n* (%)	42 (33.1)	8 (14.3)	**$\chi^2 = 7.2$, $p = 0.007$**
CECA.Q—mother neglect, *n* (%)	35 (27.6)	4 (7.1)	**$\chi^2 = 9.9$, $p = 0.002$**
CECA.Q—father antipathy, *n* (%)	45 (35.4)	9 (16.1)	**$\chi^2 = 7.7$, $p = 0.006$**
CECA.Q—father neglect, *n* (%)	36 (28.3)	15 (26.8)	$\chi^2 = 0.1$, $p = 0.733$
CECA.Q—physical abuse, *n* (%)	55 (43.3)	13 (23.2)	**$\chi^2 = 6.9$, $p = 0.009$**
CECA.Q—sexual abuse, *n* (%)	29 (22.8)	3 (5.4)	**$\chi^2 = 8.3$, $p = 0.004$**
RBANS—immediate memory	37.4 ± 9.9	51.5 ± 6.2	**$U = 690.0$, $p < 0.001$**
RBANS—visuospatial/constructional abilities	31.7 ± 6.4	37.9 ± 2.3	**$U = 1{,}073.0$, $p < 0.001$**
RBANS—language	25.7 ± 5.6	33.6 ± 6.5	**$U = 1{,}080.0$, $p < 0.001$**
RBANS—attention	38.2 ± 8.2	68.9 ± 8.9	**$U = 424.0$, $p < 0.001$**
RBANS—delayed memory	38.4 ± 11.0	55.5 ± 4.7	**$U = 476.0$, $p < 0.001$**
First admission, *n* (%)	42 (33.1)	-	-
PANSS total score	85.7 ± 30.3	-	-
CPZeq, mg/day	357.7 ± 388.7	-	-

CECA.Q, the Childhood Experience of Care and Abuse Questionnaire; CPZeq, chlorpromazine equivalent dosage; PANSS, the Positive and Negative Syndrome Scale; RBANS, the Repeatable Battery for the Assessment of Neuropsychological Status; SSD, schizophrenia spectrum disorders.
Significant differences ($p < 0.05$) were marked with bold characters.

appropriate. Spearman rank correlation coefficients were used to analyze bivariate correlations. The association between the measures of ACEs and cognitive performance was tested using the linear regression analyses. Due to non-normal distribution, the scores of specific RBANS domains were transformed to *z*-scores. Similarly, the measures of ACEs were transformed to *z*-scores to limit potential collinearity. Subsequently, interaction terms between the group status (SSD vs. healthy controls) and the measures of ACEs (*z*-scores) were created. The RBANS *z*-scores were included as a dependent variable. Group status, the measures of ACEs (age at exposure onset, severity, and multiplicity) and interaction terms were included as independent variables. Age and gender were added as covariates. Given that lower educational achievement might be strongly associated with SSD and account for cognitive impairment (18), the number of education years was added as a covariate in a hierarchical manner. The variance inflation factor (VIF) was assessed as the measure of collinearity. The VIF > 4 was considered to indicate significant multicollinearity (19). Linear regression lines were plotted according to the following equation (B refers to unstandardized coefficients): y = B (constant) + B (effect of group status)*group status + B (the effect of ACEs measure) + B (interaction term)*group status. The group status was dummy coded with the value of "1" assigned to individuals with SSD and the value of "0" assigned to healthy controls. Linear regression lines were plotted for the model that included the number of education years if a significant R^2 change was observed. Otherwise, the plot was prepared for the model without the number of education years. Results were considered statistically significant if the *p*-value was <0.05.

RESULTS

Main characteristics of the sample are reported in **Table 1**. There were no significant between-group differences with respect to age ($U = 3{,}366.5$, $p = 0.566$) and gender ($\chi^2 = 0.4$, $p = 0.518$). As expected, individuals with SSD had significantly lower education level ($U = 889.5$, $p < 0.001$) and showed worse performance on all RBANS domains (immediate memory: $U = 690.0$, $p < 0.001$; visuospatial/constructional abilities: $U = 1{,}073.0$, $p < 0.001$; language: $U = 1{,}080.0$, $p < 0.001$; attention: $U = 424.0$, $p < 0.001$; delayed memory: $U = 476.0$, $p < 0.001$). Individuals with SSD had significantly higher multiplicity ($\chi^2 = 10.4$, $p = 0.001$) and severity scores ($U = 4{,}965.5$, $p < 0.001$) of ACEs compared to healthy controls. At least one category of ACEs ($\chi^2 = 10.4$, $p = 0.001$) as well as a history of mother antipathy ($\chi^2 = 7.2$, $p = 0.007$), mother neglect ($\chi^2 = 9.9$, $p = 0.002$), father antipathy ($\chi^2 = 7.7$, $p = 0.006$), physical abuse ($\chi^2 = 6.9$, $p = 0.009$), and sexual abuse ($\chi^2 = 8.3$, $p = 0.004$) were significantly more frequent in subjects with SSD compared to healthy controls. However, both groups did not differ significantly in terms of age at first exposure to ACEs ($U = 1{,}037.5$, $p = 0.616$).

TABLE 2 | Bivariate correlations between the measures of ACEs and cognitive performance scores.

Group	Variable	1.	2.	3.	4.	5.	6.	7.	8.
SSD	1. ACEs—age at first exposure	-							
	2. ACEs—multiplicity	$r = -0.230$	-						
	3. ACEs—severity	$r = -0.047$	$r = 0.772^{c}$	-					
	4. Immediate memory	$r = 0.222$	$r = -0.183$	$r = -0.038$	-				
	5. Visuospatial/constructional	$r = 0.338^{b}$	$r = -0.271^{b}$	$r = -0.134$	$r = 0.568^{c}$	-			
	6. Language	$r = 0.243^{a}$	$r = -0.190$	$r = -0.035$	$r = 0.623^{c}$	$r = 0.418^{c}$	-		
	7. Attention	$r = 0.426^{c}$	$r = -0.301^{b}$	$r = -0.108$	$r = 0.643^{c}$	$r = 0.661^{c}$	$r = 0.539^{c}$	-	
	8. Delayed memory	$r = 0.357^{b}$	$r = -0.293^{b}$	$r = -0.156$	$r = 0.740^{c}$	$r = 0.594^{c}$	$r = 0.596^{c}$	$r = 0.626^{c}$	-
	9. Global cognition	$r = 0.435^{c}$	$r = -0.302^{b}$	$r = -0.121$	$r = 0.851^{c}$	$r = 0.745^{c}$	$r = 0.724^{c}$	$r = 0.880^{c}$	$r = 0.626^{c}$
HCs	1. ACEs—age at first exposure	-							
	2. ACEs—multiplicity	$r = -0.175$	-						
	3. ACEs—severity	$r = -0.253$	$r = 0.810^{c}$	-					
	4. Immediate memory	$r = 0.126$	$r = -0.336^{a}$	$r = -0.235$	-				
	5. Visuospatial/constructional	$r = 0.133$	$r = -0.120$	$r = 0.001$	$r = 0.195$	-			
	6. Language	$r = 0.198$	$r = -0.271^{a}$	$r = -0.134$	$r = 0.368^{b}$	$r = 0.250$	-		
	7. Attention	$r = 0.014$	$r = -0.183$	$r = -0.282^{a}$	$r = 0.444^{b}$	$r = 0.444^{b}$	$r = 0.198$	-	
	8. Delayed memory	$r = -0.102$	$r = -0.307^{a}$	$r = -0.234$	$r = 0.673^{c}$	$r = 0.298^{a}$	$r = 0.298^{a}$	$r = 0.335^{a}$	-
	9. Global cognition	$r = -0.127$	$r = -0.316^{b}$	$r = -0.216$	$r = 0.767^{c}$	$r = 0.387^{b}$	$r = 0.640^{c}$	$r = 0.741^{c}$	$r = 0.749^{c}$

ACEs, adverse childhood experiences; HCs, healthy controls; SSD, schizophrenia spectrum disorders.
[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.001$.

Bivariate correlations between the measures of ACEs and the RBANS scores are shown in **Table 2**. Younger age at first exposure was associated with significantly lower RBANS scores (visuospatial/constructional abilities: $r = 0.338$, $p < 0.01$; language: $r = 0.243$, $p < 0.05$; attention: $r = 0.426$, $p < 0.001$; delayed memory: $r = 0.357$, $p < 0.01$; global cognition: $r = 0.435$, $p < 0.001$), except for the score of immediate memory ($r = 0.222$, $p > 0.05$) in subjects with SSD but not in healthy controls (immediate memory: $r = 0.126$, $p > 0.05$; visuospatial/constructional abilities: $r = 0.133$, $p > 0.05$; language: $r = 0.198$, $p > 0.05$; attention: $r = 0.014$, $p > 0.05$; delayed memory: $r = -0.102$, $p > 0.05$; global cognition: $r = -0.127$, $p > 0.05$). Greater multiplicity of ACEs was also related to significantly lower RBANS scores (visuospatial/constructional abilities: $r = -0.271$, $p < 0.01$; attention: $r = -0.301$, $p < 0.01$; delayed memory: $r = -0.293$, $p < 0.01$ and global cognition: $r = -0.302$, $p < 0.01$ in subjects with SSD as well as immediate memory: $r = -0.336$, $p < 0.05$; language: $r = -0.271$, $p < 0.05$; delayed memory: $r = -0.307$, $p < 0.05$, and global cognition: $r = -0.316$, $p < 0.01$ in healthy controls). There was a significant negative correlation between overall severity of ACEs and the score of attention in healthy controls ($r = -0.282$, $p < 0.05$). In both groups of participants, overall severity and multiplicity of ACEs were significantly and positively correlated (SSD: $r = 0.772$, $p < 0.001$, healthy controls: $r = 0.810$, $p < 0.001$).

Results of linear regression analyses controlling for the effects of age, the number of education years and gender are presented in **Table 3**. Significant main and interaction effects are shown in **Figure 1**. There were significant main effects of multiplicity of ACEs on delayed memory ($B = -0.201$, $p = 0.040$) and global cognition scores ($B = -0.187$, $p = 0.031$), even if the number of education years was added to independent variables. Additionally, significant effects of interactions between group and age at first exposure ($B = 0.650$, $p = 0.018$) as well as between group and multiplicity ($B = -0.440$, $p = 0.017$) on attention scores were observed. More specifically, younger age at first exposure and greater multiplicity of ACEs were associated with worse performance of attention in subjects with SSD but not in healthy controls, after controlling for the effects of age, gender, and the number of education years.

DISCUSSION

Findings from the present study imply that ACEs might contribute to cognitive impairments observed in patients with SSD. Notably, we found that greater multiplicity of ACEs might be associated with impairments of delayed memory and global cognition in both groups of participants—individuals with SSD and healthy controls. However, the association between characteristics of ACEs (age at first exposure and multiplicity) and attention scores was found only in patients with SSD. No significant associations with cognition were found for the overall severity of ACEs.

It is important to note that the RBANS attention index is composed of scores from two cognitive tasks (digit span

TABLE 3 | Results of linear regression analyses.

	Independent variable	Immediate memory	Visuospatial/ constructional	Language	Attention	Delayed memory	Global cognition	VIF
Model 1	Age	$B = -0.014$, $p = 0.305$	**$B = -0.033$, $p = 0.018$**	$B = -0.024$, $p = 0.097$	**$B = -0.022$, $p = 0.009$**	$B = -0.012$, $p = 0.278$	**$B = -0.021$, $p = 0.040$**	1.726
	Gender	$B = 0.459$, $p = 0.085$	$B = 0.057$, $p = 0.915$	**$B = 0.782$, $p = 0.010$**	$B = 0.238$, $p = 0.128$	$B = 0.298$, $p = 0.206$	$B = 0.377$, $p = 0.078$	1.113
	Group	**$B = -0.724$, $p = 0.014$**	$B = -0.224$, $p = 0.543$	**$B = -0.697$, $p = 0.016$**	**$B = -0.310$, $p < 0.001$**	**$B = -0.311$, $p = 0.020$**	**$B = -0.341$, $p = 0.004$**	1.419
	Age at first exposure	$B = -0.078$, $p = 0.565$	$B = -0.048$, $p = 0.661$	$B = -0.191$, $p = 0.213$	$B = -0.190$, $p = 0.566$	$B = -0.068$, $p = 0.376$	$B = -0.120$, $p = 0.384$	2.984
	Multiplicity	$B = 0.311$, $p = 0.162$	$B = 0.523$, $p = 0.785$	$B = -0.405$, $p = 0.176$	$B = 0.046$, $p = 0.387$	**$B = -0.201$, $p = 0.040$**	**$B = -0.187$, $p = 0.031$**	3.597
	Severity	$B = 0.026$, $p = 0.560$	$B = 0.048$, $p = 0.759$	$B = -0.087$, $p = 0.724$	$B = -0.066$, $p = 0.377$	$B = 0.037$, $p = 0.744$	$B = -0.015$, $p = 0.906$	2.257
	Group × age at first exposure	$B = 0.304$, $p = 0.068$	$B = -0.038$, $p = 0.753$	$B = 0.188$, $p = 0.353$	**$B = 0.613$, $p = 0.024$**	$B = 0.157$, $p = 0.529$	$B = 0.114$, $p = 0.164$	4.000
	Group × multiplicity	$B = -0.274$, $p = 0.772$	$B = -0.741$, $p = 0.438$	$B = 0.412$, $p = 0.281$	**$B = -0.340$, $p = 0.019$**	$B = -0.210$, $p = 0.937$	$B = -0.113$, $p = 0.981$	3.874
	Group × severity	$B = 0.045$, $p = 0.803$	$B = 0.114$, $p = 0.759$	$B = 0.034$, $p = 0.981$	$B = 0.074$, $p = 0.497$	$B = 0.045$, $p = 0.800$	$B = 0.166$, $p = 0.664$	2.325
	R^2	0.295	0.225	0.359	0.594	0.361	0.435	-
	R^2 change (p)	**0.295 (0.012)**	**0.225 (0.080)**	**0.359 (0.001)**	**0.594 (< 0.001)**	**0.361 (0.001)**	**0.435 (< 0.001)**	-
Model 2	Age	$B = -0.015$, $p = 0.233$	$B = -0.036$, $p = 0.009$	$B = -0.026$, $p = 0.064$	**$B = -0.024$, $p = 0.003$**	$B = -0.013$, $p = 0.253$	$B = -0.023$, $p = 0.021$	1.745
	Education years	$B = 0.076$, $p = 0.121$	**$B = 0.103$, $p = 0.043$**	$B = 0.101$, $p = 0.084$	**$B = 0.077$, $p = 0.008$**	$B = 0.030$, $p = 0.501$	**$B = 0.079$, $p = 0.040$**	1.283
	Gender	$B = 0.404$, $p = 0.120$	$B = -0.018$, $p = 0.897$	**$B = 0.709$, $p = 0.015$**	$B = 0.183$, $p = 0.199$	$B = 0.276$, $p = 0.241$	$B = 0.320$, $p = 0.117$	1.128
	Group	$B = -0.560$, $p = 0.077$	$B = 0.001$, $p = 0.864$	$B = -0.480$, $p = 0.092$	**$B = -0.210$, $p = 0.009$**	$B = -0.567$, $p = 0.054$	**$B = -0.242$, $p = 0.037$**	1.638
	Age at first exposure	$B = -0.085$, $p = 0.551$	$B = -0.044$, $p = 0.640$	$B = -0.200$, $p = 0.200$	$B = -0.180$, $p = 0.529$	$B = -0.158$, $p = 0.376$	$B = -0.127$, $p = 0.362$	2.985
	Multiplicity	$B = 0.353$, $p = 0.932$	$B = 0.580$, $p = 0.500$	$B = -0.461$, $p = 0.310$	$B = 0.020$, $p = 0.155$	**$B = -0.238$, $p = 0.038$**	**$B = -0.220$, $p = 0.044$**	3.739
	Severity	$B = 0.027$, $p = 0.832$	$B = 0.051$, $p = 0.794$	$B = -0.085$, $p = 0.686$	$B = -0.064$, $p = 0.316$	$B = 0.022$, $p = 0.443$	$B = -0.013$, $p = 0.860$	2.258
	Group × age at first exposure	$B = 0.308$, $p = 0.239$	$B = 0.044$, $p = 0.749$	$B = 0.200$, $p = 0.346$	**$B = 0.650$, $p = 0.018$**	$B = 0.158$, $p = 0.532$	$B = 0.129$, $p = 0.153$	4.000
	Group × multiplicity	$B = -0.299$, $p = 0.932$	$B = -0.775$, $p = 0.293$	$B = 0.445$, $p = 0.387$	**$B = -0.440$, $p = 0.017$**	$B = 0.277$, $p = 0.957$	$B = -0.200$, $p = 0.702$	3.912
	Group × severity	$B = 0.010$, $p = 0.832$	$B = 0.039$, $p = 0.790$	$B = -0.040$, $p = 0.795$	$B = 0.018$, $p = 0.792$	$B = 0.022$, $p = 0.889$	$B = 0.113$, $p = 0.918$	2.388
	R^2	0.325	0.280	0.393	0.643	0.367	0.476	-
	R^2 change (p)	0.030 (0.121)	**0.055 (0.043)**	0.034 (0.084)	**0.049 (0.008)**	0.006 (0.501)	**0.041 (0.040)**	-

Significant results ($p < 0.05$) were marked with bold characters.

and digit coding) that also enable to assess cognitive domains other than attention. The score of digit span reflects working memory performance, while the digit coding task enables to record processing speed. Impairments of working memory have been widely reported in patients with SSD, also at the onset of psychosis, and may reflect neurostructural and neurofunctional alterations of the prefrontal cortex (20–22). Similarly, impairments measured by the digit coding are already present in individuals at risk of psychosis, those with first-episode psychosis and subjects with chronic schizophrenia, with poor response to treatment (23–25). Our findings are also in line with those obtained by previous studies, including most recent meta-analysis (8). As similar to the present study, Schalinski et al. (26) aimed to examine the association between various aspects of ACEs (duration, multiplicity and severity) and cognitive performance in psychosis. The authors found that abuse at the age of 3 years might be related to impairments of attention, learning and working memory. Additionally, neglect at the age of 3 years was associated with worse performance of attention. No significant associations of duration and multiplicity with

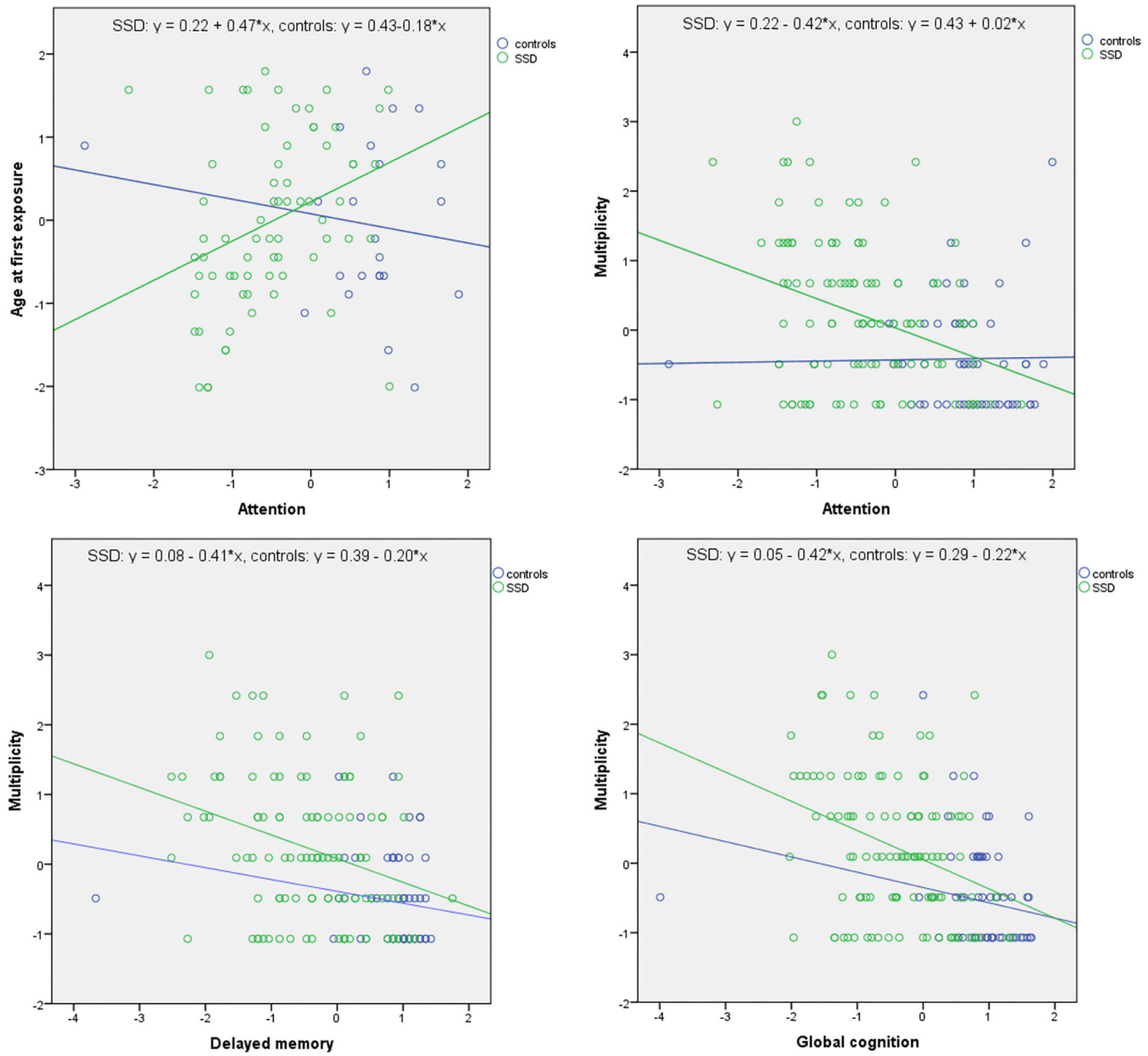

FIGURE 1 | Significant associations between the measures of ACEs and cognition in linear regression analyses. Data expressed as *z*-scores. There were significant main effects of multiplicity of ACEs on delayed memory ($B = -0.201$, $p = 0.040$) and global cognition scores ($B = -0.220$, $p = 0.040$). Additionally, significant effects of interactions between group and age at first exposure ($B = 0.650$, $p = 0.018$) as well as between group and multiplicity ($B = -0.440$, $p = 0.017$) on attention scores were found. More specifically, younger age at first exposure and greater multiplicity of ACEs were associated with worse performance of attention in subjects with SSD but not in healthy controls.

neurocognition were reported. However, greater multiplicity and neglect experienced at the age of 11–12 years were associated with worse performance of social cognition. In turn, Li et al. (27) found that a history of various ACEs is associated with lower RBANS scores of language, attention and delayed memory. Other studies, although without insights into detailed characteristics of ACEs, also reported that ACEs are associated with impairments of attention and working memory in psychosis (28–30).

Previous studies did not investigate a differential impact of ACEs on cognition in subjects with psychosis and healthy controls. Therefore, it is difficult to establish unequivocal conclusion whether ACEs differentially impact cognition in these populations. Nevertheless, in both groups of participants, multiplicity of ACEs was correlated with cognition. Similarly, in both groups, multiplicity of ACEs was associated with worse performance of delayed memory and global cognition. Although the present study demonstrated that age at first exposure was

similar in both groups of participants, severity and multiplicity scores were significantly higher in subjects with SSD compared to healthy controls. This observation might explain worse cognitive performance in patients with SSD compared to healthy controls, taking into account previous reports that ACEs increase a risk of psychosis with a dose-response effect (31). However, it is still unclear whether specific characteristics of ACEs exert qualitatively differential impact on cognition in subjects with SSD and healthy controls. Moreover, it is warranted to investigate whether neurocognitive deficits attributable to ACEs contribute to other psychopathological symptoms of psychosis. Indeed, there is evidence that there are several cognitive mediators of the association between ACEs and psychopathology. These include, i.e., cognitive styles, negative core/internalized beliefs, negative attributions, evaluating and pathogenic beliefs and early maladaptive schemas (32).

The present findings should also be referred to potential neurobiological mechanisms that may explain the relationship between ACEs and cognition. The hypothalamic-pituitary-adrenal (HPA) axis serves as one of main biological systems responsible for stress response by releasing glucocorticoids. Notably, the hippocampus and prefrontal cortex contain high density of glucocorticoid receptors. These brain regions are responsible for learning and memory processes. Prolonged exposure to glucocorticoids may lead to reduced neurogenesis and synaptic plasticity in the hippocampus and prefrontal cortex (33, 34). Previous meta-analyses have revealed that patients with psychosis show dysfunction of the HPA axis in terms of elevated blood cortisol levels (35), attenuated cortisol awakening response (36) and blunted cortisol response to social stress (37). Moreover, there is evidence that ACEs might contribute to dysfunction of the HPA axis in psychosis (38–41). Our group has recently reported that elevated cortisol levels might be associated with deficits of delayed memory in subjects with SSD (42). In turn, Aas et al. (40) found that elevated hair cortisol levels are correlated with working memory deficits in individuals with schizophrenia and bipolar disorder.

Certain limitations of the present study need to be discussed. First, our sample size, especially with respect to healthy controls, was not large. The difference in sample sizes between individuals with psychotic disorders and healthy controls might also account for observed differences in the association between ACEs and cognition in these groups of participants. However, previous studies in this field were based on similar or even smaller sample sizes. Second, a recall bias should always be taken into consideration when interpreting the data from self-reports of ACEs. This might be of particular importance to ACEs that appear very early in the developmental period. Nevertheless, sufficient test-retest reliability and consistency have been demonstrated for self-reports of ACEs in subjects with psychosis (43, 44). Another point is that the proportion of variance in cognitive performance explained by our linear regression analyses (22.5–64.3%) suggest that other factors might also contribute to cognitive performance, and were not explored in the present study. These might include duration of illness, factors related to overweight or obesity, medication effects and substance use.

In summary, our findings imply that greater multiplicity of ACEs might account for impairments of attention, delayed memory and global cognition, while earlier age of first exposure to ACEs might additionally contribute to impaired attention in subjects with SSD. The impact of ACEs on cognition in individuals with SSD and healthy controls might share some similarities, with multiplicity being the most important factor. These findings provide new support for the neurodevelopmental theory of schizophrenia. A differential impact on specific cognitive domains in individuals with SSD and healthy controls requires additional studies in larger samples. Moreover, the mechanisms underlying the relationship between ACEs and cognitive deficits in SSD also need to be established. Finally, future studies should further investigate whether cognitive impairments attributable to ACEs further shape specific symptoms of psychosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee at Wroclaw Medical University, Poland. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JK: study design, recruitment, and manuscript writing. AP: data collection and manuscript editing. BS: recruitment and manuscript editing. JS: manuscript writing. JP: recruitment and manuscript writing. KR: recruitment and data analysis. BM: recruitment, data analysis, and manuscript writing. All authors contributed to the article and approved the submitted version.

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Associations Between the Kynurenine Pathway, Proinflammatory Cytokines, and Brain-Derived Neurotrophic Factor in Hospitalized Patients With Chronic Schizophrenia: A Preliminary Study

*Naomichi Okamoto, Tomoya Natsuyama, Ryohei Igata, Yuki Konishi, Hirofumi Tesen, Atsuko Ikenouchi and Reiji Yoshimura**

Department of Psychiatry, University of Occupational and Environmental Health Japan, Kitakyushu, Japan

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Jolanta Kucharska-Mazur, Pomeranian Medical University, Poland

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Laiana Quagliato, Federal University of Rio de Janeiro, Brazil
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***Correspondence:**
Reiji Yoshimura
yoshi621@med.uoeh-u.ac.jp

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Purpose: The kynurenine (Kyn) pathway may play a role in the pathophysiology of schizophrenia. This pathway shows crosstalk with proinflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), and/or brain-derived neurotrophic factor (BDNF). Moreover, Kyn metabolites affect neurotransmission and cause neurotoxicity. To date, the influence of the Kyn pathway on proinflammatory cytokines and BDNF remains to be fully elucidated. The aim of this study was to investigate the relationships of the Kyn pathway with proinflammatory cytokines, BDNF, and psychiatric symptoms in patients with schizophrenia.

Methods: Thirty patients with schizophrenia and ten healthy control participants were recruited for this study. All patients were diagnosed with schizophrenia using the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5). The healthy controls were those who did not fulfill any of the diagnostic criteria in the DSM-5. The serum levels of Kyn and its metabolites, proinflammatory cytokines, and BDNF were measured in patients with schizophrenia and healthy controls. Patients with schizophrenia were also assessed for psychiatric symptoms using the Positive and Negative Syndrome Scale (PANSS).

Results: Patients with schizophrenia and healthy controls showed no significant differences in the levels of Kyn and its metabolites, proinflammatory cytokines, and BDNF. A significant positive correlation was found between the serum levels of TNF-α and Kyn ($r = 0.53$, $p = 0.0026$) and the Kyn/tryptophan (Trp) value ($r = 0.67$, $p = 0.000046$) in the schizophrenia group, but not in the healthy control group.

Conclusion: TNF-α affects the Kyn pathway in patients with chronic schizophrenia, but not in the healthy individuals, although serum TNF-α levels showed no difference between the two groups. Associations between the Kyn pathway and the levels of proinflammatory cytokines and BDNF or psychotic symptoms might be complicated in hospitalized patients with chronic schizophrenia.

Keywords: schizophrenia, kynurenine pathway, kynurenine, quinolinic acid, inflammatory cytokines, BDNF

INTRODUCTION

Although the pathophysiology of schizophrenia is currently unclear, inflammation has been suggested to play an important role in the pathophysiology (1, 2). In addition, there is growing evidence of an interaction between inflammation and the kynurenine (Kyn) pathway in schizophrenia (3). The Kyn pathway is regulated by the immune system, and the decomposition of tryptophan *via* the Kyn pathway is activated by proinflammatory cytokines. The Kyn pathway is also considered to crosstalk with the immune system, proinflammatory cytokines, and neurotrophic factors (4, 5). Tryptophan (Trp) is degraded to Kyn, which is catabolized to either kynurenic acid (KynA) *via* kynurenine aminotransferases or to 3-hydroxykynurenine (3-HK) *via* kynurenine 3-monooxygenase and finally to quinolinic acid (QA). Proinflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), are thought to contribute to the pathogenesis of psychiatric symptoms in schizophrenia by Kyn pathway activation.

Kyn metabolites affect neurotransmission and cause neurotoxicity. Several studies have indicated that proinflammatory cytokines and the Kyn pathway in the blood are dysregulated in patients with schizophrenia. Increase in the plasma levels of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, have been consistently reported in patients with schizophrenia (6). C-reactive protein (CRP) levels have also been reported to be elevated in patients with schizophrenia (7). Thus, these proinflammatory cytokines may accelerate the Kyn pathway (8), which may be related to changes in neurotrophic factors, which are associated with the symptoms of schizophrenia. According to the review (9), the Kyn pathway of Trp degradation generates several neuroactive compounds. KynA is an N-methyl-d-aspartate (NMDA) and alpha 7 nicotinic receptor antagonist. The KynA hypothesis of schizophrenia is based on the fact that KynA blocks glutamate receptors and is elevated in schizophrenia. KynA regulates glutamatergic and dopaminergic neurotransmission and elevated brain levels appear associated with psychotic symptoms and cognitive impairments in schizophrenia. Contributing to enhanced production of KynA, the expression and enzyme activity of kynurenine 3-monooxygenase (KMO) are reduced in schizophrenia. There were several works by Engberg and Erhardt. The authors reported cerebrospinal fluid (CSF) levels of Kyn, and KynA in schizophrenia patients (10, 11). They also reported CSF levels of Kyn and KynA were elevated in patients with chronic schizophrenia, indicating the idea of brain immune activation in patients with schizophrenia, which suggested that IL-6 induces the Kyn pathway, leading to increased production of the NMDA receptor antagonist KynA in patients with schizophrenia (12). A recent report demonstrated that proinflammatory cytokines are involved in dorsolateral prefrontal cortex volume loss and attention impairment *via* the Kyn pathway (13). However, the associations among these components are complicated and controversial. Recent review reported the following findings, (1) schizophrenia patients with prescribed antipsychotic drugs had significantly higher Kyn levels compared with controls; (2) higher Kyn levels in CSF, lower plasma Kyn levels compared with controls; (3) the Kyn levels were higher in schizophrenia patients after treatment with antipsychotic drugs compared with baseline (14). Therefore, the correlations among proinflammatory cytokines, neurotrophic factors, and the Kyn pathway and their possible relevance to schizophrenic pathophysiology, must be further elucidated.

Thus, the aim of the present study was to investigate the associations of proinflammatory cytokines, including IL-1β, IL-6, TNF-α, and IL-10, a suppressive cytokine, and brain-derived neurotrophic factor (BDNF) with the Kyn pathway, which might be related to the symptomatology of schizophrenia patients. The present study aimed to shed light on how coordination among the Kyn pathway, proinflammatory cytokines, and BDNF may influence the symptomatology in chronic hospitalized schizophrenia patients.

METHODS

Participants and Ethics Statement

Thirty patients with schizophrenia participated in this study. The patients were recruited from the Komine-Eto Hospital and Shinmoji Hospital. All patients were diagnosed with schizophrenia using the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) (15). Exclusion criteria included a history of major neurological disease, uncontrolled major medical illness, epilepsy, cerebrovascular accident, head trauma with cognitive sequelae, and intellectual disability. All patients with schizophrenia were taking antipsychotic medications. The control group of healthy controls did not currently have a DSM-5 applicable psychiatric diagnosis, nor did they have a family history of psychosis. All participants provided verbal and written informed consent. The research protocol was approved by the Ethics Committee of the University of Occupational and Environmental Health (Approval Number: UOEHCRB19-024).

Clinical Assessment and Blood Sampling

Patients with schizophrenia were assessed for clinical and neuropsychiatric symptoms using the Positive and Negative Syndrome Scale (PANSS) (16) and the Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) (17). Blood samples were collected between 7 and 9 a.m. before breakfast. Participants fasted and rested for at least 30 min prior to blood collection.

Measurement of Metabolites of the Kyn Pathway

The samples obtained at the University of Occupational and Environmental Health were transferred to Human Metabolome Technologies Inc. (HMT; Tsuruoka, Japan), where each 50-μL sample was mixed with 450 μL of methanol containing internal standards (10 μM) and vortexed. Chloroform (500 μL) and Milli-Q water (200 μL) were added, mixed thoroughly, and centrifuged (2,300 × g, 4°C, 5 min). The water layer (400 μL) was filtered through a 5-kDa-cutoff filter (ULTRAFREE-MC-PLHCC; HMT, Yamagata, Japan) to remove macromolecules. The filtrate was centrifugally concentrated and resuspended in 50 μL of ultrapure water immediately before measurement. The

compounds were measured in the cation and anion modes of a capillary electrophoresis-Fourier transform mass spectrometry (CE-FTMS)-based metabolome analysis system under conditions 1–3. The samples were diluted for the measurements to improve the quality of the CE-FTMS analysis. Metabolome measurements were conducted at HMT by using CE-time-of-flight mass spectrometry (TOFMS) in an Agilent CE System equipped with the Agilent 6210 time-of-flight mass spectrometer, the Agilent 1100 isocratic HPLC pump, the Agilent G1603A CE-MS adapter kit, and the Agilent G1607A CE-ESI-MS sprayer kit (Agilent Technologies, Waldbronn, Germany). The system was controlled by Agilent G2201AA ChemStation software version B.03.01 for CE (Agilent Technologies, Waldbronn, Germany). The metabolites were analyzed using a fused silica capillary (50 μm internal diameter × 80 cm total length), with commercial electrophoresis buffers (Solution ID: H3301-1001 for cation analysis, H3302-1021 for anion analysis; HMT) as the electrolyte. The sample was injected at a pressure of 50 mbar for 10 s (∼10 nL) for cation analysis and 25 s (∼25 nL) for anion analysis. The spectrometer was scanned from 50 to 1,000 m/z. Other conditions were as described previously (18–20). Peaks were extracted using the automatic integration software MasterHands (Keio University, Tsuruoka, Japan) to obtain peak information, including m/z, migration time for CE-TOFMS measurement (MT), and peak area values (21). Signal peaks corresponding to isotopomers, adduct ions, and other product ions of known metabolites were excluded, and the remaining peaks were annotated with putative metabolites from the HMT metabolite database based on their MTs and m/z values, as determined from TOFMS. The tolerance range for the peak annotation was configured at ±0.5 min for MT and ±10 ppm for m/z. In addition, peak areas were normalized against those of the internal standards, and the resultant relative areas were further normalized by the sample amount. Serum KynA levels were under limit of detection.

Measurement of Serum Inflammatory Cytokine and BDNF Levels

Samples were collected at the University of Occupational and Environmental Health and transferred to SRL Inc. (SRL: Kitakyushu, Japan). Serum cytokine (IL-1β, IL-6, IL-10, TNF-α) and BDNF levels were measured using the sandwich enzyme immunoassay technique. A monoclonal antibody specific for humans was pre-coated onto a microplate. Standards and samples were pipetted into the wells and any IL-1β, IL-6, IL-10, TNF-α, and BDNF present were bound by the immobilized antibody. After washing away any unbound substances, a biotinylated polyclonal antibody specific for humans was added to the wells. After a wash to remove any unbound antibody-biotin reagent, enzyme-linked streptavidin was added to the wells. After washing away any unbound streptavidin-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of IL-1β, IL-6, IL-10, TNF-α, and BDNF bound in the initial step. Color development was stopped, and the intensity of the color was measured. Serum levels of IL-1β, and IL-10 were under limit of detection.

Measurement of Serum hsCRP Levels

The high-sensitivity CRP (hsCRP) levels were measured using a commercially available enzyme-linked immunosorbent assay (MSD, Rockville, MD, USA).

Statistical Analyses

All statistical analyses were performed using the EZR software version 1.50, a modified version of R Commander designed to perform statistical functions frequently used in biostatistics (22). After confirming the normal distribution and equality of variance, continuous variables were analyzed using Student's *t*-test, Welch's test, and Mann-Whitney U test. Fisher's -test was used to analyze nominal variables. Spearman's rank correlation coefficient was used to examine the relationship among the levels of metabolites in the Kyn pathway, including their ratios (Trp, Kyn, 3-HK, QA, 5-hydroxytryptamine [5-HT], Kyn/Trp, 5-HT/Kyn, 3-HK/Kyn, QA/Kyn), and the levels of proinflammatory cytokines (TNF-α, IL-6), hsCRP, BDNF and PANSS. The correlations between the data were expressed by correlation table. Positive correlations are shown in red, negative correlations are shown in blue, and the strength of the correlation is expressed in terms of concentration. A two-tailed test was used, and a p-value < 0.05 was defined as a statistically significant difference. Dates were expressed mean(standard deviation) or

TABLE 1 | Clinical and demographic characteristics.

	Schizophrenia ($n = 30$)	Healthy controls ($n = 10$)	p-value
Age (years)	48 (9.0)	48 (8.7)	0.99
Sex (males, %)	17 (57%)	5 (50%)	0.73
BMI (kg/m^2)	23 (3.8)	23 (2.8)	0.89
PANSS			
PANSS total	95 (13)	–	–
PANSS positive	21 (4.6)	–	–
PANSS negative	26 (4.9)	–	–
PANSS general	48 (8.4)	–	–
DIEPSS	6.3 (3.8)	–	–
CP total	745 (460)	–	–
Disease period	26 (10)	–	–
Antipsychotic drugs	Olanzapine (6 cases)		
	Risperidone (6 cases)		
	Levomepromazine (5 cases)		
	Aripiprazole (5 cases)		
	Clozapine (5 cases)		
	Haloperidol (4 cases)		
	Brexpiprazole (3 cases)		
	Quetiapine (3 cases)		
	Zotepine (3 cases)		
	Asenapine (2 cases)		
	Blonanserin (2 cases)		
	Fluphenazine (1 cases)		

BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; DIEPSS, Drug Induced Extra-Pyramidal Symptoms Scale; CP total, total dose of chlorpromazine equivalence. Dates were expressed mean(standard deviation).

TABLE 2 | Serum levels of the metabolites of the Kyn pathway in the schizophrenia and healthy control groups.

	Schizophrenia ($n = 30$)	Healthy controls ($n = 10$)	p-value
Trp	1.9×10^{-1} (4.5×10^{-2})	2.1×10^{-1} (3.1×10^{-2})	0.11
Kyn	6.0×10^{-3} (2.0×10^{-3})	6.9×10^{-3} (1.3×10^{-3})	0.26
3-HK	5.6×10^{-5} [4.3×10^{-5}∼8.0×10^{-5}]	7.1×10^{-5} [5.8×10^{-5}∼1.0×10^{-4}]	0.052
QA	8.6×10^{-5} [6.6×10^{-5}∼1.4×10^{-4}]	1.1×10^{-4} [4.6×10^{-5}∼1.4×10^{-4}]	0.99
5-HT	1.1×10^{-3} (5.3×10^{-4})	1.0×10^{-3} (6.8×10^{-4})	0.80
Kyn/Try	0.03 [0.02∼0.06]	0.03 [0.02∼0.05]	0.93
5HT/Kyn	0.17 [0.094∼0.25]	0.12 [0.11∼0.20]	0.57
3-HK/Kyn	0.01 [0.01∼0.10]	0.01 [0.01∼0.02]	0.97
QA/Kyn	0.01 [0.01∼0.02]	0.01 [0.008∼0.02]	0.98

Trp, tryptophan; Kyn, kynurenine; 3-HK, 3-hydroxykynurenine; QA, quinolinic acid; 5-HT, 5-hydroxytryptamine; KynA, kynurenic acid. Dates were expressed mean(standard deviation) or median [interquartile range]. The peak areas of the metabolites were normalized against those of the internal standards, and the resultant relative areas were further normalized by the sample amount explained in the Measurement of metabolites of the Kyn pathway. Thus, each figure of Trp, Kyn, 3-HK, QA, 5-HT demonstrated as the ratio comparing with internal standard.

TABLE 3 | Serum levels of cytokines, hsCRP, and BDNF in the schizophrenia group and the healthy control.

	Schizophrenia ($n = 30$)	Healthy controls ($n = 10$)	p-value
IL-6 (pg/mL)	1.5 [0.9∼2.1]	1.1 [0.6∼2.0]	0.23
TNF-α (pg/mL)	0.9 [0.7∼1.0]	0.9 [0.7∼0.9]	0.52
hsCRP (mg/dL)	0.029 [0.0070∼0.065]	0.030 [0.017∼0.065]	0.80
BDNF (pg/mL)	22,000 (7,800)	22,000 (5,000)	0.99

hsCRP, high-sensitivity C-reactive protein; BDNF, brain-derived neurotrophic factor; IL, interleukin; TNF-α, tumor necrosis factor alpha. Dates were expressed mean(standard deviation) or median [interquartile range].

median [interquartile range]. Figures that showed statistically significant differences in the correlation table were drawn. The regression line was drawn based on the least squares method. One schizophrenia patient had outlier data for CRP (7.2 mg/dL) and IL-6 (24 pg/mL) levels; therefore, we excluded these data.

RESULTS

Background Characteristics

Thirty patients with schizophrenia and ten healthy participants were included in this study. The background and clinical characteristics of the patients with schizophrenia and healthy controls are shown (**Table 1**). No significant difference was observed in the background characteristics between patients with schizophrenia and healthy controls.

Serum Levels of the Metabolites of the Kyn Pathway in the Schizophrenia and Healthy Control Groups

We evaluated the serum levels of metabolites of the Kyn pathway (Trp, Kyn, 3-HK, QA, 5-HT, Kyn/Trp, 5-HT/Kyn, 3-HK/Kyn, QA/Kyn) in patients with schizophrenia and healthy controls. No significant differences were observed in the levels of the metabolites of the Kyn pathway between patients with schizophrenia and healthy controls (**Table 2**).

Serum Levels of Cytokines, hsCRP, and BDNF in the Schizophrenia and Healthy Control Groups

We also evaluated the serum levels of cytokines (TNF-α, IL-6), hsCRP, and BDNF in patients with schizophrenia and healthy controls (**Table 3**). No significant difference was observed in serum levels of the cytokines (TNF-α, IL-6), hsCRP, and BDNF between the schizophrenia and healthy control groups. IL-1β and IL-10 were not detected in the samples.

Relationships Among Metabolites of the Kyn Pathway and Cytokines, hsCRP, and BDNF in the Schizophrenia and Healthy Control Groups

The correlation table showed the relationships between the Kyn pathway metabolites and the cytokines (TNF-α, IL-6), hsCRP, and BDNF in the schizophrenia group and the healthy control group (**Table 4**). A significant positive correlation was found between the serum TNF-α levels and the serum Kyn levels ($r = 0.53$, $p = 0.0026$, **Figure 1**) and the Kyn/Trp value ($r = 0.67$, $p = 0.000046$, **Figure 2**) in the schizophrenia group. A significant positive correlation was found between the serum level of BDNF and the serum level of 5-HT ($r = 0.49$, $p = 0.0061$, **Figure 3**) and the 5-HT/Trp value ($r = 0.55$, $p = 0.0018$, **Figure 4**) in the schizophrenia group (**Table 4A**). A positive correlation was found between the serum levels of IL-6 and the serum levels of Kyn ($r = 0.64$, $p = 0.046$, **Figure 5**) and QA ($r = 0.78$, $p = 0.010$, **Figure 6**) as well as the QA/Kyn value ($r = 0.77$, $p = 0.021$, **Figure 7**) in the healthy control group (**Table 4B**).

Relationship Between the PANSS Scores and the Serum Levels of Metabolites of the Kyn Pathway, Cytokines, hsCRP, and BDNF in the Schizophrenia Group

The correlation table showed the relationship between the PANSS scores and the serum levels of metabolites of the Kyn pathway and BDNF (**Table 5**). A negative correlation was found between

TABLE 4A | Relationship between metabolites of the Kyn pathway and cytokines, hsCRP, and BDNF in the schizophrenia group.

	IL-6	TNF-α	hsCRP	BDNF
Trp	0.028	−0.092	0.33	0.087
	($p = 0.89$)	($p = 0.63$)	($p = 0.080$)	($p = 0.65$)
Kyn	0.3	0.53	0.36	−0.21
	($p = 0.11$)	(**$p = 0.0026$**)	($p = 0.051$)	($p = 0.26$)
3-HK	0.24	0.29	0.25	−0.21
	($p = 0.21$)	($p = 0.13$)	($p = 0.18$)	($p = 0.28$)
QA	0.42	0.34	0.27	−0.23
	($p = 0.059$)	($p = 0.12$)	($p = 0.24$)	($p = 0.31$)
5-HT	−0.3	−0.032	−0.23	0.49
	($p = 0.13$)	($p = 0.87$)	($p = 0.23$)	(**$p = 0.0061$**)
Kyn/Trp	0.27	0.67	0.18	−0.26
	($p = 0.16$)	(**$p = 0.000046$**)	($p = 0.36$)	($p = 0.16$)
5-HT/Kyn	−0.34	0.1	−0.24	0.55
	($p = 0.069$)	($p = 0.60$)	($p = 0.22$)	(**$p = 0.0018$**)
3-HK/Kyn	0.063	0.015	0.1	−0.12
	($p = 0.75$)	($p = 0.93$)	($p = 0.60$)	($p = 0.52$)
QA/Kyn	0.32	0.25	0.16	0.0085
	($p = 0.16$)	($p = 0.27$)	($p = 0.50$)	($p = 0.97$)

TABLE 4B | Relationship between metabolites of the Kyn pathway and cytokines, hsCRP, and BDNF in the healthy control group.

	IL-6	TNF-α	hsCRP	BDNF
Trp	−0.12	0.25	0.28	0.056
	($p = 0.74$)	($p = 0.49$)	($p = 0.44$)	($p = 0.87$)
Kyn	0.64	0.61	0.33	−0.25
	(**$p = 0.046$**)	($p = 0.060$)	($p = 0.35$)	($p = 0.49$)
3-HK	−0.055	−0.15	0.091	0.29
	($p = 0.89$)	($p = 0.68$)	($p = 0.81$)	($p = 0.42$)
QA	0.78	0.69	0.58	−0.071
	(**$p = 0.010$**)	($p = 0.040$)	($p = 0.10$)	($p = 0.86$)
5-HT	−0.33	0.45	0.46	0.073
	($p = 0.35$)	($p = 0.20$)	($p = 0.18$)	($p = 0.84$)
Kyn/Trp	0.55	0.46	0.22	−0.18
	($p = 0.10$)	($p = 0.18$)	($p = 0.53$)	($p = 0.62$)
5-HT/Kyn	−0.35	0.37	0.50	−0.054
	($p = 0.33$)	($p = 0.30$)	($p = 0.15$)	($p = 0.88$)
3-HK/Kyn	−0.055	−0.15	0.091	0.29
	($p = 0.89$)	($p = 0.68$)	($p = 0.81$)	($p = 0.42$)
QA/Kyn	0.77	0.63	0.58	−0.075
	(**$p = 0.021$**)	($p = 0.070$)	($p = 0.11$)	($p = 0.84$)

hsCRP, high-sensitivity C-reactive protein; BDNF, brain-derived neurotrophic factor; IL, interleukin; TNF-α, tumor necrosis factor alpha; Trp, tryptophan; Kyn, kynurenine; 3-HK, 3-hydroxykynurenine; QA, quinolinic acid; 5-HT, 5-hydroxytryptamine; KynA, kynurenic acid. Statistically significant differences at $P < 0.05$ is in bold. Positive correlations are shown in red, negative correlations are shown in blue, and the strength of the correlation is expressed in terms of concentration.

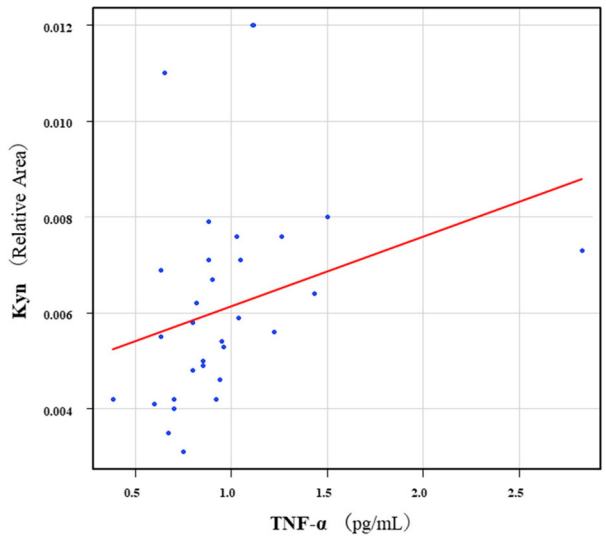

FIGURE 1 | Association between serum TNF-α levels and serum Kyn levels in the schizophrenia group. A significant positive correlation was found between the serum TNF-α levels and the serum Kyn levels ($r = 0.53$, $p = 0.0026$). Relative Area: The peak areas of the metabolites were normalized against those of the internal standards, and the resultant relative areas were further normalized by the sample amount explained in the Measurement of metabolites of the Kyn pathway. Thus, serum Kyn levels demonstrated as the ratio comparing with internal standard.

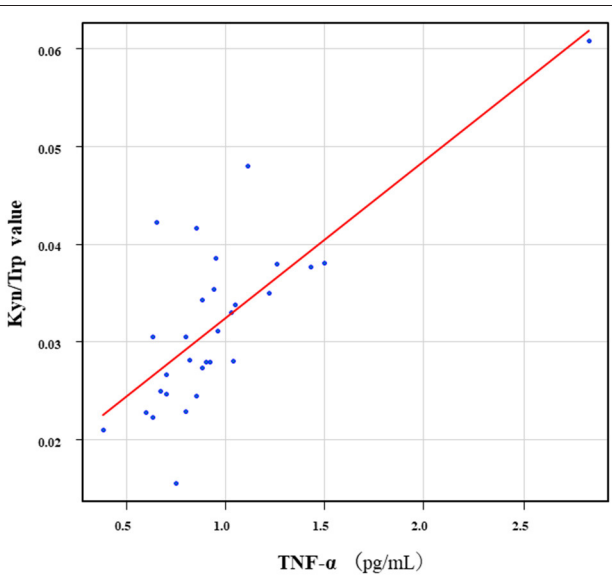

FIGURE 2 | Association between serum TNF-α levels and the Kyn/Trp value in the schizophrenia group. A significant positive correlation was found between the serum TNF-α levels and the and the Kyn/Trp value ($r = 0.67$, $p = 0.000046$) in the schizophrenia group.

the PANSS-G score and the serum QA levels ($r = -0.44$, $p = 0.043$, **Figure 8**) and the QA/Kyn value ($r = -0.64$, $p = 0.0014$, **Figure 9**). A negative correlation was found between the serum level of BDNF and the PANSS-N score ($r = -0.38$, $p = 0.038$, **Figure 10**). A negative correlation was found between the

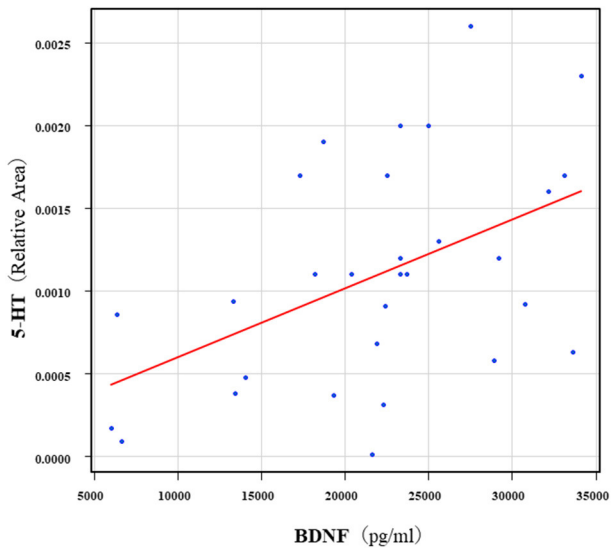

FIGURE 3 | Association between serum 5-HT levels and serum BDNF levels in the schizophrenia group 5. A significant positive correlation was found between the serum BDNF level and the serum 5-HT levels ($r = 0.49$, $p = 0.0061$) in the schizophrenia group. Relative Area: The peak areas of the metabolites were normalized against those of the internal standards, and the resultant relative areas were further normalized by the sample amount explained in the Measurement of metabolites of the Kyn pathway. Thus, serum 5-HT levels demonstrated as the ratio comparing with internal standard.

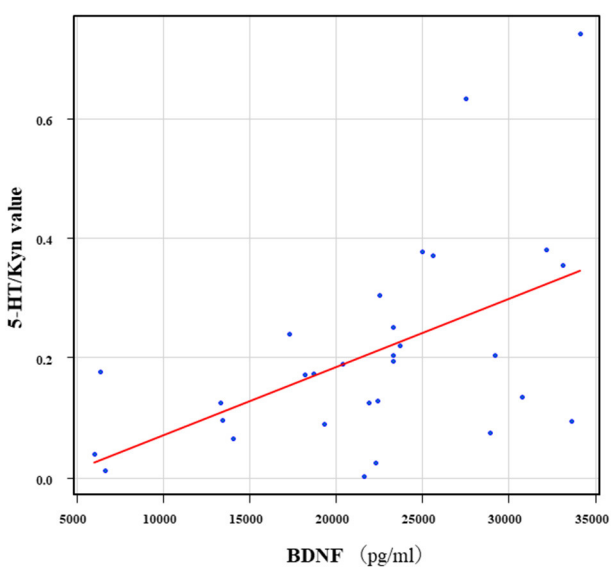

FIGURE 4 | Association between the serum BDNF levels and the 5-HT/Kyn value in the schizophrenia group. A significant positive correlation was found between the serum BDNF levels and the and the 5-HT/Trp value ($r = 0.55$, $p = 0.0018$) in the schizophrenia group.

PANSS-T score and the QA/Kyn value ($r = -0.50$, $p = 0.017$, **Figure 11**).

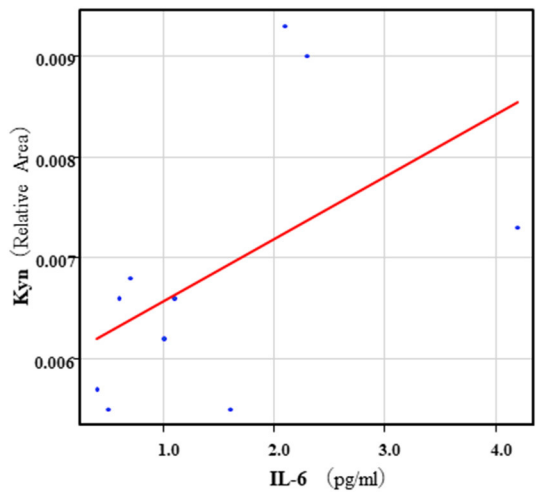

FIGURE 5 | Association between serum IL-6 levels and serum Kyn levels in the healthy control group. A positive correlation was found between the serum IL-6 levels and the serum Kyn levels ($r = 0.64$, $p = 0.046$) in the healthy control group.

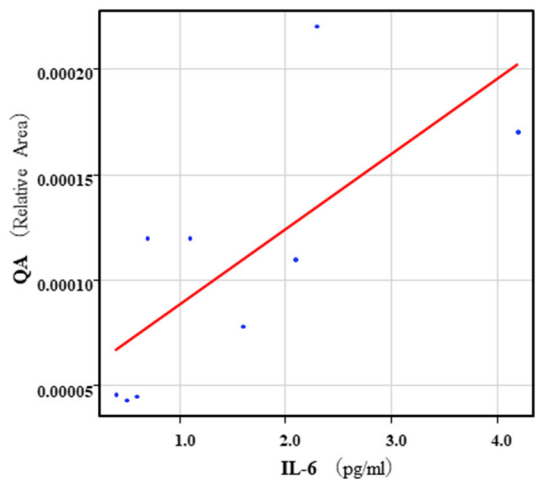

FIGURE 6 | Association between serum IL-6 levels and serum QA levels in the healthy control group. A positive correlation was found between the serum IL-6 levels and the serum QA levels ($r = 0.78$, $p = 0.010$) in the healthy control group. Relative Area: The peak areas of the metabolites were normalized against those of the internal standards, and the resultant relative areas were further normalized by the sample amount explained in the Measurement of metabolites of the Kyn pathway. Thus, serum QA levels demonstrated as the ratio comparing with internal standard.

DISCUSSION

Our findings showed a significant positive correlation between the serum levels of TNF-α and the Kyn levels and the Kyn/Trp value in the schizophrenia group, but not in the healthy control group. These results suggest that TNF-α accelerates the formation of Kyn from Trp in patients with schizophrenia. Inflammatory cytokines, especially TNF-α and IL-6, are the primary molecular

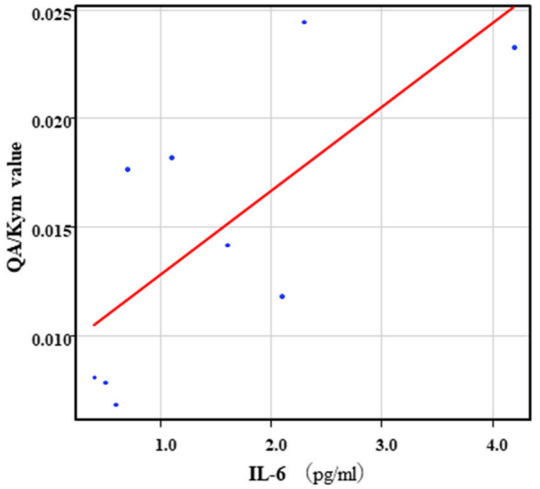

FIGURE 7 | Association between serum IL-6 levels and serum QA/Kyn value in the healthy control group. A positive correlation was found between the serum levels of IL-6 and the serum levels of QA/Kyn value ($r = 0.77$, $p = 0.021$) in the healthy control group.

TABLE 5 | Relationship between metabolites of the Kyn pathway and positive and negative syndrome scale scores.

	PANSS-T	PANSS-P	PANSS-N	PANSS-G
Trp	−0.16	0.0021	0.0019	−0.35
	($p = 0.40$)	($p = 0.99$)	($p = 0.99$)	($p = 0.06$)
Kyn	−0.17	−0.054	−0.039	−0.28
	($p = 0.38$)	($p = 0.78$)	($p = 0.84$)	($p = 0.14$)
3-HK	−0.08	0.12	−0.044	−0.13
	($p = 0.68$)	($p = 0.53$)	($p = 0.82$)	($p = 0.50$)
QA	−0.3	−0.21	−0.15	−0.44
	($p = 0.16$)	($p = 0.35$)	($p = 0.45$)	(**$p = 0.043$**)
5-HT	0.19	0.099	0.1	0.18
	($p = 0.33$)	($p = 0.60$)	($p = 0.58$)	($p = 0.33$)
Kyn/Trp	−0.025	−0.0078	−0.028	−0.0045
	($p = 0.89$)	($p = 0.97$)	($p = 0.88$)	($p = 0.98$)
5HT/Kyn	0.22	0.13	0.067	0.27
	($p = 0.25$)	($p = 0.51$)	($p = 0.73$)	($p = 0.14$)
3-HK/Kyn	0.078	0.27	0.014	0.048
	($p = 0.68$)	($p = 0.15$)	($p = 0.94$)	($p = 0.80$)
QA/Kyn	−0.5	−0.38	−0.24	−0.64
	(**$p = 0.017$**)	($p = 0.076$)	($p = 0.28$)	(**$p = 0.0014$**)
IL-6	−0.33	−0.2	−0.28	−0.29
	($p = 0.080$)	($p = 0.30$)	($p = 0.14$)	($p = 0.13$)
TNF-α	−0.24	−0.2	−0.13	−0.21
	($p = 0.21$)	($p = 0.30$)	($p = 0.49$)	($p = 0.26$)
hsCRP	−0.26	−0.28	−0.04	−0.29
	($p = 0.18$)	($p = 0.15$)	($p = 0.84$)	($p = 0.13$)
BDNF	−0.34	−0.21	−0.38	−0.23
	($p = 0.064$)	($p = 0.26$)	(**$p = 0.038$**)	($p = 0.22$)

PANSS, Positive and Negative Syndrome Scale; PANSS-T, PANSS Total; PANSS-P, PANSS Positive; PANSS-N, PANSS Negative; PANSS-G, PANSS General; Trp, tryptophan; Kyn, kynurenine; 3-HK, 3-hydroxykynurenine; QA, quinolinic acid; 5-HT, 5-hydroxytryptamine; KynA, kynurenic acid; hsCRP, high-sensitivity C-reactive protein; BDNF, brain-derived neurotrophic factor; IL, interleukin; TNF-α, tumor necrosis factor alpha. Statistically significant differences at $P < 0.05$ is in bold. Positive correlations are shown in red, negative correlations are shown in blue, and the strength of the correlation is expressed in terms of concentration.

targets for schizophrenia. Within central nervous system, microglia, the enzyme indoleamine 2,3-dioxygenase plays a role in the metabolism of Trp to Kyn and the subsequent conversion of Kyn to neurotoxic QA. At the same time, cytokine activation shunts metabolic activity from Trp to the Kyn pathway, which further reduces tryptophan hydroxylase driven serotonin synthesis (23). Serum levels of TNF-α in the schizophrenia group were not different from those in the healthy control group in the present study. Thus, it is possible that TNF-α, but not IL-6 more potently activates indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenas, two major rate-limiting enzymes of Kyn formation in the schizophrenia group than in the healthy control group. Exposure to chronic mild stress (24), or hepatic encephalopathy (25) has been shown to increase TNF-α and indoleamine 2,3-dioxygenase activity in rats. The serum levels of TNF-α are elevated in schizophrenia (6, 26). Serum levels of IL-6 (26–28), but not the cerebrospinal fluid levels of IL-6 (29), were also elevated in schizophrenia patients. Serum levels of QA were also elevated in psychiatric controls (30). QA, an endogenous metabolite of the Kyn pathway, is toxic and is involved in several neuropsychiatric diseases, including schizophrenia (7, 31). Taken together, these results suggest that IL-6 combined with QA might contribute to neuronal damage in the brain in schizophrenia. A recent systematic review (3) examined the correlation between cytokines and Kyn metabolites, and three studies showed a relationship between the Kyn pathway and elevated IL-6 and TNF-α concentrations. Only one study showed correlations between IL-8 concentrations and the Kyn pathway, and two studies showed correlations of low IL-4 concentrations with the Kyn pathway. Moreover, the authors of the systematic review did not find significant correlations of CRP ($n = 1$ study) and IFN-γ ($n = 3$ studies) with the Kyn pathway in schizophrenia. Meta-analyses of CRP levels in schizophrenia, which included a total of 26 cross-sectional or longitudinal studies evaluating 85,000 participants demonstrated that CRP levels were moderately increased (7). We found a positive correlation between serum levels of hsCRP and serum levels of Kyn in the schizophrenia group. Furthermore, a positive correlation was found between serum levels of BDNF and serum levels of 5-HT in the schizophrenia group, but not in the healthy control group. The 5-HT and BDNF identified in the serum were mainly secreted by platelets (32, 33). The discrepancies between the schizophrenia and healthy control groups might reflect differences in the secretory activity of platelets in both groups. In other words, the interaction between BDNF and 5-HT may be tighter in the schizophrenia group. However, the precise reasons underlying these results remain unknown.

A negative correlation was found between PANSS scores and the serum levels of QA and the QA/Kyn ratio in the schizophrenia group. However, when QA has neurotoxic effects,

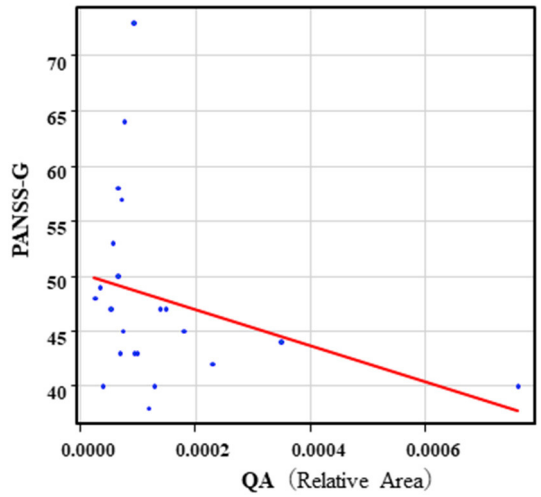

FIGURE 8 | Association between the PANSS-G scores and serum QA levels in the schizophrenia group. A negative correlation was found between the PANSS-G score and serum QA levels ($r = -0.44$, $p = 0.043$) in the schizophrenia group. Relative Area: The peak areas of the metabolites were normalized against those of the internal standards, and the resultant relative areas were further normalized by the sample amount explained in the Measurement of metabolites of the Kyn pathway. Thus, serum QA levels demonstrated as the ratio comparing with internal standard.

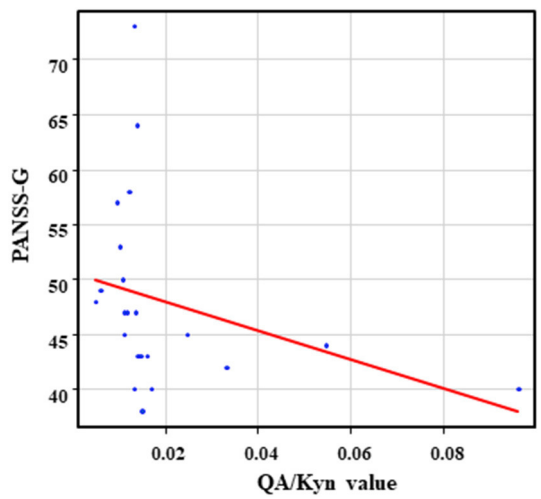

FIGURE 9 | Association between the PANSS-G scores and the QA/Kyn value in the schizophrenia group. A negative correlation was found between the PANSS-G score and the QA/Kyn value ($r = -0.64$, $p = 0.0014$) in the schizophrenia group.

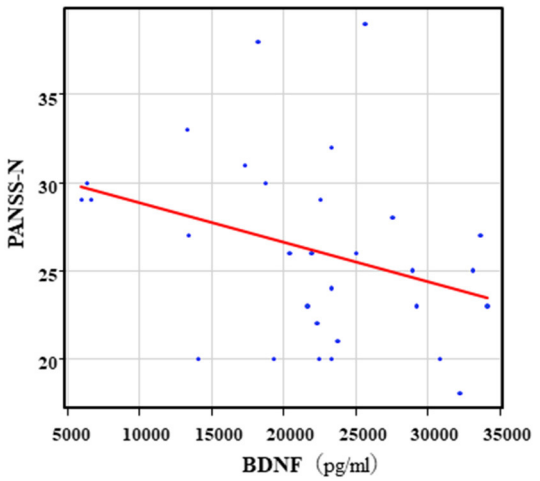

FIGURE 10 | Association between the PANSS-N scores and serum BDNF levels in the schizophrenia group. A negative correlation was found between he PANSS-N score and the serum BDNF levels ($r = -0.38$, $p = 0.038$) in the schizophrenia group.

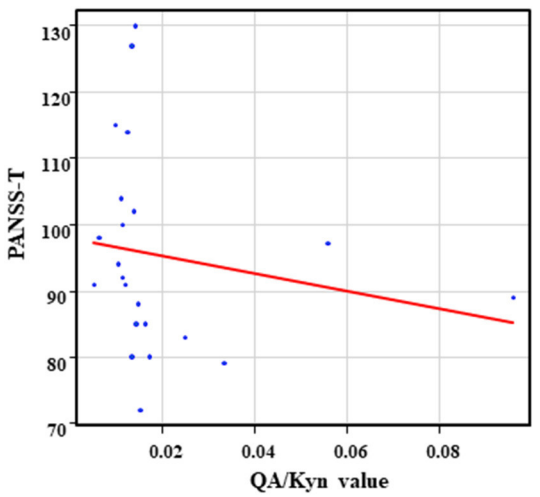

FIGURE 11 | Association between the PANSS-T scores and the QA/Kyn value in the schizophrenia group. A negative correlation was found between the PANSS-T sore and the QA/Kyn value ($r = -0.50$, $p = 0.017$) in the schizophrenia group.

a positive correlation has been reported be found between PANSS scores and the QA level or QA/Kyn ratio. This discrepancy in the present results was difficult to interpret. QA shows cellular neurotoxicity and has implications in schizophrenia. It has been speculated an imbalance in the production or removal of either of Kyn and QA would be expected to have profound implications for brain function, especially if that imbalance were present chronically (34). Recent study reviewed the roles of imbalances in Kyn metabolism in association with interactions with other neurochemicals as a major contributing pathophysiological mechanism in schizophrenia (35). Actually, QA was correlated with BDNF levels and psychiatric symptoms, suggesting that QA may have an indirect effect on psychiatric symptoms through BDNF but may also have a direct effect simultaneously. This may be biologically plausible because QA is an NMDA receptor agonist that can additionally inhibit the reuptake of glutamate by astrocytes, leading to excitotoxicity (7, 31). We also found a positive correlation between serum

QA and serum IL-6 levels in the schizophrenia and healthy control groups. Negative correlations were found between the PANSS-T scores and serum levels of IL-6 and between the PANSS-G scores and serum levels of BDNF in the schizophrenia group. A recent meta-analysis demonstrated that peripheral BDNF levels in serum and plasma were moderately reduced in patients with schizophrenia compared with controls and that this decrease was associated with disease duration. The extent of peripheral BDNF level decrease, however, did not correlate with the severity of positive and negative symptoms (4). Serum levels of IL-6 in chronic schizophrenia patients at admission showed a positive correlation with negative scores, and the serum levels of IL-6 in the patients at discharge were positively correlated with positive, negative, and total scores (36). These findings suggest that the association of serum levels of BDNF and IL-6 with psychometric findings might be complicated in schizophrenia patients. Previous studies have reported that the Kyn pathway is promoted by inflammation, which could be related to the pathological organization of many psychiatric disorders, including schizophrenia. BDNF is a protein produced by nerve cells in the brain and plays an important role in nerve cell activity. Several studies have reported serum Kyn levels in schizophrenia; however, there is no consistent view because of the many conflicting results. Our results showed that there was no significant difference in the plasma levels of Kyn pathway metabolites, cytokines, and BDNF between the schizophrenia and healthy control groups. A partial downregulation of the Kyn pathway is observed in schizophrenia patients, especially during acute symptomatic states and in older age, effects that are independent of each other. In contrast, younger and stable or remitted patients display limited to no Kyn metabolite abnormalities. The current meta-analysis illustrates the dynamic nature of Kyn abnormalities. It should be noted that all included studies investigated peripheral Kyn metabolites, which do not necessarily reflect central Kyn metabolite abnormalities in patients with schizophrenia (37). Finally, the blood levels of metabolites of the Kyn pathway, proinflammatory cytokines, hsCRP, and BDNF in patients with chronic schizophrenia remain controversial. Their interactions may also be complicated. The reasons for this discrepancy in the results remain unknown; however, the diversity of schizophrenia patients enrolled in past and current studies is a plausible explanation.

It has been reported that a positive correlation in Kyn, Trp, or Kyn/Trp ratio between serum and CSF (38), On the other hand, a discrepancy existed in cytokines between serum and CSF (39). Finally, the parallel changes in BDNF levels in plasma and CSF indicate that plasma BDNF levels reflect the brain changes in BDNF levels in schizophrenia (40). The definite discrepancy exists in metabolites of Kyn pathway, cytokines, or BDNF between the peripheral and the brain. Taken together, we could not interpret the results in peripheral as in the brain.

It has been speculated that antipsychotic drugs influence the upregulated Kyn pathway in schizophrenia patients (41). In contrast, treatment of haloperidol and clozapine did not affect the levels of brain Kyn or KynA in mice (9). The precise mechanisms how antipsychotic drugs influence the Kyn pathway and merge their efficacies remain unknown, this must be further elucidated.

This study had several limitations. First, the sample size was small, and all patients with schizophrenia were receiving several antipsychotic drugs, which could have affected the serum Kyn and Kyn metabolite levels. Second, we could not measure KynA in the Kyn pathway, IL-10 and IL-1β. Third, Trp is an essential amino acid that is consumed through diet, and aerobatic exercise but this study did not consider nutritional status, and daily activities of the schizophrenia patients.

In conclusion, TNF-α could influence the Kyn pathway in chronic hospitalized patients with schizophrenia. The relationships of metabolites of the Kyn pathway with the levels of proinflammatory cytokines, hsCRP, and BDNF and psychotic symptoms in chronic schizophrenia are complicated and must be further elucidated.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Occupational and Environmental Health (Approval Number: UOEHCRB19-024). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NO and RY: conceptualization. NO: methodology, software, and visualization. NO, YK, AI, and RY: validation and writing—original draft preparation. NO, HT, TN, RI, YK, and AI: data curation. AI, YK, and RY: writing—review, editing, and supervision. RY: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Identification of Major Psychiatric Disorders From Resting-State Electroencephalography Using a Machine Learning Approach

Su Mi Park[1†], *Boram Jeong*[2], *Da Young Oh*[1], *Chi-Hyun Choi*[1], *Hee Yeon Jung*[1,3,4], *Jun-Young Lee*[1,3], *Donghwan Lee*[2*] *and Jung-Seok Choi*[1,3*]

[1] Department of Psychiatry, SMG-SNU Boramae Medical Center, Seoul, South Korea, [2] Department of Statistics, Ewha Womans University, Seoul, South Korea, [3] Department of Psychiatry and Behavioral Science, Seoul National University College of Medicine, Seoul, South Korea, [4] Institute of Human Behavioral Medicine, Seoul National University Medical Research Center, Seoul, South Korea

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***Correspondence:**
Jung-Seok Choi
choijs73@gmail.com
Donghwan Lee
donghwan.lee@ewha.ac.kr

†Present address:
Su Mi Park, Department of Counseling Psychology, Hannam University, Daejeon, South Korea

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We aimed to develop a machine learning (ML) classifier to detect and compare major psychiatric disorders using electroencephalography (EEG). We retrospectively collected data from medical records, intelligence quotient (IQ) scores from psychological assessments, and quantitative EEG (QEEG) at resting-state assessments from 945 subjects [850 patients with major psychiatric disorders (six large-categorical and nine specific disorders) and 95 healthy controls (HCs)]. A combination of QEEG parameters including power spectrum density (PSD) and functional connectivity (FC) at frequency bands was used to establish models for the binary classification between patients with each disorder and HCs. The support vector machine, random forest, and elastic net ML methods were applied, and prediction performances were compared. The elastic net model with IQ adjustment showed the highest accuracy. The best feature combinations and classification accuracies for discrimination between patients and HCs with adjusted IQ were as follows: schizophrenia = alpha PSD, 93.83%; trauma and stress-related disorders = beta FC, 91.21%; anxiety disorders = whole band PSD, 91.03%; mood disorders = theta FC, 89.26%; addictive disorders = theta PSD, 85.66%; and obsessive–compulsive disorder = gamma FC, 74.52%. Our findings suggest that ML in EEG may predict major psychiatric disorders and provide an objective index of psychiatric disorders.

Keywords: classification, electroencephalography, machine learning, psychiatric disorder, resting-state brain function, power spectrum density, functional connectivity

INTRODUCTION

As the standard of clinical practice, the establishment of psychiatric diagnoses is categorically and phenomenologically based. According to the International Classification of Disorders (ICD) and the Diagnostic and Statistical Manual for Mental Disorders (DSM) (1, 2), clinicians interpret explicit and observable signs and symptoms and provide categorical diagnoses based on which those symptoms fall into. This descriptive nosology enhances the simplicity of communication; however, it is limited by potentially insufficient objectivity as it relies on observation by the clinician and/or the presenting complaints reported by the patient or informant. In addition,

the current system does not encompass psychopathology, in that symptom heterogeneity in the same category of disorder, or homogeneity among other disorders often is present. Research has found that symptom-focused diagnosis limits the focus of treatment to symptom relief only; therefore, data-driven approaches to study neural/biological mechanisms, such as the Research Domain Criteria project by the National Institute of Mental Health, have recently been used as a diagnostic aid (3, 4).

In mental healthcare, advances in data and computational science are rapidly changing. With respect to neural mechanisms and objective markers, the extent of evidence that we can measure has broadened. Additionally, use of machine learning (ML), such as artificial intelligence, has increased. Using out-of-sample estimates, ML can prospectively assess the performance of predictions on unseen data (test data) not used prior to model fitting (training data), thereby providing individualized information and yielding results with a potentially high level of clinical translation (5). This approach is contrary to classical inference based on null hypothesis tests (e.g., *t*-test, analysis of variance), which retrospectively focuses on in-sample estimates and group differences and thus lacks personalized explanation (6). ML is expected to help or possibly replace clinician decisions such as diagnosis, prediction, and prognosis or treatment outcomes (7).

The majority of current neuroimaging research (i.e., using functional magnetic resonance imaging) has applied supervised ML for diagnostic classification between patients and healthy controls (HCs). Studies have predominantly focused on Alzheimer's disease, schizophrenia, and depression (8–10) but have more recently expanded to other diagnostic topics (11). The literature suggests that ML can be used to discriminate psychiatric disorders using brain data with over 75% accuracy (12). A recent review (13) that used a support vector machine (SVM), a common ML method, to assess imaging data found that it is possible to distinguish patients with schizophrenia from HCs as follows: 17 of 22 studies found over 80% accuracy for the classification of validation data and top approaches, respectively (14).

Many imaging studies have compared HCs with subjects with one or several disorders, but few have comprehensively compared many disorders. This may be because acquiring imaging data is associated with high costs, especially when including sufficient patients for each group, a prerequisite for applying any supervised ML algorithm. Another alternative that can measure brain activity is electroencephalography (EEG), which delivers information about voltage measured through electrodes placed on the scalp. EEG is non-invasive, cost-effective, and suitable for measuring resting-state brain activity in natural settings, allowing easy acquisition of large amounts of data. In addition, as the acquisition technology is simplified and the calculation method is advanced, EEG is gaining attention as a core technology of brain–computer interface (BCI). One recent EEG study suggested that EEG spectra ML, using linear discriminant analysis learning method, can discriminate patients with schizophrenia from HCs with an accuracy of 80.66% (15); however, the main trend has been to differentiate between patients with single disorders [e.g., schizophrenia, depression, addiction, and post-traumatic stress disorder (PTSD), and dementia] and HCs (16–19). Notably, EEG features used for classification have differed from study to study; however, EEG studies that include a variety of psychiatric disorders are beginning to emerge (20).

Here, we aimed to establish novel classifiers for discriminating patients with major psychiatric disorders from HCs. We retrospectively collected EEG data of patients with six main categories of psychiatric disorders (i.e., schizophrenia, mood disorders, anxiety disorders, obsessive–compulsive disorders, addictive disorders, and trauma and stress-related disorders) and their specific diagnoses (i.e., depressive and bipolar disorders), excluding neurodevelopmental disorders. To increase the utility of our results, classification models were constructed using spectral power and functional connectivity (FC) features, which are commonly used EEG parameters in clinical settings (21, 22). Selected from ML methods, SVM and random forest (RF) were applied, which have been widely used in various fields of disease diagnosis; however, they struggled to explain the results of the model. Hence, we also performed a penalized logistic regression method, elastic net (EN) (23), to explain the results from the multivariate EEG parameters and facilitate a comparison of major discriminant features between disorders.

MATERIALS AND METHODS

Experimental Subjects

Data were collected retrospectively from medical records, psychological assessment batteries, and quantitative EEG (QEEG) at resting-state assessments from January 2011 to December 2018 from the Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center in Seoul, South Korea. The original diagnostic decision for clinical patients who visited the medical center was made by a psychiatrist based on DSM-IV or DSM-5 criteria and was also assessed using the Mini-International Neuropsychiatric Interview during psychological assessments. Final clinical confirmation of the primary diagnosis was established by two psychiatrists and two psychologists from March 2019 to August 2019, who reviewed both the original diagnoses in electrical medical records and psychological assessments that had been completed 1 month before and after QEEG. Concurrently, we included a HC sample ($n = 95$), which was selected from the studies performed at the SMG-SNU Boramae Medical Center. The final analyses included 945 subjects. The inclusion criteria were as follows: age from 18 to 70 years; diagnosis of the following primary diagnoses, which fall into six large-category diagnoses and nine specific diagnoses: schizophrenia ($n = 117$), mood disorders [($n = 266$); depressive disorder ($n = 119$) and bipolar disorders ($n = 67$)], anxiety disorders [($n = 107$); panic disorder ($n = 59$) and social anxiety disorders ($n = 48$)], obsessive–compulsive disorder ($n = 46$), addictive disorders [($n = 186$); alcohol use disorder ($n = 93$) and behavioral addiction including gambling and Internet gaming disorders ($n = 93$)], and trauma and stress-related disorders [($n = 128$); PTSD ($n = 52$), acute stress disorder ($n = 38$), and adjustment disorder ($n = 38$)]; and no difficulty in reading, listening, writing, or understanding Hangeul (Korean language). The exclusion criteria were as follows: lifetime and current medical history of a neurological

disorder or brain injury, neurodevelopmental disorder [i.e., intellectual disability [intelligence quotient (IQ) < 70] or borderline intellectual functioning (70 < IQ < 80), tic disorder, or attention deficit hyperactivity disorder), or any neurocognitive disorder. Ethical Approval.

This study was approved by the institutional review board (20-2019-16). In accordance with the retrospective study design, participant consent was waived.

EEG Settings and Parameters

EEG data included 5 min eyes-closed resting-state with 19 or 64 channels acquired with 500–1,000 Hz sampling rate and 0.1–100 on-line filters *via* Neuroscan (Scan 4.5; Compumedics NeuroScan, Victoria, Australia). Electrode impedances were kept below 5 kΩ by application of an abrasive and electrically conductive gel. In the analysis, the EEG data were down-sampled to 128 Hz, and 19 channels were selected based on the international 10–20 system in conjunction with a mastoid reference electrode as follows: FP1, FP2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, and O2. The ground channel was located between the FPz and Fz electrodes. Using the Neuroguide system (NG Deluxe 3.0.5; Applied Neuroscience, Inc., Largo, FL, USA), continuous EEG data were converted into the frequency domain using the fast Fourier transformation (FFT) with the following parameters: epoch = 2 s, sample rate = 128 samples/s (256 digital time points), frequency range = 0.5–40 Hz, and a resolution of 0.5 Hz with a cosine taper window to minimize leakage. Due to the mathematics of the FFT, a single epoch of time will be noisy; we used at least 60 s length of time. Details for EEG pre-processing and artifact rejection are described in a previous study (24) and are also provided in the online supplement. In the current study, power spectral density (PSD; μV2/Hz) and FC were included as EEG parameters. Each EEG parameter was calculated in the following frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), high beta (25–30 Hz), and gamma (30–40 Hz). PSD is the actual spectral power measured at the sensor level, and the absolute power value in each frequency band was included. FC was represented by coherence value, a measure of synchronization between two signals based on phase consistency (25, 26). To minimize the effects of windowing in the FFT (27), an EEG sliding average of the 256-point FFT cross-spectral matrix was computed for each subject. The EEG data were edited by advancing in 64-point steps (75% overlap), recomputing the FFT, and continuing with the 64-point sliding window of the 256-point FFT cross-spectrum for the entire edited EEG record. The mean, variance, standard deviation, sum of squares, and squared sum of the real (cosine) and imaginary (sine) coefficients of the cross-spectral matrix were computed across the sliding average of the edited EEG for all 19 channels for a total number of 81 and 1,539 log-transformed elements for each participant. The following equation was used to calculate coherence (28):

$$coherence\,(f) = \frac{(\sum_N (a(x)u(y) + b(x)v(y)))^2 + (\sum_N (a(x)v(y) + b(x)u(y)))^2}{\sum_N (a(x)^2 + b(x)^2)\sum_N (u(y)^2 + v(y)^2)}$$

and

$a(x)$ = cosine coefficient for the frequency (f) for channel x; $b(x)$ = sine coefficient for the frequency (f) for channel x; $u(y)$ = cosine coefficient for the frequency (f) for channel y; and $v(y)$ = sine coefficient for the frequency (f) for channel y. **Supplementary Figures 1–4** provide linked-ear topographic maps for PSD and FC.

Data Analysis

Statistical Analysis

Descriptive statistics were used to examine the overall distribution of the demographic characteristics for each participant (**Table 1**). To test the difference of demographic variables between each clinical subject and HC, *t*-tests and chi-squared tests were performed for continuous and binary variables, respectively. The patterns of these variables were different between clinical participants, age, sex, and/or years of education; therefore, their effects were included in the model for adjustment in further analyses. Furthermore, IQ is a major psychological variable that can be associated with QEEG (29) and can be considered a result of psychiatric symptoms (i.e., psychomotor retardation). Therefore, subsequent analyses compared models with adjusted and unadjusted IQ. Statistical analyses were conducted using R (version 3.6.3; https://www.r-project.org).

Classification of Psychiatric Disorders Based on QEEG

Feature Combination

For QEEG, feature combinations that were computed in classification models were a mixture of the following conditions: QEEG parameters including PSD (number of features = 19), FC (number of features = 171), and PSD + FC (number of features = 190); QEEG parameters in each frequency band including delta, theta, alpha, beta, high beta, gamma, and all six bands; and adjusting for age, sex, education, and IQ. The number of features computed in the ML model ranged from 22 (i.e., 19 channel PSD in the delta band + age + sex + education) to 1,144 [i.e., (19 channel PSD + 171 pair FC) × all six bands + age + sex + education + IQ; **Figure 1**].

Classification Model

We considered three ML methods for classifying psychiatric disorders: SVM, RF, and logistic regression with EN penalty.

SVM

SVM is one of the most frequently used ML methods in binary classification. The main idea of SVM is to find a linear separating hyperplane that maximizes the margin—that is, the largest distance gap between the two group's data points (30). In general, most data cannot be linearly divided, so original data are mapped to a linearly separable high-dimensional space through the so-called kernel trick. The main hyperparameter of SVM is the regularization amount related with the size of the

TABLE 1 | Demographic characteristics of samples.

Main/specific	Age		Sex		Education		IQ
	Mean (SD)	*t*	Counts (proportions)	χ^2	Mean (SD)	*t*	Mean (SD)
Healthy control ($n = 95$)	25.72 (4.55)		Male: 60 (63.2%) Female: 35 (36.8%)		14.91 (2.06)		116.24 (10.94)
Schizophrenia ($n = 117$)	31.73 (12.10)	4.58***	Male: 65 (55.6%) Female: 52 (44.4%)	1.25	12.84 (2.95)	−5.76***	89.62 (17.51)
Mood disorder ($n = 266$)	30.87 (12.70)	3.86***	Male: 151 (56.8%) Female: 115 (43.2%)	1.17	13.31 (2.48)	−5.59***	101.58 (15.70)
Depressive disorder ($n = 199$)	31.26 (13.23)	3.96***	Male: 109 (54.8%) Female: 90 (45.2%)	1.84	13.05 (2.51)	−6.25***	101.85 (15.28)
Bipolar disorder ($n = 67$)	29.71 (11.01)	3.17**	Male: 42 (62.7%) Female: 25 (37.3%)	0.00	14.11 (2.21)	−2.36*	100.81 (16.98)
Anxiety disorder ($n = 107$)	29.01 (10.56)	2.81**	Male: 79 (73.8%) Female: 28 (26.2%)	2,67	13.14 (2.42)	−5.52***	98.31 (16.31)
Panic disorder ($n = 59$)	31.05 (11.30)	4.10***	Male: 38 (64.4%) Female: 21 (35.6%)	0.25	13.45 (2.91)	−3.62***	100.31 (14.77)
Social anxiety disorder ($n = 48$)	26.51 (9.09)	0.69	Male: 41 (85.4%) Female: 7 (14.6%)	7.61**	12.78 (1.60)	−6.28***	95.85 (17.89)
Obsessive–compulsive disorder ($n = 46$)	28.48 (9.83)	2.28*	Male: 38 (82.6%) Female: 8 (17.4%)	5.53*	13.93 (2.33)	−2.45*	107.80 (15.24)
Addictive disorder ($n = 186$)	29.63 (10.89)	3.34***	Male: 164 (88.2%) Female: 22 (11.8%)	24.33***	13.23 (2.53)	−5.55***	103.88 (16.19)
Alcohol use disorder ($n = 93$)	34.16 (11.88)	6.45***	Male: 75 (80.6%) Female: 18 (19.4%)	7.09**	13.29 (3.07)	−4.22***	103.38 (13.61)
Behavioral addiction disorder ($n = 93$)	25.09 (7.48)	−0.70	Male: 89 (95.7%) Female: 4 (4.3%)	30.26***	13.16 (1.89)	−6.02***	104.38 (18.49)
Trauma and stress-related disorder ($n = 128$)	36.09 (13.82)	7.03***	Male: 44 (34.4%) Female: 84 (65.6%)	18.15***	13.57 (2.45)	−4.28***	98.89 (15.86)
Post-traumatic stress disorder ($n = 52$)	42.74 (13.0)	11.55***	Male: 14 (26.9%) Female: 38 (73.1%)	17.65***	13.37 (2.54)	−3.95***	98.90 (15.69)
Acute stress disorder ($n = 38$)	28.90 (9.05)	2.69**	Male: 3 (7.9%) Female: 35 (92.1%)	33.25***	14.26 (2.27)	−1.59	104.06 (15.43)
Adjustment disorder ($n = 38$)	34.19 (14.90)	5.01***	Male: 27 (75.0%) Female: 11 (25.0%)	0.74	13.26 (2.41)	−4.21***	94.24 (15.41)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Statistical values are results from comparison between each psychiatric disorder and healthy controls. IQ, Intelligence Quotient.

margin. It prevents the model from overfitting and improves the predictability of new data. We determined this hyperparameter with a grid search method, which finds the optimal parameter value in candidates from a grid of parameter values. The range of candidate values was set to (0.1, 0.5, 1, 5, 10). For SVM fitting, we used the R-package *rminer*, which provides various classification and regression methods, including SVM, under the same coherent function structure. In addition, it also allows us to tune the hyperparameters of the models.

RF

RF (31) is based on an ensemble technique that makes better predictions by combining multiple decision trees. The performance of a single decision tree is unstable since the generated decision trees differ according to the training dataset. To handle this problem, RF uses a bagging technique that builds many trees that randomly extract only some features and averages them. RF generally has a high level of performance by reducing the variance of prediction compared to that of a single model. The main hyperparameter of RF is the number of features randomly extracted when building a tree. Following Hastie et al. (32) we used the default value for the classification problem: the squared root of the total number of features. We used the R-package *random Forest*, which allows to fit RF by performing classification based on a forest of trees using random inputs and can examine the importance of each variable in the created model.

EN

When applying logistic classification with high-dimensional features, penalized logistic classification is commonly used for avoiding the ill-posed problem. Among the various penalty terms, the EN introduced by Zou and Hastie (23) works well when the input features are strongly correlated. Because the EN penalty is a compromise of the ridge and lasso penalty, it can effectively select the relevant variables and encourage highly correlated variables to be averaged. EN has a hyperparameter that indicates the amount of penalty used in the model. The optimal value of λ was selected by K-fold cross-validation.

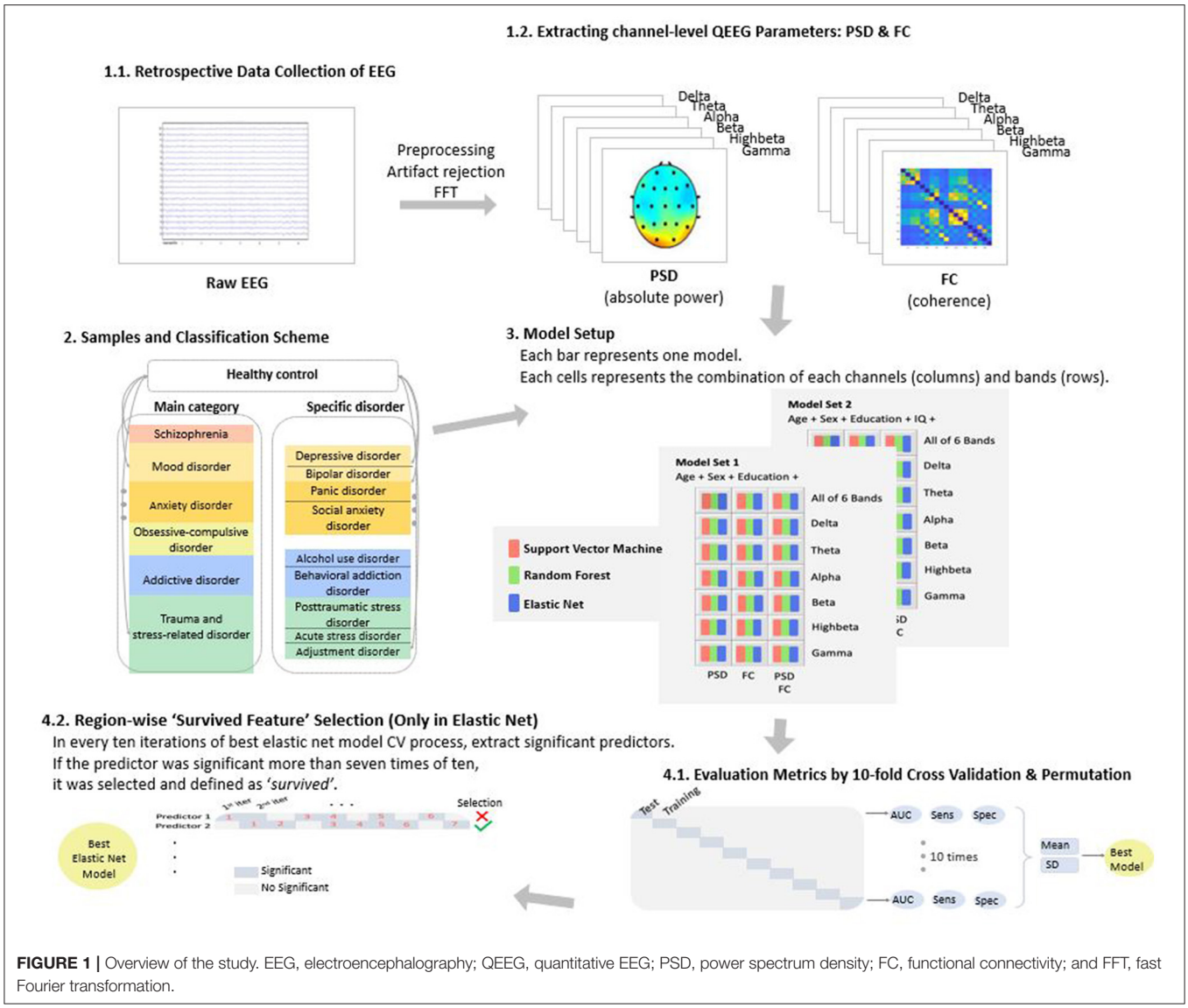

FIGURE 1 | Overview of the study. EEG, electroencephalography; QEEG, quantitative EEG; PSD, power spectrum density; FC, functional connectivity; and FFT, fast Fourier transformation.

The R-package *glmnet* was used for fitting EN. *glmnet* is a package that fits classification or regression models *via* penalized maximum likelihood. It can handle lasso, EN, and ridge penalty through the regularization parameter λ; it provides the fast automatic search algorithm for finding the optimal value of λ.

Cross-Validation and Feature Extraction. The performance of all models was compared based using 10-fold cross-validation, which partitions the original sample into 10 disjointed subsets, using nine of those subsets in the training process, and then making predictions about the remaining subset. Furthermore, for each fold, EN extracts the relevant features, which have non-zero estimates of regression coefficients. If the estimates of a feature were not zero more than seven times among 10-fold groups, we considered the feature to have "survived."

Permutation Test. We conducted a permutation test to assess the significance of each of the best EN models. We generated 1,000 random permutations and constructed the null distribution of the area under curve (AUC) (33, 34). *p*-values were obtained by calculating the number of cases that exceeded the AUC of the best EN model.

RESULTS

Comparison of Models

To select the model, we compared the performance of SVM, RF, and EN in terms of AUC. Regardless of adjusting for IQ, the accuracies of SVM, RF, and EN were each above the level of chance. With respect to the prediction of distinguishing patients with main-categorical psychiatric disorders from the HCs, EN showed the highest accuracy, in that the mean AUC for all disorders adjusted for IQ was 87.59 $\pm$ 7.92% (SVM = 86.02 $\pm$ 8.89% and RF = 87.18 $\pm$ 8.08%). EN also demonstrated

TABLE 2 | Comparison of elastic net models in predicting outcomes in patients with psychiatric disorders distinguished from healthy controls in major category diagnoses.

	Feature	AUC	Sens	Spec	Feature	AUC	Sens	Spec	*p*-value (best)
	(Entire)	Mean (SD)			(best)	Mean (SD)			
Schizophrenia	Entire	87.08	85.11	85.30	Alpha PSD	93.83	91.44	92.42	<0.001
		(5.48)	(10.57)	(12.15)		(5.74)	(9.88)	(10.73)	
Mood disorder	Entire	84.98	85.44	78.91	Theta FC	89.26	89.33	80.85	<0.001
		(5.04)	(11.25)	(13.38)		(6.20)	(11.50)	(12.19)	
Anxiety disorder	Entire	88.95	82.00	91.33	Whole PSD	91.03	83.18	91.78	<0.001
		(6.47)	(13.30)	(10.17)		(5.29)	(11.99)	(6.42)	
Obsessive–compulsive disorder	Entire	65.00	59.78	85.00	Gamma FC	74.52	65.33	90.00	0.005
		(17.40)	(17.91)	(19.44)		(18.43)	(22.10)	(21.60)	
Addictive disorder	Entire	76.70	70.58	83.67	Theta PSD	85.66	71.61	94.89	<0.001
		(10.04)	(17.25)	(19.84)		(5.22)	(12.45)	(5.40)	
Trauma and stress-related disorder	Entire	86.52	87.67	81.99	Beta FC	91.21	86.44	90.64	<0.001
		(10.09)	(15.45)	(11.21)		(5.30)	(9.58)	(6.04)	

Age, sex, education, and IQ were included in the model. Permutation test was conducted in order to assess the significance of each of the best EN models. EN, elastic net; PSD, power spectrum density; FC, functional connectivity; IQ, intelligence quotient.

the highest mean AUC performance for specific disorders (EN = 87.76 ± 8.42%, SVM = 82.83 ± 7.62%, and RF = 86.16 ± 8.97%). Therefore, EN was selected as the final method for further analyses. **Supplementary Tables 1, 2** show results for the comparisons of SVM, RF, and EN in detail.

Tables 1, **2** show the EN results of the discrimination model and feature combinations for each type of disorder. Compared to all features, PSD + FC in all bands were added to the models and select features showed superior classification accuracy (**Tables 1**, **2**). In addition, adjusting IQ enhanced the performance of discrimination models compared to leaving IQ unadjusted (**Supplementary Figure 5**).

Best Feature Combinations

All best models for each disorder from EN significantly distinguished between patients with psychiatric disorders and HCs ($p < 0.05$). The best feature combinations and classification accuracies for discrimination between patients with each large-category of diagnosis and HCs with adjusted IQ were as follows (**Table 2**): schizophrenia = alpha PSD, 93.83 ± 5.74%; trauma and stress-related disorders = beta FC, 91.21 ± 5.30%; anxiety disorders = whole band PSD, 91.03 ± 5.29; mood disorders = theta FC; 89.26 ± 6.20; addictive disorders = theta PSD, 85.66 ± 5.22; and obsessive–compulsive disorder = gamma FC, 74.52 ± 18.43. Higher accuracies of best models were found for specific diagnoses, compared to the large diagnostic category. Particularly, the maximum accuracy reached a fairly good level in that the accuracy for PTSD was 95.38 ± 4.90%.

Moreover, the best feature appeared differently based on specific diagnosis, even for those in the same category. The best accuracies for specific disorders after adjusting for IQ were as follows (**Table 3**): PTSD = beta PSD, 95.38 ± 4.90; adjustment disorder = alpha FC, 93.75 ± 7.31; acute stress disorder = beta PSD + FC, 92.00 ± 6.63; alcohol use disorder = whole band PSD, 93.21 ± 6.31; behavioral addiction = delta PSD, 84.78 ± 8.85; bipolar disorder = delta PSD + FC, 92.13 ± 3.01; depressive disorder = delta FC, 87.92 ± 5.67; social anxiety disorder = theta FC, 90.63 ± 8.51; and panic disorder = whole band PSD, 90.07 ± 5.32.

Furthermore, **Figures 2**, **3** provide region-wise predictors in the best EN model that were at a survival rate above 70% during the cross-validation (for more details, see **Supplementary Tables 3, 4**).

DISCUSSION

Our current study offers the following clinical insights: higher severity disorders increase the accuracy of the ML discrimination (e.g., classification of schizophrenia demonstrated the best accuracy); classifications for specific diagnoses (e.g., PTSD and acute stress disorder) provide higher accuracy than grouping large categories (e.g., trauma and stress-related disorders); and each disorder classification model shows different EEG characteristics.

First, consistent with our findings, previous imaging studies have found higher diagnostic accuracy for schizophrenia (92%) than bipolar disorder (79%) (35); however, the authors suggest that this may be due to the fact that although both disorders are associated with altered brain activity in several overlapping regions, the magnitude of dysfunction was more pronounced in schizophrenia. Moreover, in the present study, trauma- and stress-related disorders ranked second for accuracy with an AUC of 91.21% among large-category disorders and PTSD ranked first with an AUC of 95.38% among specific diagnoses. Similarly, one study found higher accuracy for PTSD-HC (80.00%) than for major depression-HC (67.92%) discrimination (36). While it is difficult to determine the severity of the disorder by the accuracy alone, it is plausible that functional brain alterations in specific disorders, such as schizophrenia, representative psychiatric disorders, and PTSD with an explicit traumatic event, are more pronounced than that of other psychiatric disorders.

TABLE 3 | Comparison of models in predicting outcomes in patients with psychiatric disorders distinguished from healthy controls in specific diagnoses.

	Feature	AUC	Sens	Spec	Feature	AUC	Sens	Spec	*p*-value (best)
	(Entire)	Mean (SD)			(Best)	Mean (SD)			
Depressive disorder	Entire	83.52	68.32	94.89	Delta FC	87.92	80.82	91.44	<0.001
		(10.02)	(16.05)	(8.58)		(5.67)	(15.10)	(12.35)	
Bipolar disorder	Entire	88.3	92.62	79.22	Delta PSD+FC	92.13	90.71	85	<0.001
		(7.62)	(12.32)	(11.93)		(3.01)	(11.25)	(10.76)	
Panic disorder	Entire	88.8	92.78	81	Whole PSD	90.07	89.44	88	<0.001
		(6.85)	(8.34)	(13.34)		(5.32)	(11.04)	(11.46)	
Social anxiety disorder	Entire	84.76	84.11	87.5	Theta FC	90.63	91.56	88	<0.001
		(11.99)	(10.53)	(19.61)		(8.51)	(6.5)	(13.98)	
Alcohol use disorder	Entire	84.04	84.67	82.22	Whole PSD	93.21	92.33	88.44	<0.001
		(9.63)	(20.48)	(13.71)		(6.31)	(7.45)	(13.62)	
Behavioral addiction disorder	Entire	69.6	67.56	79.33	Delta PSD	84.78	81.33	83.67	<0.001
		(10.88)	(19.26)	(25.76)		(8.85)	(13.87)	(14.34)	
Post-traumatic stress disorder	Entire	86.24	79.22	92.33	Beta PSD	95.38	95.88	92	<0.001
		(10.18)	(18.36)	(13.7)		(4.9)	(7.1)	(10.32)	
Acute stress disorder	Entire	87.18	96.66	80.77	Beta PSD+FC	92	95	89.44	<0.001
		(16.04)	(10.54)	(24.56)		(6.63)	(10.54)	(11.27)	
Adjustment disorder	Entire	86.4	92.5	82	Alpha FC	93.75	95	91.66	<0.001
		(10.16)	(16.87)	(11.76)		(7.31)	(10.54)	(13.42)	

Age, sex, education, and IQ were included in the model. Permutation test was conducted in order to assess the significance of each of the best EN models. EN, elastic netl; PSD, power spectrum density; FC, functional connectivity; IQ, intelligence quotient.

Alternatively, the homogeneity of neurodynamical states of intra-diagnostic disorders might influence the accuracy.

Second, we obtained higher accuracy in the specific categories than in the large grouping categories. In particular, in addictive disorders, when alcohol use disorder (93.21%) and behavioral addiction (84.78%) were classified rather than assessed as a large categorical diagnosis (85.78%), the accuracies were much higher. Results of repeated studies of that behavioral addiction, including Internet gaming disorder, have distinguished functional brain features from those in substance abuse disorders (37). With respect to bipolar and depressive disorders, the two were divided into different categories in DSM-5, but in the previous version of DSM and the current version of ICD, they were classified into one (i.e., mood or affective disorder). Compared to the group of mood disorders (89.26%), bipolar disorder showed higher accuracy (92.13%) when classified alone, but the accuracy of depressive disorder (87.92%) was relatively low. These findings may supplement attempts to discriminate mood disorders (38, 39). However, it should be avoided to interpret it as a more serious disease because the accuracy of bipolar disorder was higher than that of depressive disorder. This is because, as mentioned above, neurodynamical state heterogeneity can exist even within the same category. In addition, since several complex factors such as duration of disorder, recurrence, comorbidity, severity of symptoms, and psychotropic medication can affect brain function and EEG (40, 41), the results of this study are not considered to be more discriminatory than HC or inter-disease severity. It is not appropriate to interpret the results of this study by simplifying as that such disease category is better discriminated than the healthy individuals or that there is a hierarchical hierarchy of diseases.

Third, each classification model provides different best predictive features; different EEG patterns may imply the likelihood of diagnosis of distinguished psychiatric disorders. For instance, schizophrenia is best distinguished from HCs by abnormal alpha band power spectra; however, anxiety disorders are best distinguished from HCs by abnormal whole band power spectra. Several key features including beta power abnormalities in trauma and stress-related disorder, theta connectivity abnormalities in social anxiety disorder, and prefrontal connectivity abnormalities in fast frequency in obsessive–compulsive disorder are consistent with previous studies using group difference statistics (21, 42–44). In addition, dysfunctional connectivity in slow frequency bands in depressive disorder has been confirmed by a previous ML study (17). These differences in EEG patterns were also present within the same category (e.g., panic disorder vs. social anxiety disorder; PTSD vs. acute stress disorder). This implies that there is heterogeneity between disorders classified into the same category. In fact, not all patients with acute stress disorder develop PTSD. In this context, one study suggested that fear inhibition was different between acute stress disorder and PTSD groups (45). The key EEG features of each disorder suggested in the present study can provide useful information for diagnostic decisions of individuals in clinical settings. Nevertheless, cautious interpretation of the findings should be implemented, in that key features are not to be considered as directly reflecting the brain mechanisms of the disorder.

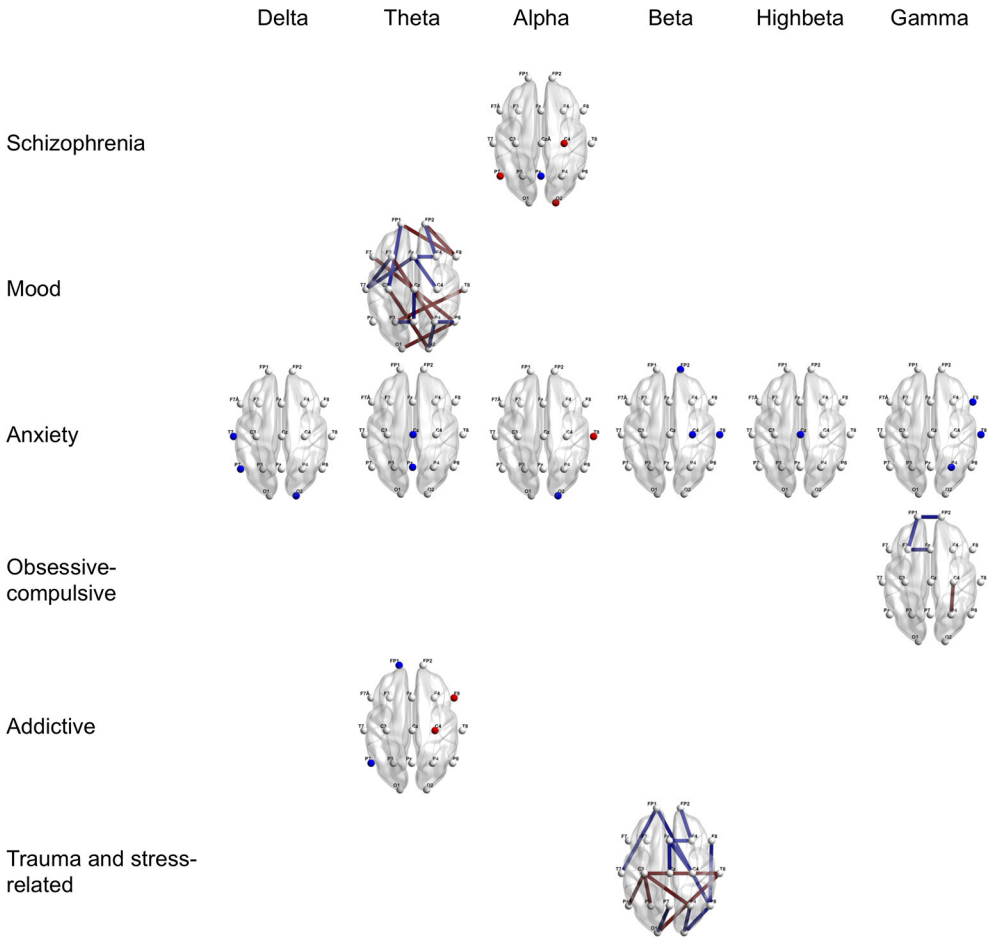

FIGURE 2 | Region-wise predictions for main categories of psychiatric disorders distinguished from healthy controls. Dots and lines represent region-wise survived predictors in the best EN model, which emerged significant above 7 times during 10 times of cross-validation. Dots mean channel-level PSD (absolute power) as QEEG parameter and lines mean channel-level FC (coherence) as QEEG parameter. Features colored in red represent higher probabilities for the psychiatric disorder when more increase. Features colored in blue represent higher probabilities for the psychiatric disorder when more decrease. Age, sex, the year of education, and the IQ score were computed in the models. EN, Elastic Net; PSD, Power Spectrum Density; FC, Functional Connectivity; QEEG, Quantitative Electroencephalography; and IQ, Intelligence Quotient.

This study focused on classification between patients with each mental disorder and HCs. We additionally performed analyses using EN ML between several psychiatric disorders. As in the previous analysis, the effects of demographic data and IQ were treated as covariates. The best EEG feature combination and AUC for each disease discrimination emerged as follows (see **Supplementary Table 5** for more details): schizophrenia vs. bipolar disorder = alpha PSD + FC, 67.84 ± 13.67%; schizophrenia vs. mood disorder = alpha PSD, 68.08 ± 7.23%, schizophrenia vs. depressive disorder = theta FC, 68.70 ± 12.67%; bipolar disorder vs. depressive disorder = alpha PSD + FC, 67.84 ± 13.67%; and panic disorder vs. social anxiety disorder = alpha PSD + FC, 70.47 ± 20.91%. Although the results had lower AUC than the comparison between patients with each disorder and HCs, all permutation results showed a higher level of discrimination than chance ($ps < 0.05$). In other words, EEG ML might be helpful for diagnostic decision between psychiatric disorders and HC and also between disorders. Multi-class ML method approach attempts in future studies would enhance the usability of EEG ML.

There is a wide variety of methods for extracting features including time series domain and frequency domain, and methods are still being developed. Extracting relevant features for modeling is crucial for ML to perform dimensional reduction and increase prediction accuracy (46). The current study used channel-level resting-state EEG absolute power as a representative PSD and coherence as the index of FC. These two parameters are where bandwidth field knowledge and research results have been accumulated for several decades (21, 47, 48). Our results can be extended to diagnostic information and help individualized treatment choices. Previous research has reported promising outcomes for predicting treatment

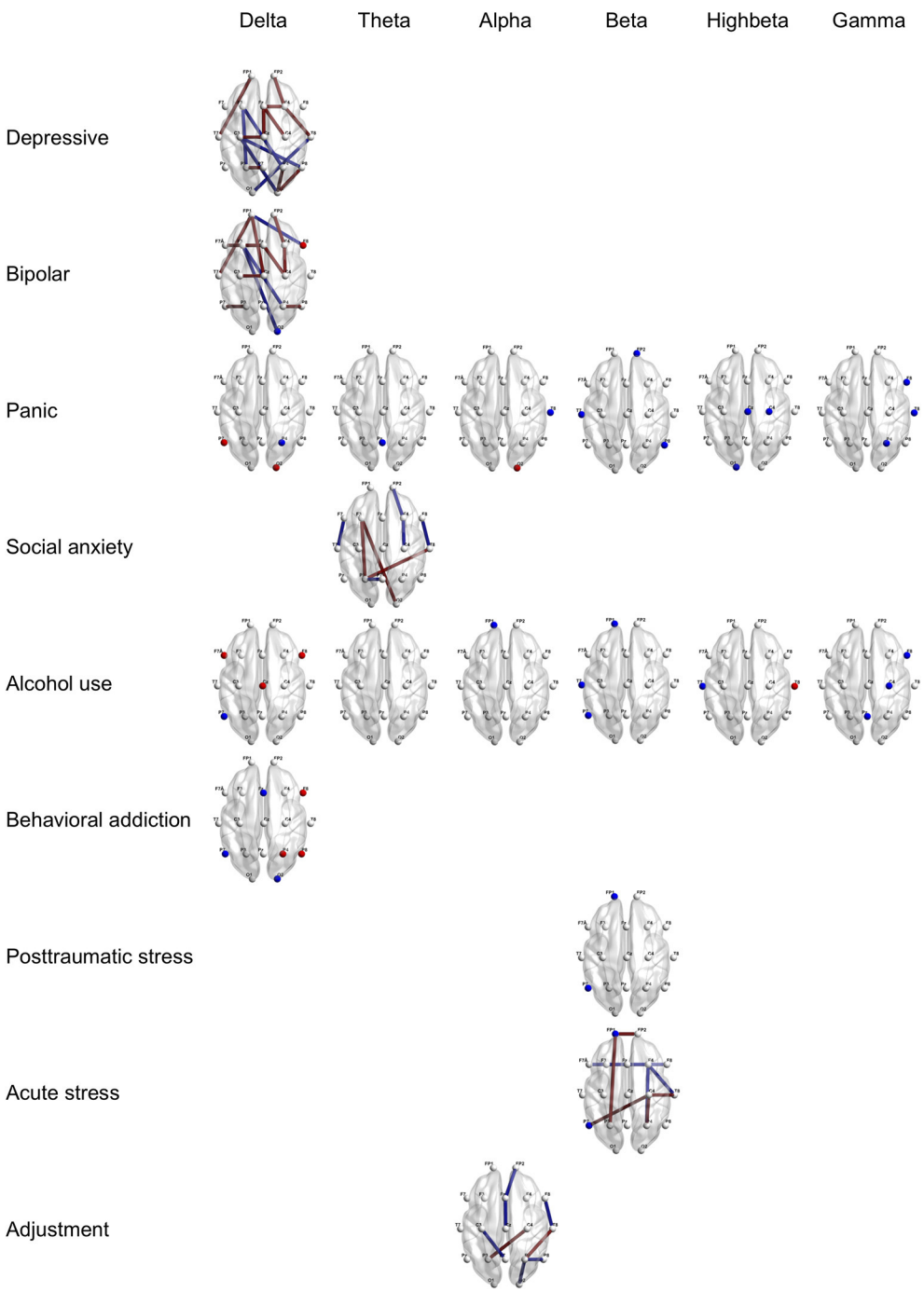

FIGURE 3 | Region-wise predictions for specific psychiatric disorders. Dots and lines represent region-wise survived predictors in the best EN model, which emerged significant above 7 times during 10 times of cross-validation. Dots mean channel-level PSD (absolute power) as QEEG parameter and lines mean channel-level FC (coherence) as QEEG parameter. Features colored in red represent higher probabilities for the psychiatric disorder when more increase. Features colored in blue represent higher probabilities for the psychiatric disorder when more decrease. Age, sex, the year of education, and the IQ score were computed in the models. EN, Elastic Net; PSD, Power Spectrum Density; FC, Functional Connectivity; QEEG, Quantitative Electroencephalography; and IQ, Intelligence Quotient.

responses, including medication and transcranial direct current stimulation, with ML using pre-treatment resting-state EEG (49, 50). In addition, the task-free and resting-state method during acquisition of EEG involves less measurement time than the paradigm using experimental stimulation; thus, it has high accessibility and scalability.

The current study has several limitations. First, the effects of medication, comorbidity, and severity of disorder were not controlled. Second, diagnoses were made near the time EEGs were measured, and we therefore cannot rule out the possibility of mixed results of patients who were subsequently diagnosed with different disorders. Third, the sample is from one center and the race and nationality are limited to Asian and Korean. Finally, our design is retrospective, and we did not prospectively verify the modeling. Moreover, external validation was not performed on other samples. Therefore, for generalization, it is necessary to verify the results with additional samples.

In conclusion, we found that an ML approach using EEG could predict major psychiatric disorders with differing degrees of accuracy according to diagnosis. Each disorder classification model demonstrated different characteristics of EEG features. EEG ML is a promising approach for the classification of psychiatric disorders and has the potential to augment evidence-based clinical decisions and provide objectively measurable biomarkers. It would be advantageous to provide the automated diagnostic tools in future medical healthcare using BCI.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://osf.io/8bsvr/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of SMG-SNU Boramae Medical Center, Seoul, Republic of Korea. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

SP performed data query and integration, EEG data analysis, statistical modeling, and interpretation of results, and contributed to writing the manuscript. BJ contributed to statistical modeling, programming, and writing the manuscript. DO contributed to data collection and writing the manuscript. C-HC, HJ, and J-YL contributed to data collection and reviewing the manuscript. DL and J-SC contributed to the conceptual design of the study and writing the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.707581/full#supplementary-material

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Do Leptin Play a Role in Metabolism–Related Psychopathological Symptoms?

Yelei Zhang[1,2†], *Xiaoyue Li*[1†], *Xianhu Yao*[3†], *Yating Yang*[1,2], *Xiaoshuai Ning*[1,2], *Tongtong Zhao*[1], *Lei Xia*[1], *Yulong Zhang*[1], *Kai Zhang*[1,2*] *and Huanzhong Liu*[1,2*]

[1] Department of Psychiatry, Chaohu Hospital, Anhui Medical University, Hefei, China, [2] School of Mental Health and Psychological Sciences, Anhui Medical University, Hefei, China, [3] Maanshan Fourth People's Hospital, Maanshan, China

Objectives: Leptin is a crucial regulator of energy balance and is associated with obesity. In recent years, it has also been recognized as involved in the psychopathological mechanism. Our study aimed to elucidate the relationships between serum leptin levels, body mass index (BMI), and psychopathology symptoms in patients with schizophrenia.

Methods: A cross-sectional assessment of 324 inpatients with schizophrenia was conducted. Schizophrenia symptoms were measured using the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS). Serum leptin levels were assessed by the Enzyme-Linked Immunosorbent Assay (ELISA).

Results: Significant differences in sex, BMI, and negative symptom subscale (PANSS-N) scores were found between the groups with high and low leptin levels in the study. Leptin levels were positively correlated with BMI ($B = 2.322$, $t = 9.557$, $P < 0.001$) and negatively correlated with PANSS-N scores ($B = -0.303$, $t = -2.784$, $P = 0.006$).

Conclusions: Our results suggest that the increase in leptin levels is responsible for antipsychotic-induced weight gain and improved psychopathological symptoms.

Keywords: leptin, body mass index, psychopathological symptoms, schizophrenia, antipsychotics

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***Correspondence:**
Kai Zhang
zhangkai@ahmu.edu.cn
Huanzhong Liu
huanzhongliu@ahmu.edu.cn

[†] *These authors share first authorship*

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INTRODUCTION

Schizophrenia is a chronic syndrome with a variety of clinical symptoms and biological characteristics (1), and its symptoms are usually divided into three categories (general psychopathological symptoms and positive and negative symptoms) (2). The life expectancy of people with schizophrenia is about 11–20 years shorter than that of the general population, and the average life expectancy is about 80–85% of that of the general population. Studies show that most people with schizophrenia die from complications such as cardiovascular disease. This phenomenon is mainly due to the higher risk of weight gain and other adverse metabolic effects caused by antipsychotics in patients with schizophrenia (3–5). Although the pathophysiological mechanisms of metabolic disorders, including weight gain induced by antipsychotics, remain unclear, associations between metabolic changes and psychopathological symptoms have been reported (6).

With the increasing use of second-generation antipsychotics (SGA), metabolic side effects are becoming more common, such as weight gain, changes in blood lipids, and glucose intolerance (7). Among second-generation antipsychotics, weight gain is the most common metabolic side effect in patients with schizophrenia who take these medications. The obesity rate is about

26–55% of mental disorders, 4.3 times higher than that of the general population (8). A meta-analysis comparing the efficacy of antipsychotics found that clozapine and olanzapine, while more effective than other drugs, were also more likely to cause weight gain than other drugs (9). Furthermore, the weight gain induced by olanzapine was dose-dependent in the short term after treatment (10). There is some evidence that antipsychotics with a faster track of weight gain during early treatment (such as olanzapine and clozapine) are more likely to gain weight than drugs with a slower track of weight gain. This phenomenon is significantly associated with clinical efficacy (11, 12). Ziprasidone and aripiprazole were also associated with weight gain in patients with schizophrenia who were first treated with antipsychotics (13, 14). However, the weight gain effect induced by aripiprazole was significantly lower than that of olanzapine (15). Pimavanserin is adjuvant clozapine, can significantly increase the weight of patients (16, 17). In addition, first-generation antipsychotics (FGA), such as chlorpromazine and thiouracil, have also been found to cause significant weight gain (18). Therefore, there is reason to suspect that the early clinical efficacy of the drug is associated with an increased cardiovascular burden.

Weight gain caused by medication, if not treated and managed, may lead to more serious consequences, that is, metabolic syndrome (19). Although clozapine and olanzapine have unique advantages in treating refractory schizophrenia, they are most likely to cause metabolic abnormalities (20). Clozapine and olanzapine also directly increase the risk of hyperlipidemia and hypertension and are unrelated to their effects on obesity and glucose tolerance (21, 22). Clozapine, in particular, increases the above risks (23). These risks will increase rapidly in a short time after treatment, endangering the lives of patients (24).

If there is a correlation between antipsychotic-induced weight gain and treatment effectiveness, the nature of the relationship is worth exploring. There are three hypotheses for this link:

1. The weight gain of patients directly improves the symptoms during treatment.
2. Clinical efficacy will lead to weight gain.
3. Antipsychotics induce weight gain and symptom improvement in patients in (a) interdependent/interdependent or (b) independent/mutually exclusive manner.

This means:

1. Antipsychotic-induced weight gain may be necessary for treatment effectiveness.
2. Weight gain caused by antipsychotics is a side effect that can be safely targeted without affecting the final therapeutic effect (e.g., lifestyle or drug intervention).

Leptin is an anorexic hormone produced by adipocytes and whose levels increase with weight gain (25). The energy-related role of leptin has been widely studied. As a satiety factor, leptin plays a vital role in maintaining energy balance by interacting with neural pathways in the brain, especially those involving the hypothalamus (26). Moreover, there was evidence that leptin promotes cognitive and behavioral functions in both rodents and humans (27). Recently, attention has been focused on the effect of leptin on psychopathological symptoms in patients with schizophrenia.

Antipsychotics can increase body weight, with a concurrent increase in leptin levels. Several studies have reported a positive relationship between weight gain and clinical status improvement after treatment. In addition, elevated serum leptin levels have been positively correlated with overall psychopathological improvement and are considered a predictor of clinical improvement (28). Although there are suggestions that leptin may be a biomarker for the prognosis of schizophrenia, it remains unclear whether this hormone is associated with particular psychopathological parameters. Few studies have explored leptin changes in patients with psychopathologies, especially in Chinese patients with schizophrenia. Therefore, our research aims to explore (1) serum leptin levels in patients with schizophrenia and (2) whether there was a relationship between serum leptin levels, BMI, and psychopathological parameters.

MATERIALS AND METHODS

Participants

We collected data on inpatients with schizophrenia from three hospitals in Anhui Province (the Chaohu Hospital of Anhui Medical University, Hefei Fourth People's Hospital, and Ma'an shan Fourth People's Hospital). The obesity rate in schizophrenia is estimated at 20% and in the general population at 10% (29), with a prevalence difference of about 10% between the two groups. Considering the following relevant parameters, $\alpha = 0.05$, $1–\beta = 0.82$, $R = 0.5$, 323 patients should be included through PASS11 calculation.

The inclusion criteria were as follows: (1) patients aged 18–75 years; (2) patients diagnosed with schizophrenia using the International Classification of Diseases, 10th Revision (ICD-10); (3) those with a disease duration of more than 5 years and was hospitalized for more than 1 month and (4) those with the ability to provide written informed consent and participate in psychopathology assessments. The exclusion criteria were as follows: (1) patients diagnosed with other mental disorders using the ICD-10; (2) those with severe physical illnesses, including severe neuroendocrine or metabolic disease; (3) those who abuse alcohol or other substances; and (4) pregnant or lactating women.

The study initially involved 443 patients, and 324 were eventually included, with an effective rate of 73.14%. Of the 119 excluded patients, 85 refused to participate in further interviews, nine refused to provide blood samples, nine were discharged from the hospital, and 16 had incomplete blood test data. In general, the study included three groups of people: (1) medically stable patients who chose to be hospitalized for family reasons; (2) patients who relapse due to irregular drug use; and (3) long-term hospitalized patients with unstable conditions. All aspects of the study protocol were reviewed and approved by the ethics. All of the participants provided written informed consent to participate in this study.

Demographic Data

The general information was collected by query and recorded on the questionnaires by professional psychiatrists trained for the task according to a uniform set of criteria. Height (m) and weight (kg) were measured. Researchers reviewed the histories of schizophrenia inpatients. We divided the subjects into three groups according to their current medication status, including the typical antipsychotics group (such as sulpiride, haloperidol), the atypical antipsychotics group (such as olanzapine, clozapine, risperidone, quetiapine, ziprasidone, aripiprazole, amisulpride), and the combination group (use both types of antipsychotics). Using the defined daily dose (DDD) recommended by the WHO as an indicator, each drug's equivalent dose of chlorpromazine was calculated for further analysis (30).

Clinical Assessment

To verify the diagnosis of schizophrenia, two independent psychiatrists conducted the Structured Clinical Interview for the ICD-10 with each patient. The psychopathological symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS). When interrater inconsistency was observed, the raters underwent consistency training and received clarifications regarding the rating scale. The intraclass correlation coefficient (ICC) of the scores given by the four scale evaluators was 0.89. The PANSS consists of three subscales: the positive symptoms subscale (PANSS-P, items P1–P7), the negative symptoms subscale (PANSS-N, items N1–N7), and the general psychopathology symptoms subscale (PANSS-G, items G1–G16) (31).

Measurement of Serum Leptin

All three hospitals stopped serving dinner after 6:30 p.m., but as a precaution, subjects were still asked to fast for more than 8 h before blood collection. Then, venous blood was collected between 6:00 and 8:00 a.m., and each subject's samples were stored in two 5 ml vacutainer tubes containing potassium EDTA. The plasma was labeled with anonymous codes after centrifugation (15 min at 1,000×g) and stored at −80°C. After all subjects were enrolled, the leptin levels in serum specimens were measured using an ELISA kit purchased from Cusabio Biotechnology Company (Code: CSB-E04649h). In brief, serum leptin was measured according to the instructions. The detection range was 0.156–10 ng/ml. An intra-lot coefficient of variation <8% and an inter-lot coefficient <10% were calculated.

Statistical Analysis

All statistical analyses were calculated by SPSS 24.0 (SPSS Inc., Chicago, IL, USA), including independent sample *t*-test (normally distributed continuous variables) and Mann-Whitney *U*-test (non-normally distributed continuous variables). The chi-squared test compared the categorical variables, including sex, smoking, drinking, obesity, and current antipsychotic drug treatment. Relationships between BMI, serum leptin levels, and psychopathology symptoms were examined by Spearman's correlation analysis. Then, taking the serum leptin levels (ng/ml) as the dependent variable, multiple stepwise regression was performed to examine the relationship between serum leptin and psychopathology symptoms among participants with schizophrenia. Subsequently, linear regressions were performed to examine the relationship between leptin, BMI, negative symptoms. Moreover, multiple tests were adjusted using Bonferroni correction, and $P < 0.05$ (two-tailed) indicated statistically significant differences.

RESULTS

General Information

The data of 324 inpatients with schizophrenia were analyzed, comprising 191 males and 133 females. Across all participants, the leptin data had a positively skewed distribution (skewness = 1.5, kurtosis = 2.1). Patients were grouped according to quartiles of the distribution of serum leptin levels. Those in the upper quartile were considered the high-level group (81 patients; 2.86 ng/mL), and the remainder were considered the low-level group (243 patients; 2.86 ng/mL). **Table 1** shows the baseline characteristics of the two groups. The average age of study subjects was 45.06 ± 11.62 years, and the onset age was 26.06 ± 8.16 years. The disease duration was 19.01 ± 10.46 years. Moreover, there were significant differences in sex, BMI, and PANSS-N scores between the low-level and high-level groups ($P < 0.05$). The high leptin level group had a significantly higher BMI than the low leptin level group (26.67 ± 3.68 vs. 23.28 ± 3.54, $P < 0.001$). In contrast, Negative subscale scores showed lower levels in the high leptin level group (19.82 ± 7.45) than in the low leptin level group (22.10 ± 7.61). There were no differences in age of onset, disease duration, type and dose of antipsychotics between the two groups ($P > 0.05$, **Table 1**).

The Correlations Between Leptin and Psychopathology Symptoms

Spearman's correlation analysis revealed that leptin was positively correlated with BMI ($r = 0.573$, $P < 0.001$) and negatively correlated with all psychopathology symptoms ($P < 0.05$). BMI was negatively associated with negative symptoms ($r = -0.159$, $P = 0.004$). BMI had no significant correlation with PANSS-P scores, PANSS-G scores, total PANSS scores, or the BPRS scores ($P > 0.05$). In general, our results indicated that leptin, BMI, and PANSS-N scores were all correlated with each other (**Table 2**). As shown in **Table 3**, Multiple stepwise regression analysis showed a negative relationship between serum leptin levels and PANSS-N ($B = -0.043$, $t = -3.102$, $P = 0.002$). Multiple stepwise regression analyses of leptin and psychopathic symptoms revealed that the residuals conformed to a normal distribution. It means the model was stable (**Figure 1**).

Regression Analysis Between Leptin, BMI, and Negative Symptoms

Table 4 showed that BMI had a positive effect on serum leptin ($B = 2.322$, $t = 9.557$, $P < 0.001$) and a negative effect on PANSS-N scores ($B = -0.303$, $t = -2.784$, $P = 0.006$). After adding leptin to the model, the effect of BMI on PANSS-N scores disappeared ($B = -0.186$, $t = -1.514$, $P = 0.131$), indicating that leptin may be a predictor for the negative symptoms.

TABLE 1 | Demographic characteristics of study participants.

	Total $N = 324$	Low-level group $N = 243$	High-level group $N = 81$	Statistics	*p*-value
Age (years), Mean (SD)	45.06(11.62)	45.05(11.15)	45.09(13.02)	$Z = -0.10$¶	0.919
Gender, *n*(%)				$\chi^2 = 72.96$	<0.001
Male	191(58.9%)	176(92.1%)	15(7.9%)		
Female	133(41.1%)	67(50.4%)	66(49.6%)		
Smoker, *n*(%)	94(29.0%)	88(93.6%)	6(6.4%)	$\chi^2 = 24.48$	<0.001
Drinker, *n*(%)	53(16.4%)	47(88.6%)	6(11.4%)	$\chi^2 = 6.32$	0.012
BMI(kg/m^2), mean(SD)	24.12(3.86)	23.28(3.54)	26.67(3.68)	$t = -7.38$	<0.001
Obesity	129(39.8%)	74(57.4%)	55(42.6%)	$\chi^2 = 35.55$	<0.001
Age of onset(years), mean(SD)	26.06(8.16)	25.69(7.96)	27.16(8.70)	$Z = -1.35$	0.177
Duration of illness(years), mean(SD)	19.01(10.46)	19.46(10.32)	17.67(10.82)	$Z = -1.62$	0.106
Current antipsychotic treatment, *n*(%)				$\chi^2 = 0.29$	0.867
Typical antipsychotics	7(2.1%)	5(71.5%)	2(28.5%)		
Atypical antipsychotics	133(41.0%)	98(73.6%)	35(26.4%)		
Combination of typical and atypical antipsychotics	184(56.7%)	140(76.0%)	44(24.0%)		
Dosage of antipsychotics (mg/d)†, mean(SD)	455.91(258.25)	467.20(266.61)	422.04(229.58)	$Z = -1.22$	0.223
PANSS‡, mean(SD)					
Positive subscale	17.91(7.42)	18.23(7.60)	16.96(6.80)	$Z = -1.14$	0.255
Negative subscale	21.53(7.63)	22.10(7.61)	19.82(7.45)	$t = 2.35$	0.019
General psychopathology subscale	38.40(12.68)	39.04(12.55)	36.47(12.96)	$t = 1.58$	0.115
Total	77.81(24.18)	79.33(23.84)	73.25(24.76)	$t = 1.97$	0.050
BPRS§ total score	42.61(13.85)	43.40(13.77)	40.24(13.92)	$Z = -1.89$	0.059
Leptin levels(ng/ml), mean(SD)	1.90(1.91)	0.97(0.72)	4.72(1.55)	$t = 21.02$	<0.001

†*Chlorpromazine equivalent.*
‡*Positive and negative syndrome scale.*
§*BPRS, Brief Psychiatric Rating Scale.*
¶*Mann-Whitney U.*

DISCUSSION

Weight gain caused by antipsychotics is related to psychopathological improvement. When the patient's weight increased by 7%, the PANSS score decreased by 12% (32). The BPRS score of patients with more than 7% weight gain decreased by 45.6%, while the BPRS score of the rest of the patients decreased by only 31.9% (33). Previous studies have found that the higher the BMI of Chinese patients with chronic schizophrenia, the higher the plasma orexin-A level and the less negative symptoms (34). Many studies have shown a significant relationship between antipsychotic-induced weight gain and good treatment outcomes (20, 35). For example, for clozapine and olanzapine, there is a significant correlation between weight gain and clinical response to these antipsychotics, but the reason is not clear (36, 37). Most studies have shown a correlation between antipsychotic-induced weight gain and treatment benefits based on the above definition. Lower baseline weight was associated with weight gain induced by antipsychotics (38). In studies of controlled baseline weight or BMI, 90% of studies showed a link between symptom improvement and weight gain (33).

Weight gain and improvement caused by antipsychotics may result from the pharmacodynamic properties of antipsychotics, but the relationship between them is not necessarily interdependent. It has also been reported that weight loss in patients with schizophrenia through life intervention and drug intervention does not affect the efficacy of antipsychotic drugs (39). In summary, there is a correlation between antipsychotic-induced weight gain and the therapeutic benefit (40). However, the direct cause-effect relationship between antipsychotic-induced weight gain and the therapeutic benefit is unclear, or weight gain is not an absolute requirement for clinical efficacy.

In this study, serum leptin was negatively correlated with positive, negative, general pathological symptoms and PANSS total BPRS score in patients with schizophrenia. Multiple stepwise regression analyses showed that serum leptin level was

TABLE 2 | Spearman's correlation analysis.

	BMI	Leptin	Positive subscale	Negative subscale	General psychopathology subscale	Total	BPRS
BMI	1.000						
Leptin	0.573**	1.000					
Positive subscale	−0.037	−0.113*	1.000				
Negative subscale	−0.159**	−0.187**	0.382**	1.000			
General psychopathology subscale	−0.085	−0.173**	0.712**	0.731**	1.000		
Total	−0.102	−0.192**	0.793**	0.798**	0.968**	1.000	
BPRS	−0.089	−0.177**	0.861**	0.677**	0.909**	0.949**	1.000

*p-value < 0.05.
**p-value < 0.01.

TABLE 3 | Multiple stepwise regression analysis between leptin and psychopathology symptoms.

	Coefficients		t	p-value	95.0% confidence Interval for B		Collinearity statistics		
	B	Std. error			Lower bound	Upper bound	Tolerance	VIF	Minimum tolerance
(Constant)	2.822	0.314	8.992	0.000	2.205	3.439			
Positive subscale	−0.071		−1.208	0.228			0.869	1.151	0.869
Negative subscale	−0.043	0.014	−3.102	0.002*	−0.070	−0.016	1.000	1.000	
General psychopathology subscale	−0.055		−0.704	0.482			0.486	2.056	0.486
PANSS total score	−0.093		−1.009	0.314			0.357	2.800	0.357
BPRS total score	−0.055		−0.745	0.457			0.545	1.835	0.545

*Indicated the Bonferroni corrected p-value, $p < 0.05$.

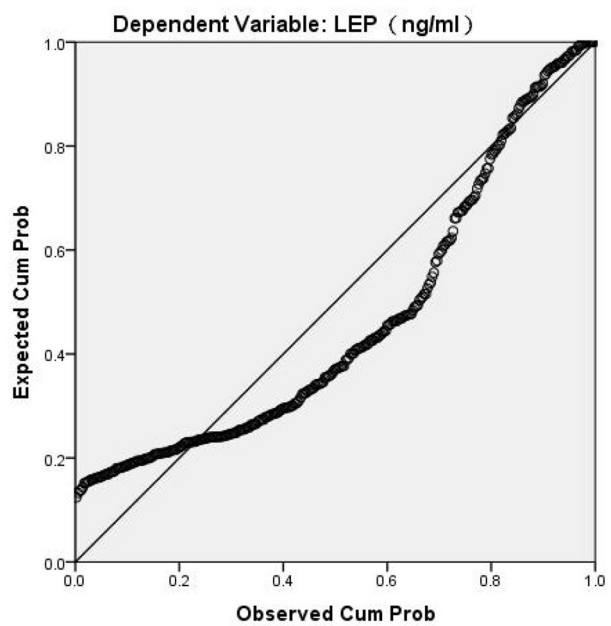

FIGURE 1 | Multiple stepwise regression analysis between leptin and psychopathology symptoms.

significantly correlated with negative symptoms. In summary, this study showed that serum leptin levels in patients with schizophrenia were negatively correlated with the three subscales of PANSS (PANSS-P, PANSS-N, PANSS-G), the total scale score, and the BPRS score. This result is consistent with the reported changes in serum leptin levels and the severity of negative symptoms (41, 42). A large body of evidence suggests that dopamine system dysfunction is associated with negative symptoms of schizophrenia, leading to a lack of will and pleasure (43–45). More studies have shown that the role of leptin in protecting cell survival, promoting apoptosis, and dopamine regulation may be the main mechanism for improving the psychopathological symptoms of schizophrenia (46). A previous study found that plasma leptin levels were negatively correlated with PANSS depression factor scores ($r = -0.255$, Bonferroni corrected $P = 0.028$) (47). These findings support the hypothesis that leptin is a predictor of the reduction of negative symptoms in schizophrenia.

If leptin can relieve psychopathological symptoms, then weight gain in patients with schizophrenia is of concern. The leptin level in cerebrospinal fluid has been positively correlated with plasma leptin level and BMI (48). Another study found that leptin levels in schizophrenic patients treated with antipsychotics were higher than those in healthy controls, which was associated with weight gain caused by antipsychotics (49, 50). In addition, studies on patients without medication have shown that low leptin levels are associated with schizophrenia, and antipsychotics will increase leptin levels. Therefore, it is beneficial to study the relationship between leptin, BMI, and psychopathological symptoms. Interestingly, there were no statistically significant differences in age of onset, disease duration, type or the dose of antipsychotics between the high-leptin and low-leptin

TABLE 4 | Regression analysis between leptin, BMI, and negative symptoms.

	Dependent	Independent(s)	B	*t*	*p*-value
b(YX)	(Y)	(X)	−0.303	−2.784	0.006
b(MX)	(M)	(X)	2.322	9.557	
b(YX,M)	(Y)	(X)	−0.186	−1.514	0.131
		(M)	−0.050	−2.031	0.043

X, BMI; Y, Negative symptoms; M, Leptin.

groups. It suggests that the antipsychotic was not the focus of the study.

The serum leptin level in women (3.24 ± 2.07 ng/ml) was higher than that in men (0.97 ± 1.05 ng/ml). There are three possible reasons for this phenomenon: Firstly, the location of fat deposition and the proportion of fat in the body (51). Subcutaneous fat is dominant in females, while visceral fat is more abundant in males. Subcutaneous fat produces more leptin than visceral fat; therefore, males' serum leptin levels are lower than females' (52). Another possibility is the effect of sex hormones: oestradiol promotes the secretion and release of leptin in cultured adipose tissue, but this process does not occur in men (53). Testosterone has been shown to have antiregulatory effects, suggesting that males' leptin concentrations may be lower than those in females, even when body fat ratios are similar (54, 55). Finally, it is possible that leptin production is higher in the female brain than in the male brain, leading to higher circulating leptin levels in female blood (56, 57).

Several limitations of this study need to be emphasized. Firstly, due to the cross-sectional design, this study cannot obtain causality. These findings must be carefully interpreted and explained in future longitudinal studies. Secondly, we focused on the effect of leptin on weight gain and included other relevant indicators, such as lipoprotein and triglyceride. In addition, leptin gene and leptin receptor gene polymorphisms may affect antipsychotic drug-induced weight gain. However, our study did not evaluate the effect of leptin receptor gene polymorphism on prognosis. Finally, we believe that different kinds of antipsychotics may have different effects on body weight. Therefore, further research is needed to evaluate and control these effects.

CONCLUSION

It is the first study to suggest that leptin may play a role in the relationship between antipsychotics-induced weight gain and favorable treatment response in schizophrenia. These findings help us further understand the relationship between leptin, weight gain, and antipsychotic response in patients with schizophrenia. Our findings may help monitor the recovery of patients with schizophrenia and develop new treatment options.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Chaohu Hospital affiliated with Anhui Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YeZ, YY, and XN collected and analyzed the data. KZ and HL gave administrative support. YeZ and XL wrote the paper. YuZ, XY, YY, TZ, and LX provided insightful discussion for the manuscript. All authors contributed to data interpretation and approved the final version for publication.

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SYSTEMATIC REVIEW
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Tips for Effective Implementation of Virtual Reality Exposure Therapy in Phobias—A Systematic Review

Marek Krzystanek[1], Stanisław Surma[1], Małgorzata Stokrocka[2†], Monika Romańczyk[1], Jacek Przybyło[3], Natalia Krzystanek[4] and Mariusz Borkowski[2†]*

[1] Clinic of Psychiatric Rehabilitation, Department of Psychiatry and Psychotherapy, Faculty of Medical Sciences, Medical University of Silesia in Katowice, Katowice, Poland, [2] Department of Research and Development, Polfa Tarchomin, Warszawa, Poland, [3] Multispecialistic Voivodship Medical Clinic in Katowice, Katowice, Poland, [4] Abramowski 18th High School, Katowice, Poland

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***Correspondence:**
Marek Krzystanek
m.krzystanek@sum.edu.pl;
krzystanekmarek@gmail.com

† These authors have contributed equally to this work and share senior authorship

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Background: The high incidence of phobias and the limited accessibility of psychotherapy are the reasons for the search for alternative treatments that increase the availability of effective treatment. The use of virtual reality (VR) technology is an option with the potential to overcome the barriers in obtaining an effective treatment. VR exposure therapy (VRET) is based on a very similar rationale for *in vivo* exposure therapy. The study aimed to answer the question of how to perform exposure therapy in a virtual reality environment so that it is effective.

Methods: A systematic review of the literature, using PRISMA guidelines, was performed. After analysis of 362 records, 11 research papers on agoraphobia, 28 papers on social phobia and 10 about specific phobias were selected for this review.

Results: VRET in agoraphobia and social phobia is effective when performed from 8 to 12 sessions, on average once a week for at least 15 min. In turn, the treatment of specific phobias is effective even in the form of one longer session, lasting 45–180 min. Head mounted displays are an effective technology for VRET. Increasing the frequency of sessions and adding drug therapy may shorten the overall treatment duration. The effectiveness of VRET in phobias is greater without concomitant psychiatric comorbidity and on the condition of inducing and maintaining in the patient an experience of immersion in the VR environment. Long-term studies show a sustained effect of VRET in the treatment of phobias.

Conclusion: A large number of studies on in VR exposure therapy in phobias allows for the formulation of some recommendations on how to perform VRET, enabling the effective treatment. The review also indicates the directions of further VRET research in the treatment of phobias.

Keywords: agoraphobia, social phobia, specific phobias, exposure therapy, virtual exposure therapy, VRET, virtual reality, VR

INTRODUCTION

Phobic anxiety disorders are characterized by the occurrence of fear and anxiety in certain situations with little or no real threat, and a behavioral strategy to avoid those situations. Agoraphobia is an irrational fear of being out in the open space, in crowds, far from home, and of traveling alone. It is often accompanied or preceded by panic attacks. Social phobia, in turn, is an irrational fear of social situations and of avoiding them and specific phobias are fear and avoidance of specific objects or situations. All these phobias are common in the population. In the group of adults, the prevalence of specific phobias is estimated at 5–12% (1, 2), social phobia at 2.4% (3), and agoraphobia at 2.3% (4). All phobias may lead to a significant disability and impairment in everyday functioning, with the loss of social and professional roles (5).

Evidence from prospective studies suggests that anxiety disorders should be viewed as a chronic disorder that begins in childhood, adolescence or early adulthood, with a peak in middle age and a decline in old age (5). According to the 2015 Global Burden of Disease Study, anxiety disorders ranks ninth in the list of the largest contributors to global disability (6). In the case of social phobia, 37.6% of people diagnosed after 12 months found severe role impairment in at least one life domain, and an average number of 24.7 days out of role per 1 year was recorded (3). In the case of panic disorder with agoraphobia, 84.7% of people diagnosed after 12 months described severe impairment of the social role, and in the case of agoraphobia without a history of panic disorder, but with panic attacks, 39.0% reported severe impairment (7). These data show the urgent need to increase the availability of effective treatments.

The standard psychotherapy for agoraphobia and social phobia is cognitive-behavioral therapy (CBT) with the participation of a psychotherapist. Despite the convincing theoretical and empirical foundations, there appear to be barriers to the accessibility of this type of therapy in routine medical care. Neudeck and Einsle (8) mentioned structural barriers (e.g., time, insurance, or logistics) and barriers on the side of the therapist (e.g., negative attitude toward exposure therapy or insufficient knowledge of the method). These limitations hinder the accurate application of exposure techniques in clinical practice. These barriers pose a problem for patients, preventing them from receiving highly effective treatment (8). The use of virtual reality (VR) technology is an option with the potential to overcome these described difficulties. VR exposure therapy (VRET) is based on a very similar rationale for *in vivo* exposure therapy, however, in VR exposure, phobic stimuli are presented to the patient in a computer created artificial reality.

VR is a computer-generated reality that provides input to the user's sensory system and interacts with the user (9). Visual VR stimuli are presented through VR glasses [smartphone with 3D frames or a head-mounted display (HMD)] or by projection-based systems such as CAVE systems (automatic virtual environment in a cave), i.e., a room with up to six projection sides or Motek Caren system (10). The audio signal is input through speakers or head-phones, and optional tactile,

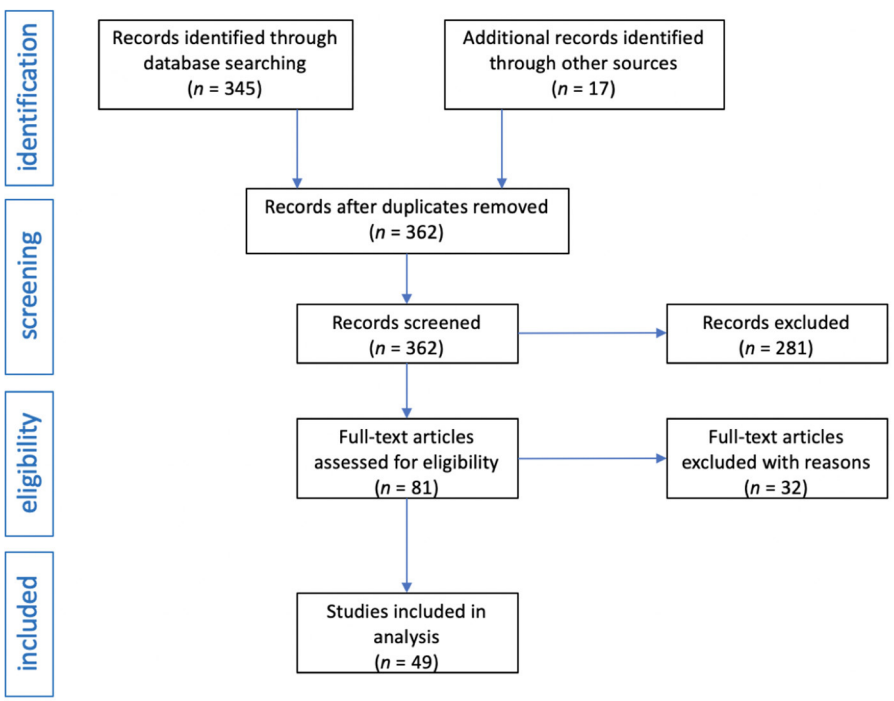

FIGURE 1 | Flow diagram of studies analysis and selection for review.

TABLE 1 | Studies on the use of VR exposure therapy in agoraphobia.

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
North et al. (20)	60	2	Controlled clinical trial in patients with agoraphobia.	The subjects were assigned to the therapeutic group with the use of VR or to the control group without intervention.	Desensitization to phobic stimuli was demonstrated in the group using VR. The feeling of discomfort decreased with successive treatment sessions.	If side effects occur during VRET, they disappear in subsequent sessions and are not a reason for dropping out of therapy. Therapy with HMD.
Moore et al. (21)	9	3	Healthy subjects (8 women and 1 man); age: 22–27 years. Heart rate, skin conductivity, respiratory rate, and body temperature were analyzed before and after the VR intervention.	The display showed the environment: an elevator without people and crowded with people, a grocery store, a city square without people and with people, and a beach without people and with many people. The exposure to each environment lasted 2 min.	Most of the respondents experienced the realism of VR. There was an increase in skin conductance, an initial increase and then a decrease in heart rate, and insignificant changes in body temperature.	Even a 2-min VR exposure causes a feeling of realism accompanied by symptoms of neurovegetative excitation. Therapy with HMD.
Vinelli et al. (22)	12	2	Controlled clinical trial. Patients with panic attacks and agoraphobia.	Subjects were randomly divided into three groups: receiving CBT using VR (8 sessions) or conventional therapy who had experienced the traditional CBT (12 sessions) or control group without intervention.	Clinical improvement was achieved in the VR group during 8 and not 12 sessions as was the case with conventional therapy.	VRET is effective after 8 sessions. The duration of VRET may be shorter than *in vivo* therapy. VRET with HMD.
Alcaniz et al. (23)	1	3	Patient with agoraphobia.	Supporting psychological therapy of agoraphobia at home using VR on a personal computer (PC).	Not characterized. Authors conclusion was that he use of VR may be helpful in the treatment of agoraphobia.	VRET can be performed on a personal computer (PC).
Choi et al. (24)	40	2	Randomized controlled clinical trial. Patients with panic attacks and agoraphobia.	Subjects were randomized to either conventional CBT combined with VR (4 sessions) or a panic control program (12 sessions). The observation time was 6 months.	Significant improvement was demonstrated after treatment compared to the pre-treatment results in both treatment groups.	VRET may be effective in combination with CBT psychotherapy. No data available on the technique of VRET.
Botella et al. (25)	37	2	Controlled clinical trial. Patients with panic attacks with or without agoraphobia.	The subjects were qualified to the group using VR or the group with *in vivo* exposure or a control group. Clinical assessments were made before and after the treatment, and in the 12-month follow-up. The treatment programs consisted of 9 sessions weekly.	Clinical improvement has been demonstrated in both therapeutic groups.	VRET is effective when sessions are held over 9 weeks weekly. VRET on PC.
Pelissolo et al. (26)	92	2	Randomized controlled clinical trial. Patients with panic attacks and agoraphobia.	Subjects were randomized to either VR or classical CBT or the control group. The intervention consisted of 12 therapy sessions.	Clinical improvement was shown in both active treatment groups. There were no statistically significant differences in the effectiveness of the therapy between the two groups.	VRET is effective with 12 sessions of therapy. Therapy with HMD.

(Continued)

TABLE 1 | Continued

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
Malbos et al. (27)	18	2	Randomized controlled clinical trial. Patients with agoraphobia.	The subjects were classified into two groups: therapy with the use of VR or therapy with the use of VR and cognitive therapy. The subjects were exposed to 9 different virtual environments.	Questionnaires, behavioral tests, and physiological measurements indicated a positive influence of VR. The addition of cognitive therapy did not bring any significant additional benefits.	For VRET to be effective, it does not have to be combined with conventional CBT therapy. Therapy with HMD.
Meyerbroeker et al. (28)	55	3	Randomized controlled clinical trial. Patients with panic attacks and agoraphobia.	Subjects were randomly assigned to 4 sessions of CBT and then to 6 sessions using VR or 6 sessions with *in vivo* exposure, or a control group without intervention.	Both CBT and VR therapy were more effective than no intervention. In the panic disorder severity scale, *in vivo* exposure CBT was more effective than CBT with VR.	*In vivo* exposure may be more effective than in VR exposure in agoraphobia with panic attacks. Therapy with HMD or CAVE.
Castro et al. (29)	80	3	Clinical trial in patients with chronic agoraphobia.	Subjects were assigned to either VR therapy or conventional cognitive behavioral therapy or receiving treatment only. All subjects received anti-stress therapy. The observation period was 6 months.	All treatments were statistically effective after both treatment and 6 months of follow-up. The VR group showed clinical improvement in most of the variables measured during observation. The *in vivo* CBT group showed the highest dropout rates.	Patients treated with VRET are less likely to discontinue therapy than patients treated with CBT. Therapy with HMD.
Pitti et al. (30)	99	2	Randomized controlled clinical trial.	Subjects were randomly assigned to receive paroxetine and CBT, paroxetine and CBT and VRET, and paroxetine alone. Both combined groups received 11 CBT sessions, and one group also received 4 VR therapy sessions. Treatments were performed in individual sessions once a week for 3 months.	The three treatment groups showed statistically significant improvement. For some measures, the combined treatment groups showed greater improvement. The group exposed to VR showed greater improvement in the face of phobic stimuli.	VRET in combination with paroxetine is more effective than either of these methods alone. When combined with paroxetine, VRET is effective after 4 sessions a week. Therapy with HMD.

The risk of bias and study quality assessed with the Effective Public Health Practice Project's Quality Assessment Tool for Quantitative Studies (QATQS) was presented as the global rating for each publication (1—strong, 2—moderate, 3—weak).

or olfactory stimulation is possible but seldom provided. The goal of VR is to replace sensory stimuli from the real world and create an impression that a user is immersed in the real world experiencing. To interact with a user in real time, the VR system collects information about the user's position and head movements through sensors and input devices such as a head tracking system or a joystick.

To date, many clinical trials have been conducted, including randomized and controlled trials on the effectiveness of VRET in agoraphobia and social phobia. Due to a large amount of research, meta-analyzes assessing the above issue are also available in the literature. A summary of the most recent meta-analyzes on the use of VRET in the treatment of phobias is presented below.

In the meta-analysis by Wechsler et al. conducted in 2019 and involving 9 randomized and controlled clinical trials, the effectiveness of using VR in the treatment of agoraphobia and social phobia was assessed. It was shown that the use of VR in the treatment of social phobia compared to *in vivo* therapy did not bring any greater benefits (negative Hedges coefficient: −0.50). In the case of agoraphobia, no statistically significant advantage of *in vivo* therapy over VR was found (negative Hedges coefficient: −0.01). The authors indicated the need to conduct further randomized controlled clinical trials with the use of VR in order to expand the knowledge in this field (11).

Similar results were obtained by Carl et al. in a meta-analysis of 30 studies on the use of VR in the treatment of various phobias, including social anxiety and agoraphobia (12). These researchers showed a large effect size for VR compared to those who were not subjected to the intervention (positive Hedges coefficient: 0.90). In addition, an average to large effect size for VR was found compared to the psychological placebo conditions (positive Hedges coefficient: 0.78). The comparison of VR with conventional *in vivo* therapy did not show significant differences

TABLE 2 | Studies on the use of VR exposure therapy in social phobia.

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
Harris et al. (31)	14	2	Randomized controlled clinical trial. Students with social phobia.	Four weekly sessions using VR, each lasting 15 min.	It was shown that the applied intervention decreased the level of anxiety, feeling of discomfort, and the heart rate in the subjects.	VRET is effective with 4 sessions performed once a week. The session may be short, 15 min long. Therapy with HMD.
Roy et al. (32)	10	2	No information on randomization. Social phobia 6 women and 4 men Average age: 36.11 years Average duration of social anxiety disorder: 22.4 years.	12 sessions with the use of VR in the presence of a psychotherapist. Twenty minutes exposure to stressful situations during each session (identified during the first session). 6 subjects were included in the group cognitive-behavioral therapy and 4 in the VR therapy.	Improvement of the depressive symptoms; reduction of anxiety and avoidance of stressful situations in reality.	VRET is effective when exposed to a stressful situation for 20 min and after 12 sessions. Therapy with HMD.
Anderson et al. (33)	2	3	2 women with social phobia.	Each patient received a different VR intervention: weekly therapy (10 sessions) and intensive therapy (6 sessions) for 3 days.	Both subjects responded with a reduction in the perceived anxiety during public speaking.	VRET can be effective even after 6 sessions performed twice a day. It is also effective after a week with 10 sessions per week. Therapy with HMD.
Klinger et al. (34)	36	2	Controlled clinical trial. Patients with social phobia.	The subjects were assigned to the group of VR therapy or group CBT therapy. The virtual environments related to performance, intimacy, mindfulness and assertiveness. The intervention lasted 12 weeks and consisted of 12 sessions.	The results showed significant improvement in both treatment groups.	VRET is effective after 12 weekly sessions. VRET on PC
Grillon et al. (35)	10	2	Clinical trial with single-arm. Patients with social phobia.	The subjects were subjected to 11 sessions with the use of VR including situations containing phobic stimuli.	Reduction of social anxiety experienced during public speaking and reduction of the avoidance of eye contact with the audience were observed.	VRET is effective after 11 sessions. Therapy with HMD.
Anderson et al. (36)	11	3	Single-arm clinical trial. Patients with social phobia.	Individual sessions, including 4 sessions of psychoeducation and cognitive therapy and 4 sessions of exposure therapy using a virtual audience presented on a computer screen. A therapist was available in another room to answer questions and summarize up to 10 min after each session. Three months follow-up.	All self-report measures of social anxiety decreased; the improvement was maintained throughout the follow-up period. Participants reported that they were satisfied with the treatment, that they felt better after treatment, and that the computer program was user-friendly.	VRET is effective after 4 sessions. VRET on PC.
Wallach et al. (37)	112	2	Randomized controlled clinical trial. Patients with social phobia.	The subjects were randomly assigned to CBT in direct contact or with the use of VR or to the control group. The intervention included 8 sessions.	Reduction of anxiety in the group receiving active therapy was observed. During the study, twice as many respondents discontinued cognitive-behavioral therapy in direct contact than in VR group.	VRET is effective after 8 sessions. Therapy with HMD.

(Continued)

TABLE 2 | Continued

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
Donahue et al. (38)	20	1	Randomized controlled clinical trial. Patients with social phobia.	Subjects were exposed to a 4-min VR public speaking after receiving either quetiapine or placebo (double-blind) an hour earlier. A concurrent placebo/quetiapine VR exposition occurred 1 week later.	There was no significant effect of quetiapine on the outcome. However, quetiapine was associated with significantly increased heart rate and somnolence.	4 min VRET is less effective than drug therapy. Therapy with HMD.
Robillard et al. (39)	45	2	Randomized controlled clinical trial. Patients with social phobia.	Patients were assigned to either conventional CBT or VR therapy or to a control group. The intervention included 16 sessions.	The intervention groups showed similar significant reductions in social anxiety.	VRET is effective after 16 sessions. No information about the technic of VRET.
Lister et al. (40)	20	2	Randomized controlled clinical trial. Patients with phobia of public speaking.	The subjects were assigned to the active intervention group consisting of 4 VR sessions or to the control group.	Skin conductance and heart rate were shown to increase, suggesting that the virtual reality intervention was effective in triggering a fear response. VRET was found to reduce anxiety and negative beliefs about public speaking skills.	VRET is effective after 4 sessions. Therapy with HMD.
Wallach et al. (41)	20	2	Randomized controlled clinical trial. Patients with social phobia.	The subjects were assigned to the intervention therapy group using VR or cognitive therapy or CBT or waiting lists (WL). The intervention consisted of 12 sessions.	Cognitive therapy was no better than VR in cognitive measures, but was better than VR in one behavioral measure (LSAS fear). VR was more effective than cognitive therapy in terms of one behavioral parameter (reduction of fear in a behavioral task). There were no differences between the three treatments and all were superior to WL group.	VRET is effective after 12 sessions. Therapy with HMD.
Price et al. (42)	41	3	Randomized controlled clinical trial. Patients with social phobia.	The subjects were exposed to 8 sessions during which they were exposed to various social situations in VR: a conference room with 5–100 participants. Three factors characterizing the subject's immersion in virtual reality were analyzed: the sense of spatial presence, commitment, and the sense of reality.	Various components of the sense of reality were related to the experience of fear and the response to treatment with VR. Efficacy was significantly associated with the highest anxiety ratings reported by individuals during the exposure. The scale of involvement was the only factor that was significantly associated with response to treatment.	Eight sessions were required for VRET to be effective. The effectiveness of treatment is related to the sense of realism of the exhibition environment. Therapy with HMD.
Cornwell et al. (43)	32	2	A clinical trial involving 16 healthy people and 16 with social anxiety disorder.	The subjects were influenced by VR representing a conference room in which they were to deliver a short speech.	Patients with social phobia reported greater stress and anxiety than healthy people throughout the procedure.	The use of VR causes similar reactions to those accompanying reality, so that technology can be used in the treatment of social phobia. Therapy with 3dVisor.

(Continued)

TABLE 2 | Continued

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
Heuett and Heuett (44)	120	3	Controlled clinical trial. Students with phobia of public speaking.	The subjects were qualified for exposure to public speaking in virtual reality or during video visualization, or for a control group.	In both groups of active intervention, the feeling of fear of public speaking was reduced. Students who were exposed to VR reduced their fear of public speaking more than students exposed to video visualization.	It seems that the use of VR in treating social phobia is more effective than video visualization. Therapy with HMD.
Safir et al. (45)	49	2	Randomized controlled clinical trial. Patients with social anxiety. A follow-up of the study by Wallach et al. (37).	Subjects were assigned to either a VR or conventional CBT intervention group or a control group. The intervention consisted of 12 sessions. The observation period was 1 year.	After 1 year of observation, it was shown that the reduction of anxiety during social appearances was still maintained in both intervention groups.	The effectiveness of VRET requires 12 sessions. Therapy has long-term success. No information about the technic of VRET.
Anderson et al. (46)	58	2	Randomized controlled clinical trial. Patients with social phobia.	The subjects were assigned to the actual exposure group or the virtual or pending exposure group. People from active therapy groups participated in 8 sessions. The observation period was 12 months.	Subjects receiving active therapy improved compared to the waiting group. There were no differences between the active treatments in any process or outcome measure at any time, nor were there differences in the achievement of partial or complete remission.	Eight sessions are required for VRET to be effective. VRET is effective in treating social anxiety and the improvement is sustained for 1 year. No information about the way VRET was performed.
Gebara et al. (47)	21	2	Single-arm clinical trial. Patients with social phobia.	The subjects were exposed to 12 sessions of 50 min each, during which they were exposed to VR. The observation period was 6 months.	Improvement of social anxiety was observed in all scales and instruments used, including the follow-up period 6 months after the end of treatment. The average number of sessions was seven as participants quickly got used to the process.	VRET is effective on average after 7 sessions. The effect persists after the end of treatment. Therapy with HMD.
Kampmann et al. (48)	60	3	Randomized controlled clinical trial. Patients with social phobia.	The subjects were assigned to the *in vivo* or virtual exposure group or to the control group. The intervention included 10 sessions.	Compared to the waiting list, in active treatment groups social anxiety, perceived stress and beliefs related to avoidant personality decreased and the duration of speech increased. Subjects in the *in vivo* exposure group but not the VR group improved in terms of fear of negative judgment, speech performance, overall anxiety, depression, and quality of life compared to those on the waiting list. During the observation period, all improvements were significant for the *in vivo* exposure group. In the case of VR, only the effect of perceived stress was significant.	VRET may be slightly more effective than *in vivo* exposure. Therapy with HMD.

(Continued)

TABLE 2 | Continued

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
Anderson et al. (49)	28	2	Randomized controlled clinical trial. Patients with social phobia. A follow-up of the study by Anderson et al. (46).	Subjects completed 8 therapy sessions using VR or group conventional therapy.	It was shown that the 54% of subjects no longer met the diagnostic criteria for social phobia and 68% subjects reported that their condition improved.	For VRET to be effective, 8 therapy sessions are required. The effect lasts after the end of the treatment. No information how VRET was executed.
Stupar-Rutenfrans et al. (50)	35	3	Single arm clinical trial. Students with fear of speaking in front of an audience.	All subjects were exposed over 4 weeks to 8 sessions with the use of virtual reality imitating a lecture hall: without people and with a small and large audience.	It was shown that the fear of speaking decreased significantly after VRET sessions, and the decrease was strongest in participants with initially high levels of this anxiety. Participants with moderate to severe baseline anxiety levels had different anxiety patterns over time.	The effectiveness of VRET requires 8 sessions, conducted twice a week. The therapy is more effective in people who have a greater severity of anxiety in their first VRET sessions. Therapy with HMD.
Bouchard et al. (51)	59	2	Randomized controlled clinical trial. Patients with social phobia.	Subjects were randomly assigned to VR exposure ($n = 17$), actual exposure ($n = 22$) or waiting list ($n = 20$). Subjects receiving active intervention participated in 14 weekly sessions.	Social anxiety reduction was found in the active therapy group. Conducting therapy with exposure to VR was more effective than real exposure. The beneficial effects lasted 6 months.	VRET is effective with 14 sessions performed once a week. Therapy with HMD.
Kim et al. (52)	52	2	Controlled clinical trial. Patients with social phobia ($n = 22$) and healthy patients ($n = 30$).	The subjects were assigned to a VR intervention group or a control group. The intervention included 8 self-study sessions and lasted 2 weeks.	It was shown that the use of VR was associated with a reduction in anxiety and social anxiety and with an increase in speech time during public speaking.	VRET is effective after 8 sessions. A mobile VR application may be the treatment option at home. Therapy with HMD.
Kovar (53)	10	3	A comparative clinical trial without randomization. Patients with social phobia.	The subjects were divided into groups receiving therapy using VR and a group receiving psychotherapy. The intervention included 8 sessions.	Improvement in health and a reduction in the feeling of social anxiety was demonstrated in both therapeutic groups, but it was more pronounced in the group using VR.	VRET is effective with 8 sessions of therapy. VRET may be more effective than *in vivo* exposure. Therapy with HMD.
Denizci Nazligul et al. (54)	14	2	Randomized controlled clinical trial. Patients with social phobia.	The subjects were divided into a group using VR and a control group with conventional CBT. The intervention lasted 4 weeks and included 4 sessions.	Virtual reality and psychotherapy have been shown to be similarly effective in reducing public speaking anxiety.	VRET is effective after 4 sessions once a week. Therapy with HMD.
Geraets et al. (55)	15	2	Clinical trial with one therapy arm. Patients with severe social phobia.	The subjects were exposed to 16 sessions of cognitive-behavioral therapy with the use of VR. The observation period was 6 months.	VRET reduced social anxiety and improved the quality of life of respondents. During the observation period, symptoms of depression decreased.	VRET is effective in therapy involving 16 sessions. The treatment effect is maintained after the end of treatment. Therapy with HMD.
Yuen et al. (56)	26	2	A comparative clinical trial without randomization. Patients with social phobia.	The subjects were assigned to the intervention group using videoconferencing plus ACT (acceptance and commitment therapy) or VR + ACT. The intervention included 6 sessions.	Both treatment groups demonstrated a reduction in anxiety during social exposure. The satisfaction of the respondents was also comparable between the groups.	VRET is effective after just 6 sessions. VRET on PC.

(Continued)

TABLE 2 | Continued

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
Kahlon et al. (57)	27	3	A clinical trial in adolescents with social anxiety disorder.	Participants met for one 90-min training session 1 week after completing online initial therapy questionnaires. The treatment protocol included seven tasks of varying difficulty, ranging from 1 to 2 min, each with little or no preparation time. Adolescents used VRET only during the actual exposure tasks to avoid getting used to the virtual environment. Follow-up was 3 months.	The mixed-effect linear model revealed a significant reduction in social anxiety symptoms (Cohen's d = 1.53) before treatment, and the improvement was maintained throughout the follow-up period. Physiological data revealed a slight increase in heart rate during exposure tasks. Based on feedback from adolescents, the feasibility of the intervention was increased during the study.	The effectiveness of VRET requires appropriately intensified stimuli so as not to get use to digital environment too quickly. Therapy with HMD.
Lindner et al. (58)	23	2	A clinical trial. Patients with social anxiety in a routine medical care setting.	The subjects were exposed to sessions in VR. Follow-up was 3 months.	There was a significant decrease in public speaking anxiety after the first 3-h session. Multilevel modeling of in-session process measurements confirmed reduction of disastrous expectations and stress and the increase of quality of performance. Adherence to the online transition program that followed *in vivo* exposure was relatively poor, but symptoms continued to decrease. No changes were observed during the 3-month follow-up period.	VRET may be an effective form of continuing therapy *in vivo*. Therapy with HMD.

The risk of bias and study quality assessed with the Effective Public Health Practice Project's Quality Assessment Tool for Quantitative Studies (QATQS) was presented as the global rating for each publication (1—strong, 2—moderate, 3—weak).

in the size of the effects (negative Hedges coefficient: −0.07). These results were relatively consistent across all analyzed disorders and they indicate that VR is effective and equal to conventional *in vivo* therapy as a medium for treating phobias (12).

In the most recent meta-analysis of 22 clinical trials with 703 participants by Horigome et al. the effectiveness of the use of VR in the treatment of social phobia was analyzed (13). The effectiveness of VR in treating social phobia was shown to be significant and sustained over a long observation period. Compared to *in vivo* exposure, the effectiveness of VR was similar after the intervention, but decreased in subsequent observation. The dropout rates of the participants showed no significant difference from the *in vivo* exposure results. Thus, the authors stated that VR is an acceptable method of treating patients with social phobia and has a significant long-term effect, although it is possible that its effectiveness will be reduced during long-term follow-up compared to conventional therapy.

Regarding the effectiveness of VRET in the treatment of specific phobias, a meta-analysis by Parsons and Rizzo (14) included 21 clinical trials involving 300 patients. VRET has been shown to be effective in reducing the symptoms of anxiety and phobias, especially in well-selected patients. The authors concluded that the use of VRET is effective in the treatment of anxiety and several specific types of phobias like social phobia, arachnophobia, acrophobia, agoraphobia, and aviophobia (14).

The impact of VRET on the behavior of patients with specific types of phobias in the real environment was also the subject of a meta-analysis of 14 studies conducted by Morina et al. (15). Behavioral evaluation results after treatment and during follow-up showed no significant differences between VRET and *in vivo* exposure ($g = -0.09$ and 0.53, respectively). The authors concluded that VRET cause significant changes in behavior in real-world situations (15). Also, in the last systematic review by Botella et al. (16), which included 11 randomized clinical trials, the effectiveness of using VRET in the treatment or support of the treatment of various types of phobias was assessed and found that

TABLE 3 | Studies on the use of VR exposure therapy in specific phobias.

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
Triscari et al. (59)	65	3	Randomized controlled clinical trial in patients with aerophobia.	The subjects were randomized into three groups: - CBT ($n = 22$) - CBT + combined with eye movement desensitization and reprocessing therapy (CBT-EMDR) ($n = 22$) - CBT + VRET - 10 sessions of 2 h - Sessions 1–3: psychoeducation, cognitive and behavioral techniques and relaxation techniques. Flying education - Sessions 4–6: specific to each treatment group - Sessions 7–10: visit to the faith of flight control, flight simulation, and airplane flight.	All groups showed a reduction in the fear of flying. The performance measurements maintained a significant effect after the 1-year follow-up period.	10 VRET sessions combined with exposition *in vivo*. No information about the used device.
Levy et al. (60)	6	3	Single arm intervention clinical trial including acrophobic patients.	Patients were exposed to six sessions (two sessions per week) of VR exposure therapy. The first three were remote sessions, while the last three were traditional sessions with a therapist. The anxiety level, heart rate, presence, technical difficulties, and therapeutic alliance were analyzed.	It was shown that anxiety, presence, and therapeutic alliance were comparable in both VRET sessions and traditional therapy with the therapist.	VRET is effective in acrophobia after 6 sessions. Therapy with HMD.
Botella et al. (61)	63	2	Randomized controlled clinical trial in patients with small animal phobia.	- Participants were randomized to the group: - Exposure to real cockroaches (*in vivo*) ($n = 31$) - Exposure to spiders in VR ($n = 32$). - Patients were assessed prior to the session, then received one 3 h session. A reassessment was performed after the session and after 3 and 6 months.	Participants using VRET significantly improved on all outcome measures after treatment and at follow-up visits. When the two treatment conditions were compared, there were some post-treatment differences favoring participants who received *in vivo* exposure. However, these differences disappeared with 3- and 6-month follow-up.	VRET is effective in patients with small animal phobia after one session of 1 h. The effect lasts after the end of the therapy Therapy with HMD.
Gujjar et al. (62)	10	2	A controlled clinical trial involving patients with dental phobia.	The subjects were assigned to the VRET group or the educational advice group. The effectiveness of VRET was assessed by comparing the reduction in dental anxiety scores (measured 16 times over the 14-week study period and after 6 months of follow-up).	It has been shown to reduce the symptoms of dental phobia assessed on the Dental Anxiety scale and the Dental Fear scale, and to reduce behavior avoidance in VRET. Of the nine people who completed treatment, six (four in the VRET group and two in the education group) no longer had dental phobia after 6 months of follow-up.	Dental phobia resolves after 14 VRET sessions. Therapy with HMD.

(Continued)

TABLE 3 | Continued

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
da Costa et al. (63)	13	3	Single arm intervention clinical trial in women with driving phobia.	The respondents were exposed to 8 sessions with a computer game containing car driving scenarios covering several road situations. Participants' sense of presence, subjective suffering, and physiological responses were assessed during the eight VRET exposures. Participants' clinical features, cognitive abilities, and quality of life were also analyzed.	After VRET, there was a reduction in the incidence of distorted thoughts and state anxiety scores, as well as a slight improvement in quality of life. The subjective results of the discomfort, heart rate variability, and sense of presence scores confirmed that there was a sense of presence in the VRE environment.	VRET is effective in dromophobia after 8 sessions. VRET on PC.
Gujjar et al. (64)	30	1	Single-blind, randomized controlled clinical trial in patients with dental phobia.	Patients were randomized to VRET or an information booklet. A single VRET session with five scenarios was used. The measures of anxiety were assessed before and after the intervention as well as 1 week after and 3 and 6 months after.	It was shown that only patients in the VRET group showed a significant reduction in dental anxiety.	VRET is effective after 1 session with an in VR exposure of 45 min in which 5 different phobic scenarios were performed. Therapy with HMD.
Miloff et al. (65)	100	2	Randomized clinical trial in patients with arachnophobia.	Patients were randomized to one session of standard *in vivo* therapy or VRET The subjects were assessed using the behavioral approach evaluation test, a scale self-assessment of fear of spiders, depression, and quality of life before and after treatment, as well as after 3 and 12 months.	Behavioral avoidance and reported fear were significantly reduced in both groups after treatment discontinuation, with VRET approaching the strong treatment benefit of standard *in vivo* therapy over time.	VRET is effective in arachnophobia after just one session, lasting 3 h. The effect lasts after the end of the therapy. Therapy with HMD.
Kaussner et al. (66)	14	2	Randomized clinical trial in patients with fear of driving a car.	The subjects were randomized to VRET or waiting. The intervention included a medical and psychotherapeutic examination, two preparatory sessions with a psychotherapist, five sessions with VRET and a behavior avoidance test (BAT) in real traffic, a closing session and two further telephone assessments after 6 and 12 weeks.	The treatment helped to overcome fear and avoid driving. In the final BAT, all patients mastered the driving tasks they had previously avoided, 71% showed adequate driving behavior as assessed by the driving instructor, and 93% could maintain treatment success until the second control phone call.	5 VRET sessions are effective in dromophobia. The effect lasts after the end of the treatment. VRET was performed with high-fidelity fixed base driving simulator. The visual system comprises five image channels that provide a view of 300° horizontally and 47° vertically as well as a four-channels sound system.

(Continued)

TABLE 3 | Continued

References	*n*	QATQS (points)	Characteristics of participants	Intervention used	Results	Conclusions
Jiang et al. (67)	43	2	Randomized controlled clinical trial in patients with blood-injection-injury phobia.	Patients were randomized to the group: - VRET - Waiting list. One treatment session was used and was followed for 3 months.	Medium to large differences in catastrophic cognitions (probability [$g = 0.88$] and cost [$g = 0.66$] scores) were shown in favor of VRET. There were medium to large differences in favor of VRET in the post-injection anxiety and trauma subscale (MBPI $g = 0.64$–1.14) 1 week after treatment and after 3 months of follow-up, and in the MBPI syncope subscale ($g = 0.84$) and injections subscale medical anxiety test ($g = 0.63$) during observation.	One 90-min VRET session is effective in treating blood-injection-injury phobia. Therapy with HMD.
Lindner et al. (58)	25	3	A single-arm clinical trial in patients with arachnophobia.	One VRET session was used. The self-assessment of spider anxiety and quality of life was assessed twice before, 1 week and 2 weeks after treatment, and at 6 months.	It was shown that the symptoms of arachnophobia decreased both after treatment and during the 6-month follow-up period.	One session lasting 3 h is effective in the treatment of arachnophobia. The effect lasts after the end of the treatment. Therapy with HMD.

The risk of bias and study quality assessed with the Effective Public Health Practice Project's Quality Assessment Tool for Quantitative Studies (QATQS) was presented as the global rating for each publication (1—strong, 2—moderate, 3—weak).

applications using VRET have become an effective alternative that in terms of effectiveness can equal the results of traditional treatments for phobias (16).

The presented meta-analyzes confirm the effectiveness of VRET and its equivalence with *in vivo* exposure therapy. The authors decided to conduct their own review of studies to answer the question of how to perform exposure therapy in a virtual reality environment so that it is effective. The results of this literature review may provide clues for the planning of therapy protocols using VRET and for the construction of the VR environment for therapeutic means. They may also be considered to implement in subsequent projects of phobia exposure treatment using VRET.

MATERIALS AND METHODS

The review included clinical trials, as well as case series and case reports. The authors' assumption was that even in single case reports of patients treated with VRET, there may be data on VRET elements that affect the effectiveness of exposure therapy. PRISMA guidelines were used when preparing this systematic review (17). The criteria for including the study in the analysis were the presence of a diagnosis of agoraphobia, social phobia and specific phobias and VRET treatment. The analysis also included studies in which, apart from VRET, a different treatment method was used. Full-text publications available in English were included in the analysis. In each study, at least the baseline and endpoints of treatment efficacy had to be characterized.

The following medical databases were searched in the study: PubMed, Scopus, Web of Science, and Google Scholar (effective date 10/06/2021). The search was performed according to the PICO framework (P—patient, problem or population, I—intervention, C—comparison, control or comparator, O—outcomes). During our search, we used the following terms: "virtual reality" (Title/Abstract), "virtual exposure" (Title/Abstract), "agoraphobia" (Title/Abstract), "social phobia" (Title/Abstract), "social anxiety" (Title/Abstract); and "specific phobia" (Title/Abstract).

The review was conducted independently by two investigators. After obtaining 345 records from the medical databases searched, the same terms were entered in the Google search engine and an additional 17 publications were obtained. When duplicate records were removed, 173 records were obtained for further analysis. In the next stage, an initial selection was carried out, excluding meta-analyzes, reviews, mini-reviews, systematic reviews, letters to the editor, editorials, comments, and errata. This pre-selection resulted in 81 publications. An in-depth selection was then performed and publications with only abstracts, papers in a language other than English, studies not directly related to the topic, and studies with methodological errors or data gaps were excluded. Ultimately, 49 clinical trials were included in the systematic review. The flow diagram of the analysis is presented in **Figure 1**.

To assess the risk of bias and study quality in quantitative studies, the Effective Public Health Practice Project's (EPHPP) Quality Assessment Tool for Quantitative Studies (QATQS) was used (18, 19). This tool enables quality evaluation of a wide range of study designs, including RCTs, observational studies with and without control groups and case studies. The instrument contains eight different sections, each with multiple questions: selection bias, study design, confounders, blinding, data collection methods, withdrawals and drop-outs, intervention integrity, and analyses. Each section receives a score of 1 (strong), 2 (moderate), or 3 (weak), and a final score is determined by the number of "weak" ratings. Strong rating is given to a study if there is no weak component score. Moderate rating is given with one weak component score. Weak rating is given with two or more component rating scores.

RESULTS

The tables below show the results of the systematic review of the literature on the use of VRET in the treatment of patients with agoraphobia (**Table 1**), social phobia (**Table 2**), and specific phobias (**Table 3**).

DISCUSSION

Taking for granted the previously demonstrated effectiveness of VRET in the treatment of phobias, the current review focuses on parameters regarding the duration of therapy, session duration, session frequency, combining VRET with other types of therapy as well as technology used in exposure therapy. It was assumed that the conditions of using VRET in studies in which in VR exposure proved to be an effective form of phobia treatment determined its effectiveness. They should be considered as guidelines for the development of protocols and applications for running VRET.

With regard to the number of sessions and the duration of therapy, as shown by the analysis of the literature in agoraphobia, the number of sessions should be from 8 to 12. On the other hand, in social phobia, the number of sessions ensuring the effectiveness of VRET is more diverse. Its efficacy was demonstrated in therapies performed with one-time session (57), and the highest number of sessions performed with great success was 16 (39). Most often, however, the number of sessions giving the effectiveness of VRET in the treatment of social phobia was, similarly to the treatment of agoraphobia, from 8 to 12 sessions. In the treatment of specific phobias, short therapies, most often consisting of one VRET session, were preferred, although longer protocols, including up to 14 sessions, were also successfully used.

The duration of one VRET session varies greatly depending on the study. If a single session therapy is to be effective, the exposure must last at least 60 min (57). It seems that for VRET sessions to be effective, they must last at least 15–20 min (31, 32), especially if at least 4 are performed during the therapy (31). As mentioned, VRET in specific phobias is most often conducted in the form of a one-time session, however, these sessions must be longer. Based on the analysis, the VRET session in specific phobia should not be shorter than 45 min (64), but most often they last longer, even up to 3 h (58, 61, 65, 67).

The conducted literature analysis shows that in agoraphobia the effectiveness of therapy is ensured by performing an average of one in VR exposure per week. It is similar in VRET in social phobia, and it is most often performed once a week. Perhaps performing VRET more than once a week may shorten the overall duration of therapy. In one study, it lasted 3 days with two VRET sessions a day (33). The possibility of reducing the duration of VRET therapy by increasing the frequency of sessions, for example twice a day, is a promising direction for further research.

Regarding the technology used in VRET, the most common are head mounted displays. They were used in 71.4% of the analyzed studies. Literature review demonstrates greater effectiveness of HMD technology over 2D image viewing (44). Contemporary technology offers portable HMDs that enable convenient home therapy (52). Such a set can also be a smartphone with an application for VRET installed on it. It will certainly allow for increased availability in the future, and thus may popularize VRET in the treatment of phobias.

Regarding the combination of different treatment methods, although VRET is an effective method used in monotherapy (11–16), however, it may be much more effective when combined with pharmacotherapy (30). When VRET is used with pharmacotherapy, the number of sessions can be shortened [e.g., 4 sessions in agoraphobia; (30)]. There are still too few studies on the augmentation of pharmacological treatment with VRET to draw conclusions about the number of sessions, their frequency and duration of a single session. This is a topic that requires further research. In addition to pharmacotherapy, VRET can be combined with *in vivo* exposure therapy, either as a pre-phase to *in vivo* therapy or as a follow-up to it. Also, in this case, it is necessary to conduct research on the possibilities and indications for combining these two types of exposure treatment.

An important issue is compliance with the eligibility rules for the exposure treatment of phobias in VR. Improper qualification for treatment without excluding comorbidity reduces the effectiveness of VRET (14). The analyzed studies and previously conducted meta-analyzes indicate that VRET is an effective exposure therapy in the treatment of phobias, but, if in addition to phobia, a patient suffers from another mental disorder, the effectiveness of exposure therapy is lower (28). This indicates the importance of proper qualification for VRET and avoidance of psychiatric comorbidity in order to ensure its effectiveness.

For the effectiveness of VRET, it is important for the patient to feel real and immersed in the environment provided by in VR exposure therapy (42, 43). With regard to the sense of immersion in virtual reality, it has been shown to occur very quickly. After just 2 min of using VRET, patients feel the realism of the virtual world (21). An important condition for the effectiveness of VRET is also the way of its conduct so that the patient does not get used to the digital VR environment too quickly without habituation to phobic stimuli. A way to counteract this familiarization with the digital environment may be the creation of many scenarios for the development of the exhibition environment (64). Also, the greater intensity of phobic stimuli may make it difficult to

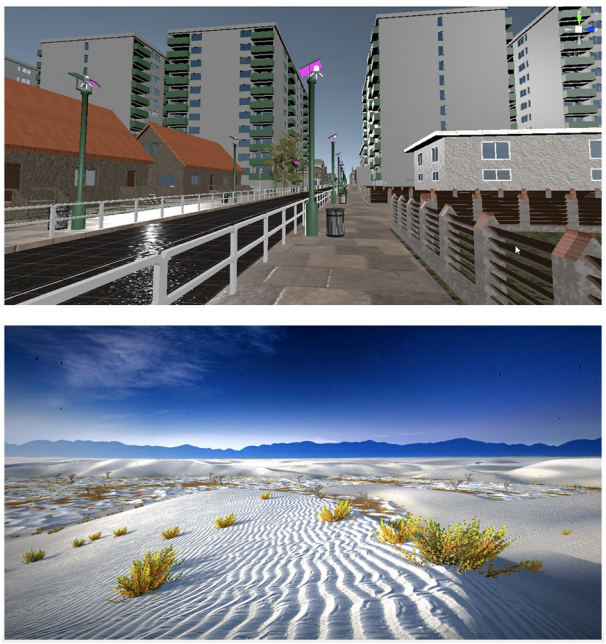

FIGURE 2 | The virtual exposure environment must provide the patient with a sufficient level of realism for the VRET to be effective. The photos show examples of high-quality computer graphics of opened space exposure environment from the VR voice-BOT application, developed (photos made by MK). Before treatment, the patient determines the type of phobic environment, as well as customizes it depending on his preferences, specifying the time of day, weather and the type of exposure. Exposure in a three-dimensional graphics environment is enriched with three-dimensional sound, recorded in real conditions. Next, VR voice-BOT, thanks to the speech recognition system, conducts an exposure hierarchy with the patient, increasing the intensity of phobic stimuli in the environment previously defined by the patient and asking him to determine the subjective level of distress in the subjective units of distress scale (SUDS). During the exposure, the patient uses his own smartphone with the application installed on it, and a joystick, and moves freely in a virtual environment.

get used to the digital environment and to lose the sense of immersion in real experience (57). This is indirectly indicated by the greater effectiveness of in VR exposure in people with greater severity of phobias (50). In the technology of conducting therapy by automated voice-BOT therapeutic applications with a speech recognition system, it is possible to create an algorithm that increases the level of exposure to phobic stimuli depending on the speed of habituation to the VR exposure environment (**Figure 2**). The evidence that it is possible to provide a full sense of reality in digital reality at least at the level of *in vivo* exposure are the reports that in VR exposure is more effective than *in vivo* (48, 53). The more virtual reality will imitate reality in terms of graphic resolution, a variety of scenarios and their dynamic adaptation to the patient's behavior, the greater will be its effectiveness.

As indicated by the conducted analysis, VRET exposure may give a lasting effect. However, long-term efficacy has not been studied for more than a year it seems satisfactory. Safir et al. (45) showed that after 1 year of clinical improvement, the reduction of social phobia symptoms is still maintained, regardless of whether the therapy was performed with VRET or *in vivo* exposure (42). Similar in other studies that conducted long-term follow-up of patients after treatment, it was possible to demonstrate the durability of the treatment effect after the completion of VRET (46, 47, 49, 51). This may indicate no need for maintenance therapy with VR. To confirm that, in subsequent studies of the effectiveness of phobia therapy with VRET, long-term follow-up of patients after the completion of VR therapy should be considered.

CONCLUSIONS

A large number of studies on in VR exposure therapy in phobias allows for the formulation of some recommendations on how to perform VRET, enabling the effective treatment. The conducted analysis of clinical trials allows to conclude that VRET in agoraphobia and social phobia is effective when performed from 8 to 12 sessions, on average once a week for at least 15 min. In turn, the treatment of specific phobias is effective even in the form of one longer session, lasting 45–180 min. Head mounted displays are an effective technology for VRET. Increasing the frequency of sessions and adding drug therapy may shorten the overall treatment duration. Moreover, the effectiveness of VRET in phobias is greater without psychiatric comorbidity and on the condition of generating and maintaining in the patient a sense of immersion in the VR environment.

Further studies should focus on the possibility of augmentation of pharmacological treatment with VRET, indications for combining in VR exposure with *in vivo* exposure, as well as the durability of VRET effects with possible maintenance therapy. In the future, it is also necessary to check the effectiveness of treatment protocols in which VRET is used more than once a week in terms of the possibility of reducing the total duration of treatment of phobias.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MK: conceptualization, data curation, and visualization. MK, SS, and MR: methodology. SS and MR: software. MK, MS, and MB: validation. SS, MR, MB, JP, MK, and NK: literature selection and analysis. MK, SS, MR, and JP: writing and original draft preparation. MK, MB, SS, MR, and NK: writing, review, and editing. MB and MS: supervision and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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METHODS
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Brain+ AlcoRecover: A Randomized Controlled Pilot-Study and Feasibility Study of Multiple-Domain Cognitive Training Using a Serious Gaming App for Treating Alcohol Use Disorders

*Nicolaj Mistarz[1], Anette Søgaard Nielsen[1,2], Kjeld Andersen[1], Anneke E. Goudriaan[3,4], Lotte Skøt[1], Kim Mathiasen[5], Tanja Maria Michel[1] and Angelina Isabella Mellentin[1,2,5]**

[1] Unit for Psychiatric Research, Department of Clinical Research, University of Southern Denmark, Odense, Denmark, [2] Brain Research-Inter-Disciplinary Guided Excellence, Department of Clinical Research, University of Southern Denmark, Odense, Denmark, [3] Amsterdam University Medical Centers, Department of Psychiatry, University of Amsterdam, Amsterdam, Netherlands, [4] Department of Research, Amsterdam Institute for Addiction Research, Arkin, Amsterdam, Netherlands, [5] Centre for Telepsychiatry, Mental Health Services of Southern Denmark, Odense, Denmark

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Edited by:
Hanna Karakula-Juchnowicz,
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Mauro Ceccanti,
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Łukasz Wieczorek,
Institute of Psychiatry and Neurology (IPiN), Poland

***Correspondence:**
Angelina Isabella Mellentin
amellentin@health.sdu.dk

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Background: Patients with alcohol use disorder (AUD) exhibit deficits in various cognitive domains, including executive functioning, working memory, and learning and memory, which impede the effectiveness of conventional AUD treatment and enhance relapse. Mobile health (mHealth) services are promising in terms of delivering cognitive training in gamified versions. So far, studies examining the effects of mHealth-based cognitive training in AUD patients have, however, focused on specific rather than multiple cognitive domains and overlooked the importance of clinical outcomes. Furthermore, research has yet to investigate the acceptability and feasibility of this type of cognitive training.

Aims: The aims of this pilot study are to examine (1) whether using smartphone-based, multi-domain cognitive training with gamified elements as part of conventional treatment for AUD indicate effect, and (2) whether the intervention is acceptable and feasible as a part of conventional treatment for AUD.

Methods: Patients from the alcohol outpatient clinic, Odense Municipality, Denmark will be invited to participate in the study on a consecutive basis until a total of 60 patients have been recruited. The study will be performed as a combined parallel randomized controlled trial (RCT) and qualitative feasibility study. The patients will be randomly assigned to one of two groups. The intervention group ($n = 30$) will receive smartphone-based, multi-domain cognitive training with gamified elements together with treatment as usual (TAU). The active control group ($n = 30$) will receive a sham version of the same cognitive training together with TAU. Cognitive outcomes will be assessed *via* the training application at baseline and post-treatment. Clinical outcomes will be assessed at baseline, post-treatment, and at 6-month follow-up using the Addiction Severity Index. Furthermore, the 30 patients randomized to the intervention group will be invited to participate in the second phase, that is the feasibility study, at post-treatment. A questionnaire inquiring about the use of mHealth treatment in general

will be administered. Further, feedback regarding functionality and meaningfulness of the application in addition to other qualitative aspects relating to the use of the application will be collected. The patients will also be asked to provide suggestions about how to improve and potentially implement the tool.

Implications: It is anticipated that this pilot study will provide tentative evidence for the effectiveness of smartphone-based, multi-domain cognitive training as well as information about the usability and feasibility of this type of training, including acceptability and compliance. The study will also contribute with feedback derived from the patients about how to improve and implement the tool. If promising, the findings will be used to plan a large-scale RCT. Since cognitive deficits are not addressed in current treatments for AUD, gamified cognitive training delivered through smartphones may increase the effectiveness of current treatment for AUD as well as introduce more mHealth-based treatment that is both accessible and cost-effective.

Keywords: alcohol use disorder, cognitive disability, cognitive training, randomized controlled trial, feasibility

BACKGROUND

The encumbering nature of alcohol use disorder (AUD) is indisputable—high rates of prevalence, comorbidity with other disorders, and recurrence (1–5) indicate the urgency of efficacious treatment for relapse prevention. Current AUD treatment encompasses psychotherapy and pharmacotherapy, which aim to reduce craving and consumption of alcohol to achieve controlled drinking or abstinence and maintain it (6, 7). However, patients with AUD often have cognitive dysfunctions, and while contemporary evidence-based treatments, such as cognitive behavioral therapy (CBT), may indirectly increase cognitive capacity through the acquirement of alcohol relevant coping skills (6, 8), there is evidence that cognitive deficits tend to persevere and still be present not only at post-treatment but also even after successful treatment with a full year of abstinence [for more information, see (9–11)]. Thus, it seems that current treatments are not adequate to ameliorate cognitive deficits.

The cognitive dysfunctions in AUD involve the domains for processing speed, executive functioning, working memory, and memory (i.e., visual, and verbal memory), underlining that the whole brain is affected by the neurotoxic effects of alcohol (10, 12, 13). Further, cognitive deficits have been found to be associated with worse treatment outcomes and a higher risk of relapse (8), and, therefore, addressing cognitive deficits during treatment for AUD may contribute positively to the long-term outcome (14).

A direct way of targeting cognitive deficits in AUD could be cognitive training. Several studies have investigated the efficacy of cognitive training in subclinical and clinical AUD samples, but these have mostly focused on cognitive training targeting executive functions and working memory [WM; for an overview, see (15)]. In subclinical samples, one study found that training of inhibitory response (i.e., a subdomain of executive functioning) did not lead to improvement on cognitive and clinical drinking outcomes (16), whereas another study training executive functions and WM found an effect on cognitive and clinical drinking outcomes (17). This discrepancy may be explained by the fact that the two studies focused on training different cognitive domains (i.e., inhibition vs. WM). The improvement in cognitive outcomes reported by Houben et al. (17) may also be due to the training tasks being like the cognitive tests used for assessment.

In clinical samples, several studies have demonstrated improvements in cognitive outcomes after cognitive training [for reviews, see (8, 15)]. Overall, the results of cognitive training seem more promising for patients diagnosed with AUD compared to subclinical samples. However, like the subclinical studies, most of the clinical studies performed so far only focused on examining the effects of cognitive training on executive functions and WM [e.g., (18–21)], and only a few recent studies have examined the effects of training multiple cognitive domains [e.g., (22, 23)].

The premise of cognitive training is that the trained cognitive domain(s) can be transferred to neuropsychological tests targeting a similar domain(s) (i.e., proximal transfer) and/or a dissimilar cognitive domain(s) [i.e., distal transfer; (15)]. Most of the studies examining the effects of WM-specific cognitive training have only found proximal transfer effects [e.g., (19–21)], and only one study showed that WM-specific training could be transferred distally to untrained measures of verbal learning and memory (18). Since recent research suggests that patients with AUD present with diffuse and non-specific cognitive deficits [for reviews, see (10, 11)] it is highly relevant to uncover distal transfer effects as well as the effects of multi-domain cognitive training.

To date, little is known about the effects of cognitive training on clinical outcomes (i.e., craving and severity of relapse). Only one clinical study has examined the effects of WM-specific cognitive training on alcohol consumption, which found no effect of the training (21). However, the training was not delivered as adjunctive treatment and the patients completed the training at home without further support, and the findings indicated that cognitive training as stand-alone treatment is unlikely to have a clinically meaningful effect among AUD patients. Rather, it might be effective as an add-on intervention in combination with treatment as usual. Using it as add-on treatment would

also allow clinicians, therapists, and other health care providers to become gradually accustomed to the cognitive training as a part of the conventional intervention programs applied at the treatment facilities.

Current options for delivering cognitive training are based on standardized neuropsychological tasks with poor ecological validity (23). It has been reported that patients find it challenging to maintain their attention and motivation during the training sessions, and performing the training requires a solid alliance between the patient and health provider (23, 24). Technological advancements such as electronic health (eHealth) and mobile health (mHealth) services have, therefore, caught interest. They offer innovative approaches for delivering serious gaming over the internet or smartphone devices (25). The term serious gaming (SG) is derived from the notion of gamifying mundane tasks, which refers to the use of game elements in non-gaming contexts (26). Thus, if it is accepted by the patients, this may be a promising method of delivering treatment to AUD patients in a way that is not only effective but also enjoyable during training, which may improve treatment compliance (23, 24). Cognitive specific SG delivered through mHealth services also allows for feedback to be given to the patients, permitting them to track their own progress and accomplishments, which is important for increasing the effectiveness of the training itself (27). Nevertheless, studies examining cognitive specific SG delivered through mHealth services are scarce, and to date, only one study has examined the use of tablets for cognitive training targeting executive functions (23). In this study the authors developed an multimodal application with SG-elements that made use of both visual and auditive stimuli in, which not only resulted in improved executive functioning, but it also showed that mHealth-based training was more motivating and engaging for the patients (23). In addition to the benefits of multimodal treatment delivery, cognitive specific SG delivered through smartphone applications provide the means from which it is possible to create personalized cognitive training programs. This aspect is essential for patients with AUD, which is a heterogenous populations showing diffuse deficits that varies across patients (10, 11). A cognitive training program that constantly adapts to the performance of the patient, would not only be more motivating, but it would also be able to adjust the level of difficulty depending on the qualitative and quantitative pattern of cognitive impairment.

Although a few studies examining cognitive training have applied SG-elements (21, 22), they have, perhaps due to rapid developments in technology, either used less engaging game designs or overlooked the mHealth and eHealth capabilities by constructing games with poor accessibility (i.e., training programs only available for computers). Cognitive specific SG that is either unintuitive or prerequisites specific electronic equipment and demanding hardware, may obstruct the applicability in clinical facilities, which in turn may result in health care providers and patients being less willing to adopt the treatment (27). On the contrary, the results in the study by Gamito et al. (23) highlights that accessible and intuitive mHealth-based treatment with SG-elements delivered on tablets or smartphones may be well-accepted by both patients and therapists. Treatment options that rely on SG-elements have also been shown to be highly feasible and accepted by patients with other mental disorders (28, 29). Nevertheless, current mHealth-based treatments are not proportional to the ongoing technological advancements, which points to the need for more studies examining the feasibility of newer and more modern mHealth-based, multi-domain cognitive training with SG-elements in patients with AUD (i.e., whether the patients will use the training programs as add-on intervention to treatment as usual, and how they will use them). In this process, studies should ensure that patients are involved in developing strategies to use the cognitive training programs as this will help improve and ease the implementation of the intervention.

The aims of this pilot study are to examine (1) whether using smartphone-based, multi-domain cognitive training with gamified elements as part of conventional treatment for AUD shows some effect, and (2) whether the intervention is acceptable and feasible as part of conventional treatment for AUD.

METHODS

Design

This pilot study will be conducted in two phases: (1) a parallel small-scale randomized controlled trial (RCT) and (2) a feasibility study.

Setting

The study will be carried out at the outpatient alcohol clinic, Odense Municipality, Denmark. Outpatient treatment is publicly financed and accessible to individuals AUD with varying levels of severity or other alcohol-related problems. Individuals with AUD and comorbid disorders such as psychotic or affective disorders or individuals with other substance-related disorders are presented with treatment options localized at different facilities (30). Furthermore, individuals at the outpatient clinic are offered anonymous treatment.

Treatment-As-Usual

Before the primary treatment is offered, it is possible for patients to receive a personalized, pharmacological detoxification program at the clinic. Here the patients will be administered the benzodiazepine, chlordiazepoxide, and the specific dosage and duration is adapted to the needs of each individual patient. In 2019, the outpatient facility received 230 patients, where 18.26% (i.e., 42 patients) had undergone pharmacological detoxification.

Psychotherapy and pharmacotherapy are used as the primary treatment either alone or in combination. The former includes motivational interviewing and CBT administered as eight individual or group-based sessions with the option for extension, and the latter often encompasses treatment with acamprosate, disulfiram, or naltrexone. The treatment lasts for 3 months, and it is conducted by therapists, nurses, and social workers. Psychiatrists monitor the progression of patients during the treatment. For the treatment to be attuned to the individual patient, both the therapist and patient co-plan the course of the treatment, but typically the patient receives psychoeducation, is instructed in adaptive coping strategies (e.g., thinking about

positive aspects of sobriety and negative aspects of drinking), and functional analyses are conducted for drinking scenarios.

Phase 1–Parallel Randomized Controlled Trial

Recruitment

Patients from the alcohol outpatient clinic will be invited to participate on a consecutive basis until a total of 60 patients have been recruited. The clinic receives 600 patients over the course of 1 year.

Eligibility Criteria

To be eligible for participation in the pilot and feasibility study, patients must: (1) have a confirmed AUD diagnosis; (2) agree to participate in the study and provide verbal and written informed consent; (3) be aged between 18 and 60 years; (4) speak Danish; (5) have completed detoxification (if needed); (6) not have any sensory or motor deficits complicating the provision of the intervention (e.g., color-blindness, fine or gross motor deficits in upper extremities); (7) not meet diagnostic criteria for other substance use disorders (SUD); (8) not have a severe psychiatric or neurological illness (e.g., psychotic disorders, intellectual disability, or dementia) or terminal somatic illness; (9) own or be able to acquire a smartphone or tablet with internet access.

Enrollment and Randomization

Shortly after completing a personalized, pharmacological detoxification program (i.e., 1–2 weeks) at the outpatient facility and prior to starting primary treatment, the patients will be briefly informed of the study by the health care providers at the outpatient facility and asked if they would be willing to meet with a research assistant from the project for provision of full information on the study. The patients will also be informed about the possibility of bringing a visitor, either a friend, family member, or therapist at the clinic, for the meeting with the research assistant.

Before recruiting the patient, the research assistant will read out a standardized manuscript with information regarding the study, and the patients will also be provided with written information about the study. After this initial introduction, the research assistant will ask the patients whether they would be interested in participating in a baseline interview earliest the next day.

Upon receiving informed consent from the patients, the baseline interview will be administered, where the history of the AUD will be assessed (e.g., age of onset, life-time use, alcohol use, and alcohol excessive use). The first 60 patients fulfilling the eligibility criteria will shortly after the baseline interview be randomized to one of two groups. The intervention group ($n = 30$) will receive smartphone-based, multi-domain cognitive training with gamified elements together with treatment as usual (TAU), and the active control group ($n = 30$) will receive a sham version of the same cognitive training together with TAU.

Randomization Procedure

An urn randomization technique will be used to reduce bias and achieve balance in the allocation of patients to the intervention and active control groups. An allocation sequence will be provided by an off-site data manager (independent of the research team) and will be based on a computer-generated list of random numbers.

Intervention: Smartphone-Based, Multi-Domain Cognitive Training With Gamified Elements

The intervention consists of using Brain+ Recover, a gamified smartphone application developed by Brain+ ApS, which is available to the public and can be downloaded to iOS and Android devices. In the application, the patient has access to various cognitive training games, each targeting a set of complementary cognitive functions (see **Appendix**). The cognitive functions have been categorized by the developers into the following domains: attention (i.e., general visual attention and short-term memory), logic (i.e., planning, reasoning, and problem solving), perception (i.e., visual perception and WM), and memory (i.e., memory capacity). Each time the patient completes a game, feedback about performance is provided, and the level of difficulty is attuned accordingly (e.g., increment or decrement of speed, and higher or lower number of symbols, distractors, and obstacles). The first time the application is opened, the patient must complete a cognitive assessment, which is used to automatically create a personalized training program targeting the specific cognitive domains found to be impaired. Information about improvement in performance in each cognitive domain as well as a general cognitive profile can be accessed in the application itself at any given time. The application can either be used with Danish or English language, and this is automatically adapted to the default language on the device of the patient.

Active Control Group

The active control group will be provided with the same Brain+ Recover application as the experimental group. However, the difficulty of the tasks will be kept constant at a low level. Because of the fixed level of difficulty, the active control group will not have access to a brain profile. The active control group will receive the same instructions as the intervention group. This type of sham-cognitive training has been used in previous studies evaluating WM-specific serious gaming, which found no differences between the experimental and active control groups in terms of study completers (26, 27).

Usage of the Brain+ Recover Application

All patients will be helped with downloading the Brain+ Recover application on their own smartphone or tablet. All the games can be accessed at any time during the entire study period. The patients will be recommended to use the application for at least 20 min a day, 5 days a week, for 1 month (i.e., 20 sessions with 400 min of total training). This recommendation is based on previous studies on gamified cognitive training reporting improvements in cognitive outcomes after 2–5 sessions per week (each session varying between 45 and 60 min) with a total of 4–5 weeks of training [for more information, see (21–23)]. Actual time spent playing the games will be monitored. The patients are encouraged to allow notifications from the Brain+

Recover on their device, which will remind them about their daily training schedule once per day (e.g., Keep up the good work, remember to complete your daily training). There is, however, no option for the researchers to monitor whether the patients choose to deactivate the notification system after they leave the treatment facility.

Outcome Measures

The baseline interview will yield data on sociodemographic characteristics and AUD diagnosis and severity of the AUD (e.g., the age of onset, duration, alcohol consumption, and number of heavy drinking days). Cognitive outcomes will be assessed *via* the Brain+ Recover application at baseline and post-treatment. Clinical outcome measures will be assessed at baseline, post-treatment, and at 6-months follow-up.

The Mini-International Neuropsychiatric Interview (MINI) is a structured interview and will be used to confirm the diagnosis of AUD according to the criteria from the fifth version of the Diagnostic and Statistical Manual of Mental Disorders [DSM-5; (31)]. The cognitive outcomes include the cognitive functions trained by the Brain+ Recover application: processing speed and attention, executive functions, WM, and learning and episodic memory.

The Addiction Severity Index (ASI), a standardized international assessment instrument, will be used to generate an addiction severity profile for each patient. The profile covers seven areas of the patient's life: medical status, employment, drug use, alcohol use, legal status, family/social status, and psychiatric status (32). Based on the ASI alcohol concern area, ASI drinking measures will be derived from question A (days with any alcohol consumption in the past 30 days) and question B (days with excessive drinking, i.e., three units or more, in the past 30 days) hence reflecting the frequency and intensity of drinking, respectively. A composite ASI score will be calculated for each of the seven areas. The composite scores fall between 0 and 1, where 0 denotes no problems, 1 signifies severe problems (33). The primary outcomes are cognitive measures derived from Brain+ Recover, and the secondary outcomes are drinking measures and composite ASI scores for the seven problem areas.

Statistical Analysis

Repeated-measures Analysis of Variance (ANOVA), with group as the between-subjects factor and time of assessment as the within-subjects factor, will be used to test the effectiveness of the intervention across the assessment points, which will be indicated by a significant Time x Study Group interaction. If there is an overall significant interaction effect between any time-point and group, contrasts will be used to examine whether the change over time differs between the groups and the time-point. If the assumptions for the repeated measures ANOVA are violated, then a non-parametric equivalent will be used to address this issue. An intention-to-treat analysis and a completer analysis (on-training analyses) will be conducted for each outcome. The intention-to-treat analyses will be carried out for all patients, irrespective of whether they have completed the training or were re-interviewed. The significance level in the models will be set at $\alpha = 0.05$, and two-tailed tests will be conducted. Effect sizes will be reported in accordance with the statistical modeling. All data will be analyzed in Stata version 16.

Power Analysis

Since this is a pilot study, no power calculation has been conducted. Nonetheless, prior small-scale studies have been able to detect effects on cognitive and clinical outcomes in similar sample sizes (include references).

Phase 2–Feasibility Study

The 30 patients randomized to the intervention group will be invited to participate in the feasibility study. After completing the training, the patients will be asked to complete a short questionnaire focusing on their general experience with using the application (e.g., would you use it again?), which elements of the cognitive games they found the most engaging (e.g., processing speed, memory etc.), how they think the application can be improved (e.g., by adding daily training notifications, more feedback etc.), and what could motivate them to use the application more (e.g., increased therapist involvement, completing the training at the outpatient clinic). In addition, the validated System Usability Scale (SUS) will be used to evaluate how the user-interface is perceived by the patients (34).

Furthermore, three focus group interviews will be performed, for which 30 patients will be invited to participate. The themes of the focus group interviews will be inspired by the data recorded in the application and the questionnaires, and in particular address (1) patients' experience of the training; (2) possible improvements; and (3) aspects of importance when implementing the cognitive training as an adjunct to conventional AUD treatment. Furthermore, the patients that did not follow their daily training schedule or who refrained from using the application, will be asked whether they experienced any technical difficulties over the course of the study. Based on the feedback provided by the patients, consisting of both quantitative and qualitative data, the Brain+ Recover application will be modified and subsequently renamed Brain+ AlcoRecover before implementing it in the subsequent large-scale RCT (expected $n = 252$).

To progress to the large-scale RCT, the patients must have used the application at least eight times for a total of 80 min during the entire study period (i.e., 20% of the recommended usage time). If this is not achieved in the first trial, a further 60 patients will be recruited and invited to participate in another pilot study using an adapted version of Brain+ AlcoRecover.

Data Management

The data collected during the baseline interview and during the 6-month follow up will be treated as strictly confidential and managed by Odense Patient Data Explorative Network (OPEN). After the patients have been randomized to either of the two groups, they are assigned an ID-number, which ensures that the data collected through the Brain+ Recover application is anonymous so that the data cannot be traced back to any of the personal information of the patient. Treatment of data will comply with the Data Protection Regulation and

the Data Protection Act. No analysis or publication will contain information that allows person identification.

Economical Compensation

Since this is a study examining a psychological intervention expected to cause no damage and, in the worst-case scenario, only cause transient and minor discomfort, there is no economical compensation system linked to the trial.

Economy

The study was developed on the initiative of the Unit of Clinical Alcohol Research and is unconditionally funded by the Psychiatric Research Foundation, Region of Southern Denmark.

Ethical Considerations

All the patients in this study will be offered either pharmacological or psychological treatment at the outpatient alcohol clinic. There are no known harmful effects of the smartphone-based training program. Hence, the current study does not pose any ethical problems, and it will adhere to the World Medical Association Declaration of Helsinki. In addition, the protocol has been approved by the Research Ethics Committee for Southern Denmark (Project ID: S-20200199) and will be conducted in accordance with the General Data Protection Regulation. Before signing the consent agreement for participation in the research project, the patients are informed that they at any given time during the study have the option to withdraw their consent without it having any implications for their current or future treatment options. If the patients choose to withdraw their consent, they are informed that all their data will be erased.

Perspectives

Since the present study relies on feedback regarding modifications to the Brain+ Recover application, patients with AUD will take active part in the development of the final version of Brain+ AlcoRecover. Collaboration with the patients will ensure that the smartphone-based cognitive training is well-suited to the requirements of patients with AUD. Thus, this study will uncover how compliance and adherence to gamified and smartphone-based cognitive training can be optimized for it to be a putative instrument for clinical practice in terms of the future treatment for AUD. In keeping with this, to bridge the gap between research and clinical practice even further and to maximize the effectiveness of the intervention, the current study will also include patients who underwent pharmacological detoxification recently (e.g., 1 day after completing detoxification program) well-knowing that such treatment with benzodiazepines have an impact on cognitive functions [for more information, see (35, 36)].

In this study the mHealth-based cognitive training is delivered as adjunctive treatment, therefore, it is hypothesized that it will be less disruptive for the conventional treatment, which in turn would make it easier to adapt it to the clinical facilities. If the Brain+ Recover shows a trend toward effectiveness and feasibility, this pilot study will constitute the fundament for a future large-scale RCT in which the effects of smartphone-based, multi-domain cognitive training with gamified elements delivered as an adjunct to TAU will be compared to sham-control training in combination with TAU as well as TAU only. Given the scarcity of evidence on SG and cognitive training as adjunctive treatment delivered through smartphone applications, which could create the groundwork for future research to explore the effects of mHealth-based cognitive training in patients with AUD. The cognitive heterogeneity of patients with AUD emphasizes the need of this type of mHealth focused research, as it could create the groundwork for more motivating personalized treatment options. Future smartphone based personalized cognitive training could also give patients the opportunity to be more in charge of their own treatment, making it more anonymous and less stigmatizing for the patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee for Southern Denmark (Project ID: S-20200199) and will be conducted in accordance with the General Data Protection Regulation. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM and NM wrote the manuscript. All authors were responsible for the design of the whole study, wrote the protocol, supported the manuscript preparation, and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.727001/full#supplementary-material

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REVIEW
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Procrastination, Perfectionism, and Other Work-Related Mental Problems: Prevalence, Types, Assessment, and Treatment—A Scoping Review

Christiane Steinert[1,2]*, *Nikolas Heim*[3] and *Falk Leichsenring*[2,4]

[1] International Psychoanalytic University, Berlin, Germany, [2] Clinic for Psychosomatics and Psychotherapy, Justus-Liebig-University of Giessen, Giessen, Germany, [3] Tavistock and Portman NHS Foundation Trust, London, United Kingdom, [4] Clinic of Psychosomatic Medicine and Psychotherapy, University of Rostock, Rostock, Germany

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***Correspondence:**
Christiane Steinert
christiane.steinert@ipu-berlin.de

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Work-related mental problems can be defined as behaviors, emotions and cognitions that impede the successful completion of a task in a given time frame, i. e., the difficulty or inability to achieve important work-related goals. They are highly prevalent but have been neglected in psychology in general and as a target of psychotherapy in particular. Although work-related problems do not represent a mental disorder *per se*, they are associated with severe distress and high psychosocial costs. In this article, the prevalence of work-related problems, associated burden, diagnostic assessment and treatment are reviewed. So far, research has primarily focused on procrastination, i.e., the act of postponing or delaying tasks until the last minute or past the deadline. However, procrastination represents just one type of work-related problems among several others. Further forms of work-related problems are presented (e.g., perfectionism, or work-related problems in the context of specific personality types). The relation of work-related problems to specific mental disorders is discussed. Psychosocial interventions are the treatment of choice for work-related mental problems. However, response rates for the treatment of procrastination are limited, which calls for further research into which treatments work for whom. No evidence-based treatments are currently available for other types of work-related problems, with the exception of perfectionism, a personality trait that is also linked to problems in the field of work. Thus, there is a need to further improve the treatment of work-related problems including procrastination. For other types of work-related problems, effective treatments need to be developed and validated. They may be based on existing manualized treatments and extended by specific aspects or modules focusing on work-related problems.

Keywords: work-related problems, procrastination, perfectionism, diagnostics, personality, psychotherapy

INTRODUCTION

From a philosophical point of view, meaningful labor is regarded as a fundamental need and characteristic of human beings (1–3). Working is related to both social needs and needs of self-realization (2, 4, 5). Already Freud reportedly considered the ability to love and to work as the cornerstones of mental health (6, 7), which is supported by research showing that even entertaining the thought of unemployment leads to greater mortality-related cognitions (8). Furthermore, the World Health Organization (WHO) acknowledges that work and leisure have a significant impact on health (9). For these reasons, not being able to work effectively and satisfyingly can be regarded as a fundamental psychological impairment and a possible target of psychotherapy.

DEFINITION

Work-related mental problems is an umbrella term for a heterogeneous group of difficulties that can arise at school, training, university, at work or in creative contexts. They can be defined as behaviors, emotions and cognitions that impede the successful completion of a task in a given time frame, i.e., the difficulty or inability to achieve important work-related goals (10). Research and treatment of work-related problems has primarily focused on procrastination (11, 12), i.e., the act of postponing or delaying tasks until the last minute or past the deadline. Procrastination is consistently related to the aversiveness of tasks and duties, i.e., less pleasant tasks are the ones most frequently associated with procrastination (13). However, procrastination represents just one type of work-related problems among others. A broad spectrum of different types of work-related problems exists, which are described in more detail below (e.g., being afraid of negative evaluation or of making one's own decisions, difficulty continuing work, distractibility, passive-aggressive opposing, or overconfidence). Workaholism and burn-out are not addressed in this review as a recent meta-analysis (14) of 14 samples ($N = 12{,}417$) showed a strong overlap of depression and burn-out ($r = 0.80$), which casts doubt on whether burn-out depicts a discrete clinical condition. Therefore, burn-out can be understood as a work-related depression and as a psychiatric disorder that will not be subsumed under work-related problems as defined in the present review.

METHODS AND SEARCH TERMS

In view of the speed at which new research findings are accumulated (15, 16), different forms of evidence synthesis are necessary to inform a particular field about important findings and developments, but also about problems, gaps, limitations and possible future directions (17). This is also true for the field of mental health and psychotherapy. Scoping reviews are particularly useful when a certain field of research or problem is broad or heterogeneous and therefore needs to be outlined and conceptually sharpened, or when a prior comprehensive assessment of findings is missing (17). Thus, scoping reviews include a wider range of literature sources and research designs, serve different purposes and follow different methods in contrast to more well-known forms of reviews such as systematic reviews, meta-analyses or umbrella reviews (16, 18).

Given the broad and exploratory research question, a scoping review (16) was conducted using the English terms "working disorder," "work disruption," "inhibition of work," "procrastination," "writer's block," and "perfectionism" in the electronic databases PubMed and PsycINFO. Additionally, the German term for working disorder, respectively, work-related problems ("Arbeitsstörung") was used. We also searched reference lists of retrieved articles, the psychoanalytic library pep-web as well as books and book chapters on work-related problems (e.g., EBSCO eBook Collection). Additionally, experts in the field were contacted. No time limit was set. Two authors (CS, FL) screened the literature focusing on clinical, etiological, diagnostic and therapeutic aspects. Topics that seemed relevant for this review were chosen by consensus in discussions by all authors. Following the recommendations on scoping reviews by Colquhoun et al. (16), we aimed to synthesize the existing knowledge on work-related problems by "mapping key concepts, types of evidence, and gaps in research" (p. 1294) in a systematic fashion.

PREVALENCE AND BURDEN OF WORK-RELATED PROBLEMS

Work-related problems are highly prevalent (11, 19). Procrastination alone, representing just one form of work-related problems, has a prevalence of about 20% (19) with a tendency to increase (11). Furthermore, the majority of university students show high levels of procrastination (11, 20). In general, work-related problems are associated with considerable psychosocial impairments and suffering. Procrastination, for example, is associated with poor academic performance (11, 20), more perceived stress (21) and higher levels of depression and anxiety (21). Procrastination appears in various aspects of peoples' lives, including studying (20), preparing taxes and saving for retirement (11) as well as practicing healthy behaviors (22–24). Thus, it is not restricted to occupational achievements, which emphasizes the great importance of this maladaptive behavior even more.

As work-related problems are not restricted to procrastination, but also include other types described below, the prevalence of work-related problems in general is unknown and can be expected to be considerably higher than that reported for procrastination alone.

Related to this is the general question of when work-related problems should be considered serious impairments in need for treatment (see also sections Work-Related Problems and Mental Disorders and Treatment: Self-Help, Counseling, Psychotherapy, and Evidence). Procrastination, for example, is a behavior that possibly anyone may encounter sooner or later in their life and it is difficult to determine, when such a behavior crosses a "pathological" threshold (25). Personal suffering and failure to achieve important academic or professional goals may be important indicators.

WORK-RELATED PROBLEMS AND MENTAL DISORDERS

Work-related problems do not *per se* represent a mental disorder according to ICD-10, ICD-11 or DSM-5, but may occur in the context of mental disorders. They may have developed on the background of a mental disorder or may belong to the symptoms of a disorder (10). This applies especially to depressive disorders, social anxiety disorder, generalized anxiety disorder, adjustment, trauma- and stress-related disorders, attention and hyperactivity disorder (ADHD), as well as obsessive-compulsive disorder.

Depressive disorders are characterized by a loss of interest and reduced energy, sleeping disorders, fatigue, diminished ability to think or concentrate, and a low self-esteem which can severely affect the ability to work effectively. *Social anxiety disorder* and its characteristic fear of being negatively evaluated and ashamed is associated with test anxiety, fear and avoidance of presenting one's work and reduced achievement. *Generalized anxiety disorder* may lead to permanent worries related to one's work. In *adjustment, trauma- and stress-related disorders* emotional distress may be associated with work-related problems. In *ADHD*, hyperactivity, impulsivity, and distractibility may lead to work-related problems. *Obsessive-compulsive disorder* may be associated with an over-emphasized focus on details and perfectionism, compulsive ordering, checking and delaying of tasks. As described below, this applies especially to obsessive-compulsive personality disorder.

"Like sexuality, work is such a major sphere of human activity that any neurosis affects it and nearly any case is, among other things, a neurosis of work." [(26), p. 203]. Thus, it may be difficult or even impossible to disentangle work disruptions from mental disorders as the former often occur in the context of the latter and work-related symptoms may overlap with symptoms of different diagnostic categories (27). Additionally, they may also be associated with specific personality disorders, personality styles, psychodynamic conflicts, structural impairments or dysfunctional cognitions (see below, Types of work-related problems). In the context of this review we relate to individuals presenting with work-related problems or in whom these problems are especially salient. In a hierarchy of problems, they may be the most urgent to focus on in an attempt to alleviate negative consequences like job loss or academic failure.

A PSYCHOLOGICAL MODEL

Several psychological approaches exist that offer explanations for the etiology and development of work-related problems. From a cognitive-behavioral perspective, a conceptual model has been proposed suggesting an interplay between a person's individual conditions (e.g., skills, dysfunctional cognitions, mental disorders, personality traits, distractibility, aims, motives, resources) and characteristics of the task (e.g., type and amount or number of tasks, interpersonal factors, controllability, safety of job, job image) (10). The higher the degree of discrepancy between individual conditions and task characteristics, the higher the likelihood of work-related problems and work-related discontent (10). Although partly acknowledged by the job image, this model can be extended by the societal dimension. A society putting emphasis on working ethic or professional achievements might mediate the effect of the discrepancy between individual preconditions and task characteristics.

From a psychodynamic perspective, unresolved conflicts (e.g., dependency vs. autonomy, submission vs. dominance, unresolved conflicts with authorities) and ego-structural impairments [e.g., impaired self-regulation including regulation of affects, impulses and self-esteem, impaired judgment and anticipation, disturbed internalized object-relations (28, 29)] may constitute further individual preconditions (30–32). Within the psychodynamic framework, it has been hypothesized that procrastination may be seen as an unconscious rebellion against internalized parents with exaggerated ambitions, whose love depended on achievement (33). When the child's performance does not seem good enough to the parents, the unconscious anger of the child at the parents leads the child to linger and delay tasks. As an adult the same behavior may supposedly bring independence from demanding "parents" as well as deadlines and maybe even time in general (33). Interestingly, empirical research using projective tasks has shown that procrastinating students produced themes related to death more often than punctual students (34). Thus, Blatt and Quinlan (34) conclude that procrastination may be related to an unconscious fear of death, which is dealt with internally through the denial of deadlines, calendars and time. From the point of view of attachment theory (35, 36), the conditional proximity and affection of the caregiver depending on achievements might result in an avoidant attachment pattern. Avoidantly attached individuals might constantly fear that they are not good enough at their job, which in turn might lead to increased anxiety and perfectionism (37). Furthermore, secure attachment correlates with higher work satisfaction (38), whereas insecure attachment styles (avoidant or anxious) are associated with less adaptive coping in response to workplace stress (39).

A more comprehensive overview of models explaining work-related mental problems from behavioral, cognitive, cognitive-behavioral, volitional, third wave and psychodynamic approaches is summarized in **Table 1**.

TYPES OF WORK-RELATED PROBLEMS

As noted above, research and treatment has primarily focused on procrastination (11). However, there exists a broad spectrum of different types of work-related problems. Perfectionism is another relevant construct in this area and is consistently related to psychopathology and maladjustment (47), which is why it has been proposed as a transdiagnostic process of psychopathology (48). In professors of psychology, for example, self-oriented perfectionism (i.e., demanding perfection of oneself) was negatively related to the total number of publications, number of first-authored publications, number of citations, and journal impact rating, even after controlling for competing predictors (e.g., conscientiousness) (51). The authors concluded that self-oriented perfectionism may represent a form of

TABLE 1 | Work-related mental problems from different theoretical and clinical perspectives, with a focus on procrastination.

Behavioral approach
Procrastination has been described in behavioral terms as an attempt to balance unpleasant and pleasant experiences (25, 40). In the short-term, procrastination leads to improved mood, which can be seen as a positive reinforcement. In addition, if procrastination serves avoiding unpleasant feelings, it can be seen as negative reinforcement, depending on the alternative tasks and distractions at hand. Interestingly, such distractions may be chosen although they are not *per se* pleasant or even aversive (e.g., cleaning, emptying the dishwasher), as they can be accomplished within a short time frame (10, 25, 40). Behavioral treatments mainly focus on reinforcement, punishment, stimulus control, strategies for time management as well as personalized, meaningful setting of priorities (25, 31, 40).
Cognitive approach
This perspective focuses on cognitive processing and attributional theories in relation to work-related actions and their relationship with self-confidence, e.g., many studies showed a relationship between low self-worth and procrastination (11, 25). Anticipating failure may lead to procrastination by actively seeking distracting behaviors as an excuse. When failure occurs, it can be attributed to external adverse circumstances rather than a lack of skill or personal failure (25). Related to this is the cognitive concept of "self-handicapping" (41).
Cognitive-behavioral approach
Cognitive-behavioral approaches combine the aforementioned strategies, and may additionally include problem- und motivational analyses, psychoeducation, relaxation therapy, cognitive restructuring, enhancing working techniques, work on interpersonal problems, and finding a more suitable work-life-balance (10, 40–43).
Volitional approach
From a volitional perspective, procrastination can be viewed in the context of impaired decision making and disturbed action regulation (25). This may entail problems in evaluating, planning, carrying out, or completing a task and may lead to excessive planning or a lack thereof, vague goals, misjudgment of available time, distraction, lowered self-monitoring or giving up too early. Planning can be become more important than the actual work (25). When deadlines are approaching, enormous efforts can be undertaken which prevents feelings of self-worthlessness but maintains procrastination (25, 40).
Third wave approach (acceptance and commitment therapy, ACT)
From the perspective of ACT (44, 45), it is essential to reduce experiential avoidance in favor of psychological acceptance. Experiential avoidance is the process of avoiding unpleasant mental or bodily sensations (46) and takes various forms such as thought suppression, self-harm or procrastination. Psychological acceptance does not mean approval, but the acceptance of the momentary reality (for example of having work-related problems), which is an indispensable precondition for clients in order to assess whether they are able to change it on their own – provided that a change is desirable for them. If change is not possible, again acceptance is required: *That's how it is and I cannot do anything about it* (25). If change is possible, clients are instructed to find out which commitment is required and whether they are willing to invest the necessary time and effort (25). If this is not the case, again acceptance is required: *The problem exists in this way and it will remain because I'm not willing to invest the necessary commitment to make a change.* In order to build up acceptance the therapist and the client should regularly discuss the costs and benefits of neglecting to accept reality, i.e., the consequences of experiential avoidance. Doing so

(Continued)

TABLE 1 | Continued

Third wave approach (acceptance and commitment therapy, ACT)
will promote the insight that denying reality is always unfavorable and that acceptance at least offers a possibility to work on undesirable states that can be changed (25). Readiness and motivation for commitment may be achieved by formulating desirable goals. As discussed above, procrastination puts an emphasis on short-term reinforcement by avoiding unpleasant feelings or gaining pleasure. Thus, therapeutic action should constantly and consistently focus on meaningful and desirable long-term goals and foster the commitment to actually put them into practice (25). This may be enhanced by letting clients weigh long-term goals against short-term symptom gains and long-term symptom costs, and checking the functionality of currently applied plans and strategies (25).
Psychodynamic approach
In contrast to the aforementioned approaches psychodynamic approaches do not mainly focus on procrastination, but target a wider variety of work-related mental problems. From a psychodynamic perspective, both unresolved conflicts and impaired ego-functions (28, 29) may constitute individual preconditions for work-related problems (30–32). The latter, among others, comprise reality testing, judgment, anticipation, and regulating object relations (28–32). Thus, work ability is closely linked to personality functioning. Within the psychodynamic framework, a central focus lies on (unconscious) inner conflicts, i.e., conflicts including a wish (impulse or affect) and opposing needs, wishes or moral values, which trigger anxiety and must therefore be warded off. It has been hypothesized that procrastination can be seen as an unconscious rebellion against overly ambitious internalized parents (33). From the perspective of attachment theory the conditional proximity and affection of the caregiver depending on achievements might result in an avoidant attachment pattern which in turn might lead to increased fear of not being good enough and perfectionism (35–37). Furthermore, insecure attachment styles (avoidant or anxious) are associated with less adaptive coping in response to workplace stress (39). Perfectionism is another relevant construct regarding work-related problems that is related to psychopathology and maladjustment and has been proposed as a transdiagnostic process of psychopathology (47–50). Especially self-oriented perfectionism may represent a form of counterproductive overstriving (51). Consistent with this broad description of work-related problems, psychodynamic therapy early in history addressed various forms of these problems and related them to personality styles (30–32, 52–54). Psychodynamic treatment strategies focus on conflicts and warded-off affects in the context of a good working alliance. Patients' insight into repetitive (unconscious) conflicts sustaining their problems is improved through confrontation and interpretation. Therefore, transferential and countertransferential aspects and the way in which patients "work" in therapy are focused, e.g., getting distracted or doing the work for the therapist by offering explanations. When impairments in ego-functions are dominant, more supportive techniques to build or restore ego-functions are applied (55).

counterproductive overstriving that limits research productivity (51). Whereas earlier research regarded procrastination as closely related to perfectionism, the relationship has turned out to be more complex (56, 57). Perfectionistic concerns were found to be positively related to procrastination, whereas for perfectionistic strivings a negative relation to procrastination was reported (57).

Perfectionism was found to be multidimensional, including self-oriented perfectionism (high standards on one's own performance), socially prescribed perfectionism

(experiencing others as demanding perfectionism), other-oriented perfectionism (high standards on others' performance) and perfectionistic concerns vs. perfectionistic strivings (58).

Perfectionistic concerns were found to be substantially and positively related to neuroticism whereas perfectionistic strivings were found to be substantially and positively related to conscientiousness (59). As procrastination, perfectionism seems to increase over time (60). Furthermore, maladaptive perfectionism was found to be an important personality trait in imposter syndrome (48, 61), which is characterized by low self-esteem, fear of being exposed and over preparing. Counter-intuitively, individuals with imposter syndrome, who are typically described as delivering superior work, score low on conscientiousness (61, 62), which questions this public image and thus could be classified as work-related problem. Related to this, a combination of perfectionism, low self-esteem and the fear of being exposed may underly the phenomena of feelings of incompetence as described in novice psychotherapists (63, 64), which might prevent them from working effectively with patients or supervisors.

Furthermore, if the various personality types are too pronounced or personality disorders (65) are present, they may be related to specific forms of work-related problems (10, 32). On the other hand, certain personality styles (66) are associated with potential strengths which may be focused and fostered in psychotherapy or counseling. Other personality styles, which are commonly regarded to be maladaptive or psychopathological might be considered a strength in certain work contexts. For example, senior business managers show significant elements of personality disorders, particularly of psychopathic personality traits (67). Related to this is a line of research on the so called "dark triad" (68, 69), including the traits machiavellism, narcissism and (subclinical) psychopathy and covering counter-productive as well as advantageous aspects of these traits when it comes to the workplace and attaining leading positions (69–71). According to a review on the dark triad [(69), p. 206], Hogan coined the term that people showing higher levels of dark traits may "get ahead of" but not necessarily "along with" others in working environments (72).

Following König (32) and Fydrich (10) individuals with an ***anxious-avoidant personality disorder/interactional style*** may be permanently worried about their performance and reluctant to take any personal risk or engage in new activities including work. On the other hand, they may be able to anticipate problems and question premature actions and decisions. Individuals with a ***dependent interactional style*** tend to avoid making independent decisions, are in an excessive need of reassurance from others, and have difficulties initiating projects. As a more positive aspect, they may make good deputies, balancing out interpersonal difficulties among colleagues. A ***compulsive style*** may be related to over-emphasizing details while losing track of what is important, dysfunctional perfectionism, reluctance to delegate tasks and to postponing activities. On a positive note, a strength of this style may be a particularly thorough working style, relieving colleagues with different working styles from bothersome duties. A ***histrionic interactional style*** is associated with an initial excitement when beginning a new task, followed by problems in sticking with the task when it becomes less exciting or involves routine activities. A focus on attention seeking, physical appearance, sexually provocative or charming behavior may be related to success in some areas of work but lead to problems and frustration in others. Individuals with strong ***narcissistic tendencies*** tend to overestimate their abilities, exaggerate their achievements and talents, have an excessive need for admiration and a sense of entitlement. They may expect to be recognized as superior without commensurate achievements or feel entitled to a particularly favorable treatment while being reluctant to take over simple or routine tasks that are perceived as unreasonable (10, 32). On the other hand, they may be very successful, e.g., if they are able to reflect on some of their socially problematic styles.

Consistent with this description of work-related problems linked to personality traits or disorders, psychodynamic therapy early in history addressed various forms of work-related problems and related them to personality traits (30–32, 52–54), including those described for the personality disorders listed above (10). Furthermore, they discuss additional personality styles, such as the schizoid style (e.g., being able to see the whole picture but neglecting details, or avoiding the exchange with colleagues which may put constraints on their career), the depressive style (e.g., difficulties in starting a work or setting priorities) (32) or fear of success (52, 53, 73, 74). Fear of success is related to the assumed consequences of success (e.g., surpassing important others) (52, 53, 73, 74). Whether fear of success is particularly prevalent in women is not yet clear (74). Psychodynamic models of work-related problems focus on associated personality traits, unresolved conflicts and impairments in ego-functions (28) (e.g., self-regulation of affects, impulses and self-esteem) (30–32, 52, 53). On a conscious level, test anxiety, for example, represents the fear of not being successful, but may unconsciously represent the opposite, that is the fear of being successful and being more successful than important others such as one's mother or father which may trigger feelings of guilt.

The ability to work entails adequately handling demands of the external world and is therefore closely related to ego-functions (28). Ego functions in a work-related context enable a person to differentiate between fantasy and reality (reality testing), make reasonable decisions (judgment, anticipation), deal with interpersonal difficulties (regulation of object relations), regulate self-esteem and emotions (self-regulation), set oneself apart from inner or outer stimuli (stimulus barrier), concentrate (autonomous functioning) or integrate contradicting tasks (e.g., being in charge at home but mostly follow instructions at work (synthetic-integrative functioning) (28). Thus, work ability is closely linked to personality functioning and it can be expected that more severe impairments in functioning lead to more severe difficulties in a broad range of areas (e.g., in borderline or narcissistic personality pathology or psychosis).

Work-related problems may be ego-syntonic or ego-dystonic. As long as individuals are not confronted with work-related failures or interpersonal problems, their working style can often be expected to be ego-syntonic. For example, as long as someone with a narcissistic style is successful, it is rather the others who

are likely to suffer from this personality style, e.g., the employees of a narcissistic boss. Patients with an anxious or dependent style may function well as long as there are people they can rely on (directing objects). Thus, there are specific situations that may trigger failures at work, such as the loss of a person to rely on in individuals with an anxious or dependent style. An obsessive-compulsive style may be functional as long as the subject is not procrastinating or lost in details. The same is true for a histrionic, schizoid or depressive style as long as attention seeking, neglecting details or problems in setting priorities, respectively, do not result in work-related failures. Work-related failures and related interpersonal difficulties may contribute to work-related problems becoming ego-dystonic which can be a helpful first step toward insight into problems and seeking help or treatment.

Another psychological phenomenon in the context of work that occurs in professional and creative writing, but is sometimes [maybe unjustifiably (75)] also used in a student context, is "writer's block," a term coined by Bergler in the mid 20th century (76). Writer's block can be defined "as an inability to begin or continue writing for reasons other than a lack of basic skill or commitment" [(77), p. 18]. Hereby, "blocking is not simply measured by the passage of time (...) but by the passage of time with limited productive involvement in the writing task" [(77), p. 18]. Writer's block can be associated with feelings of anxiety, anger, or confusion and can take different forms, i.e., producing too little text or producing only fragments (77). Furthermore, it has been described as being related to perfectionism and procrastination (78). A famous and funny series of articles around this phenomenon concerns the unsuccessful self-treatment of writer's block [e.g., (79–81)]. Different causes have been attributed to writer's block among them the lack of basic writing skills or strategies (77), fear of imperfection (78, 82), inner conflicts around expectations (75, 76, 83) or the loss of the ability to be spontaneous or playful (75, 84). An important aspect in writer's block seems to be related to achievement and success. As Amado put it based on ideas originally presented by Freud ["On those wrecked by success" (52)]: "The elimination of an external frustration, the achievement of a wish, uncovers the internal frustration in all its intensity. This is the very Freudian idea that sometimes the last thing you want is to get what you want" [(75), p. 2]. This may be related to creative writing but also be true in academic writing and other work-related contexts when important goals have been completed and certain positions have been reached.

WORK-RELATED PROBLEMS FROM A DIMENSIONAL VIEW

With its alternative "hybrid" model of personality disorders (AMPD), the DSM-5 provided a more dimensional view of personality disorders that is compatible with the specific work-related problems discussed above for the various types of personality disorders. The criteria of disturbances of self (including the subdimensions identity and self-direction) and interpersonal relationships (including the subdimensions empathy and intimacy), which are central to the DSM-5 alternative model of personality disorders [(65), p. 762], encompass features or mechanisms of work-related problems. This applies, for example, to avoidant personality disorder for which DSM-5 lists low self-esteem and shame (identity), unrealistic standards associated with reluctance to pursue goals or take personal risks (self-direction) and sensitivity to criticism (empathy) [(65), p. 765], which may contribute to work-related problems. For narcissistic personality disorder [(65), p. 767], this applies, for example, to exaggerated self-appraisal (identity), setting goals on gaining approval, unreasonably high personal standards (self-direction), impaired ability to recognize the needs of others (empathy), and relationships serving self-esteem regulation (intimacy). In obsessive-compulsive personality disorder [(65), p. 768], work-related problems are associated with a sense of self that is predominantly derived from work (identity), difficulties in completing tasks, and unreasonably high and inflexible internal standards (self-direction). Furthermore, work-related problems in obsessive-compulsive personality are characterized by difficulties in understanding and appreciating the ideas and feelings of others (empathy) as well as rigidity and stubbornness that negatively affects relationships with others (intimacy). In antisocial personality disorder, traits associated with work-related problems are egocentrism (identity), goal-setting based on personal gratification, lack of prosocial internal standards (self-direction) and concerns for feelings or suffering of others (empathy) as well as exploitation as a primary means of relating to others (intimacy). In borderline personality disorder [(65), p. 766], work-related problems may be associated with an unstable self-image (identity), instability in goals (self-direction), compromised ability to recognize the feelings of others associated with interpersonal hypersensitivity (empathy), intense unstable and conflicted close relationships that are viewed in extremes of a idealization and devaluation (intimacy).

The categorical diagnoses of personality disorders are not retained in the latest version of the ICD (ICD-11). Instead, with the exception of borderline personality, existing distinct categories are replaced by a dimensional model which is built on a psychodynamic model of personality functioning and determines the severity of the personality pathology (i.e., mild, moderate, severe), based on functioning of aspects of the self and interpersonal dysfunction as well as six trait domain qualifiers whose use is optional (85). The latter comprise negative affectivity, detachment, disinhibition, dissociality, anankastia and a borderline pattern qualifier. A "tentative cross walk" from ICD-10 personality disorders to ICD-11 trait domain qualifiers has been provided [(85), p. 8]. For example, in terms of ICD-11 the previous dependent personality disorder consists of the traits negative affectivity (with specific trait features like low self-confidence and anxiety) and low dissociality (in the sense of an overly consideration of others' needs) while narcissistic personality disorder can be described in terms of high dissociality (here in the sense of grandiosity and entitlement) and negative affectivity (with the specific trait feature of dysregulated self-esteem). Thus, with regard to DSM-5 and ICD-11 it is important to note that work-related problems may be conceptualized in

the context of dimensional approaches to personality disorders which will become more important in the future (86).

DIAGNOSTIC ASSESSMENT

As other psychiatric symptoms, work-related problems are not an isolated phenomenon but must be considered in the context of a person's life. For this reason, a thorough biographic interview is required. Comorbid mental disorders need to be assessed, for example, through structured interviews such as SCID-5-CV (87) and SCID-5-PD (88). To assess the level of personality functioning and of specific ego-functions, the operationalized psychodynamic diagnosis (OPD), the AMPD described in DSM-5, the diagnostic assessment according to ICD-11 (85) or the structured interview of personality organization [STIPO, (89)] may be applied (29, 65). Interestingly, the AMPD and related diagnostic instruments emphasize the importance of "love and work as the cornerstone of humanness" [(90), p. 318, (91)]. The STIPO, for example, covers several domains (i.e., identity, object relations, defenses, aggression and moral values), focusing on the past 5 years. The very first section of the STIPO deals with identity and the capacity to invest. Its items are centered around work effectiveness, work ambition, and work satisfaction {e.g., how effective someone is in their work and how important work is, whether the work performance is in accordance with once abilities and whether working is enjoyed [(92), p. 4–6]}. With regard to interpersonal relationships, conflicts with co-workers, supervisors, bosses, subordinates etc. are explored [(92), p. 25]. Additionally, perfectionistic strivings and the fear of being negatively evaluated by others when things are not perfectly right are investigated {higher level defenses [(92), p. 46]}. Thus, this may be a good starting point for a more in depth exploration in people presenting with work-related problems.

In addition, especially in psychodynamically oriented treatments, dreams and phantasies about work, exploration of biographical and familial attitudes toward work and the therapist's countertransference should be explored. The idea behind using the countertransference for diagnostic purposes is that work-related disorders entail problems in internal and external object relationships that can be understood and dealt with in the context of the therapeutic relationship. The above-mentioned psychodynamic model conceptualizes work-related problems as being inherently interpersonal, i.e., embedded in real, internalized or imagined object-relations, which can be assessed by the Core Conflictual Relationship Theme Method (CCRT) (93). Based on relationship anecdotes, the CCRT method operationalizes central relationship patterns by systemizing wishes, needs and motivations of a subject (W), the anticipated response of others to the subject's wishes (RO) and the following response of the subject (RS) to the anticipated response of others to their wish. For example, the wish for appreciation of achievements (W) might be associated with the experience that caregivers react with withdrawal of affection or hostility (RO) resulting in being submissive or even fearing success (RS). A student with this CRRT might suffer from procrastination as success (W) is unconsciously associated with losing the affection of important others (RO) and thus own achievements are sabotaged (RS).

Most diagnostic instruments for the assessment of work-related problems refer to procrastination [e.g., General Procrastination Scale, Adult Inventory of Procrastination, Decisional Procrastination Scale, Adult Inventory of Procrastination Scale, Irrational Procrastination Scale, Pure Procrastination Scale (42, 94–97)]. For the assessment of perfectionism, several self-report instruments are available such as the Multidimensional Perfectionism Scale, the Perfectionistic Self-Presentation Scale or the Perfectionism Cognitions Inventory (47, 98, 99). Additionally, a 58-item list of work-related problems in the context of academia has been developed, focusing on different problems like procrastination, exam anxiety, writer's block, lack of motivation, tiredness, demands, and worries about the future (27). The diagnostic assessment of other forms of work-related problems seems to have been neglected. Especially instruments focusing on work-related problems in the context of personality are lacking. For this reason, the authors of this review are currently developing a self-report questionnaire comprising items on work-related problems in the context of different personality styles (unpublished). The questionnaire is currently being empirically examined in a sample of adults and will be psychometrically evaluated, improved, and published.

TREATMENT: SELF-HELP, COUNSELING, PSYCHOTHERAPY, AND EVIDENCE

Work-related problems may be addressed by self-help programs, counseling or psychotherapy.

According to some authors, clinical experience and research evidence show that problems related to procrastination cannot simply be addressed by advice on better time management or by putting together to-do-lists (13, 40). Thus, more deeply rooted dysfunctional aspects have to be targeted in those suffering from more severe work-related problems (25, 40).

For these forms of work-related problems, psychotherapy is the method of choice (10, 12, 30–32, 49, 52). Treatments need to be tailored to the work-related problem in focus. Thus, a thorough diagnostic assessment is the starting point for any treatment decision. This applies to both, a careful description on a phenomenological level (type of work-related problem) and on a level of functioning (maintaining mechanisms). Depending on the respective treatment approach, the latter may involve unresolved conflicts (55, 100), ego-functions (28, 29, 65) or dysfunctional cognitions (10) associated with the work-related problems. Psychodynamic approaches, for example, focus on the maintaining conflicts and ego-functions which also become manifest in the way someone "works" in therapy, e.g., in the way they handle the basic principle to speak as freely as possible (30). Thus, individuals may not adhere to the task, may not know where to start, may produce too many details, may not engage sufficiently and need constant encouragement or may tend to do all the therapeutic work themselves (in psychodynamic therapy, for example, patients interpreting the material themselves). An

early example for a psychodynamic treatment of work-related problems is reported by Lang (101). According to Lang, Freud treated the famous conductor Bruno Walter who had developed an arm cramp that made conducting an orchestra impossible, by gradually encouraging him to move his arm while addressing the conductor's fear of disturbing the concert [(101), p. 93, (102), p. 234].

This exemplifies the idea that creative acts are changing our relationships with all sorts of others, in this case an audience (75). Drawing on Winnicott's idea that there is no such thing as an infant without a mother, there is also no such thing as a conductor without listeners or a writer without readers (75, 103). However, a real or imagined audience can be strict, critical, even brutal which may lead to negative reactions of the self and work-related problems (see above CCRT). Such relationship patterns may be understood and worked through in psychodynamic treatments with the goals of tolerating uncertainty, being playful, spontaneous, and without feeling the urge to adjust or correct original work to satisfy others.

Cognitive and cognitive-behavioral approaches include, for example, a functional analysis of work-related problems, an analysis of motivations and interpersonal aspects, a definition of goals and steps to reach them, task related interventions, working skills, identification and modification of problematic cognitions, improving interpersonal skills at the work-place, and measures to achieve a healthy work-life balance (10). Depending on the problem at hand, an exploration of certain basic work techniques should be undertaken. When these are not sufficiently available or developed, a positive treatment outcome is less likely. This entails prioritizing work related tasks and accomplishing tasks step by step in order to gain small successes and reduce anxiety, time management, practicing, doing unpleasant tasks first, finishing tasks without being distracted, finding a balance between leisure and work (10, 31).

As mentioned above, procrastination seems to be stronger when tasks are perceived as less enjoyable, i.e., "boring, frustrating, done resentfully, forced upon them by others and (...) generally more stressful, less meaningful and less structured" [(13), p. 165]. Thus, therapeutic or counseling approaches rooted in personality and motivational psychology argue for addressing these aversive aspects by finding projects more in line with core personal values and meaningful strivings (104, 105). See also strategies from acceptance and commitment therapy (**Table 1**).

Some more details on behavioral, cognitive-behavioral as well as third wave (acceptance and commitment therapy) and psychodynamic approaches to treatment can be found in **Table 1**.

For the treatment of perfectionism, a psychodynamic-interpersonal therapy has been developed which focuses on the dynamic and relational underpinnings of perfectionism (50). Perfectionism is regarded as both a defense against intolerable affects resulting from unfulfilled needs (e.g., for acceptance, self-worth) and as a means of gaining acceptance or garnering self-worth. However, the elusiveness of perfection implies the impossibility of having one's needs fulfilled (50). In psychodynamic-interpersonal therapy the interrelations of needs, affects, defenses and their relationship with significant others are worked through. The central aim is to help the patient accept that humanness includes strengths and limitations, all falling short of perfectionism [(50), p. 4].

With regard to empirical evidence, primarily various models of CBT with a focus on procrastination have been applied (12). With regard to self-help, there is evidence from an RCT including 150 participants that internet-based self-help using CBT principles is effective in reducing procrastination when compared to a waitlist control condition with moderate to large effect sizes for guided self-help and moderate effect sizes for unguided self-help (106). Clinically significant change was achieved among 31.3–40.0% of participants for guided self-help and 24.0–36.0% for unguided self-help. With regard to psychotherapy, CBT models proved to be superior to waiting list or no treatment (12, 107). In one study examining long-term outcome, results were stable at 1-year follow-up (108) with rates of 30–40% post-therapy and 8–36% at 1-year follow-up. However, the rates of patients achieving clinically significant improvements are limited (108, 109).

There is only anecdotal evidence or evidence from clinical experience for psychodynamic approaches to work-related problems, no evidence from randomized controlled trials (RCTs). For perfectionism, in a controlled but not randomized study short-term psychodynamic therapy proved to be superior to a waiting list in reducing perfectionism, depression and interpersonal problems with large effect sizes (49). Presently, a randomized controlled trial of psychodynamic treatment of perfectionism is being carried out (110).

There are no RCTs investigating the treatment of writer's block. However, treatment concepts have been proposed [e.g., (111)] and there are several published case illustrations focusing on psychoanalytic (83), behavioral (112) or paradoxical interventions (symptom prescription) (84).

A problem in RCTs targeting work-related problems is the primary endpoint. Studies addressing procrastination, for example, often assess a tendency for procrastination, but a reliable criterion for what constitutes a clinically meaningful amount of procrastination that justifies a need for professional treatment seems to be currently lacking (25).

FUTURE RESEARCH

For the reasons discussed above, there is a need to further improve the treatment of procrastination in particular and work-related problems in general and to offer individuals a variety of evidence-based treatments that may fit their treatment needs. To achieve these goals, the following approaches seem to be promising.

(1) With success rates of 30–40% one treatment does not seem to fit all. Thus, developing and applying further models of treatment is a promising approach.
(2) In the studies included in the meta-analysis by Malouff and Schutte (12) between 2 and 10 sessions were applied (107). Data on dose effect-relationships suggest that especially for chronic problems a higher treatment dose is required. By

applying 20 or 24 sessions, success rates between 55 and 60% can generally be achieved (113).

(3) Furthermore, research has almost exclusively focused on procrastination, other types of work-related problems have been widely neglected. Treatments that address other forms of work-related problems need to be developed and tested empirically. They may be based on CBT, psychodynamic therapy, interpersonal therapy, systemic therapy or other models.

For example, for the various types of work-related problems described above a unified transdiagnostic and manual-guided psychodynamic treatment approach is presently being developed, integrating the existing psychodynamic treatment approaches (30–32, 49, 50, 114) in form of a unified protocol.

LIMITATIONS

According to recent guidelines, there is no mandatory scheme on how to conduct a scoping review, however, certain methodological standards have been introduced to enhance the quality of this type of review (16, 17). In light of these standards, some limitations have to be mentioned. Firstly, we did not publish a pre-specified protocol. Secondly, we based our review on published findings in English and German which carries the risk of missing relevant aspects, especially with regard to cultural-specific phenomena. Thirdly, all authors have a psychodynamic background, which may have resulted in reporting bias. We tried to mitigate this potential effect by taking it critically into account while selecting topics, as well as by contacting two cognitive-behavioral scholars regarding further relevant literature. Fourthly, the present scoping review covers a wide range of topics in a field that is *per se* not well-defined, dates back many decades, but also has seen very recent developments. The iterative search and selection process, and the openness of the review team for a wide range of topics within the chosen field may have resulted in a broad and possibly not fully balanced review which can be seen as a first point of orientation toward further research. Finally, consumers and stakeholders were not included in designing and conducting the review.

CONCLUSIONS

When Otto Kernberg was recently asked, how he would distinguish between an unconventional, eccentric or somehow odd person and a person with a personality disorder who needed therapy, he first answered by referring to the occupational functioning of that person: "...is he effective, on the top of his knowledge and his possibilities, is he satisfied with his work, does he get along well with his coworkers and so on." [own translation, (115), p. 41]. Thus, according to Kernberg, whether an individual is able to work effectively, productively and satisfactorily may—among other things—be used to distinguish between normal and disordered personality and is considered essential in describing personality structure.

Considering the high prevalence of work-related problems with an even increasing tendency and associated psychosocial impairments, suffering, poor academic performance, more perceived stress and higher levels of depression and anxiety, they should become a more essential part of diagnostics in the mental health field. Psychotherapy is the method of choice to treat severe work-related problems (10, 12, 30–32, 49). At least for the treatment of procrastination, however, response rates are presently limited. For non-responders of the available treatments of procrastination, long-term treatments may be helpful and should be tested (113). No treatments have been proposed and tested for other types of work-related problems, with the exception of a psychodynamic treatment for perfectionism (49, 110). Thus, there is a need to further improve the treatment of work-related problems. For this purpose, the whole spectrum of work-related problems needs to be taken into account, not just procrastination. Further treatments based on various theoretical approaches need to be developed and validated.

AUTHOR CONTRIBUTIONS

CS and FL conceived of the idea of the article, performed literature searches, screened results, and wrote the first draft of the manuscript. NH critically revised the manuscript for intellectual content and aided in interpreting findings. All authors discussed the contents, methods and outline of the manuscript and approved the final version for publication.

DEDICATION

This article is dedicated to Karl König who raised our interest in work-related problems.

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Antianhedonic Effect of Repeated Ketamine Infusions in Patients With Treatment Resistant Depression

Alina Wilkowska, Mariusz Stanisław Wiglusz, Maria Gałuszko-Wegielnik, Adam Włodarczyk and Wiesław Jerzy Cubała*

Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland

Anhedonia constitutes one of the main symptoms of depressive episode. It correlates with suicidality and significantly effects the quality of patient's lives. Available treatments are not sufficient against this group of symptoms. Ketamine is a novel, rapid acting strategy for treatment resistant depression. Here we report the change in symptoms of anhedonia measured by Snaith-Hamilton Pleasure Scale as an effect of eight ketamine infusions as an add-on treatment in 42 patients with treatment resistant depression. We also determined the effect of this change on the severity of depressive symptoms measured by Inventory for Depression Symptomatology-Self Report 30-Item (IDS-SR 30). We have observed statistically significant decrease in the level of anhedonia during ketamine treatment. After adjusting for potential confounders we have found that significant reduction in Snaith-Hamilton Pleasure Scale (SHAPS) after each infusion and 1 week post treatment was observed only among patients who did not use benzodiazepines. The reduction in symptoms of anhedonia mediates the antidepressive effect of ketamine. The results need replication in a larger randomized placebo controlled trial.

Keywords: ketamine, anhedonia, treatment resistant depression, benzodiazepines, antianhedonic

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****Correspondence:***
Alina Wilkowska
ali.wilkowska@gmail.com

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INTRODUCTION

Anhedonia, the reduction of the ability to experience pleasure, is one of the core symptoms of depression, and approved treatments do not address it sufficiently (1). The presence of anhedonia strongly correlates with suicidality, and this effect is independent of the severity of depressive symptoms (2). It has been shown that anhedonia is a risk factor of completed suicide during the 1-year follow-up (3). Symptoms of anhedonia turned out to be a robust predictor of a poor outcome of antidepressant treatment in a factor analysis of data from two large studies: Genome-based Therapeutic Drugs for Depression (GENDEP) and Sequenced Treatment Alternatives to Relieve Depression (STAR*D). This was true irrespective of which antidepressant was used and did not depend on the level of baseline depression (4). Ketamine is a novel, effective, and rapid-acting antidepressant in unipolar patients (5, 6) and bipolar treatment resistant depression (7). It has also antisuicidal properties (8). Ketamine is an N-methyl-d-aspartate receptor (NMDAR) antagonist. The mechanism of the antidepressant effect of ketamine is still not fully understood. Studies have indicated that it involves the inhibition of presynaptic and postsynaptic NMDARs in GABAergic interneurons.

This effect causes a disinhibition of glutamate transmission and the subsequent glutamate release activates ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and the brain-derived neurotrophic factor-tyrosine kinase receptor B (BDNF-TrkB) signaling pathway, thus, leading to the release of BDNF. Ketamine elicits the activation of neuronal connection through the (long-term potentiation) LTP-like enhancement of glutamatergic synapses, increasing synaptic plasticity (9, 10).

Anhedonia involves various neural circuits, mostly in the reward system of the brain. Studies on anhedonia both in rodents and humans indicate that dopaminergic and glutamatergic signaling is responsible for this symptom (11). A meta-analysis of 11 studies has shown that acute ketamine administration leads to DA release in the brain and increases DA levels in the striatum, nucleus accumbens, and the prefrontal cortex, and correlates with significant increases in DA neuron activity in rodent models of depression, although primate and human studies were inconsistent (12). Ketamine is also a partial agonist of the dopamine D2 receptor (13). A human study using PET found a decreased ability of dopamine D2 receptors to bind (11C)raclopride after s-ketamine administration, indicating increases in the striatal dopamine levels (14). Preclinical evidence suggests that glutamate may have a role in anhedonia (15). Taken together, these findings suggest that the glutamatergic system and its downstream modulation of dopaminergic activity may be one potential route of the antianhedonic efficacy of ketamine in both unipolar and bipolar treatment resistant depression (TRD). Limited evidence on the effect of IV ketamine on anhedonia in humans supports this hypothesis (16–18).

Here, we present the changes in the severity of anhedonia with SHAPS in the course of eight intravenous ketamine infusions in patients with treatment-resistant depression. We hypothesized that subsequent ketamine infusions would improve depressive symptoms and anhedonia and cause a decrease in the SHAPS and IDS 30-SR scores. We also expected that this effect would be smaller in patients taking benzodiazepines.

MATERIALS AND METHODS

Patients

The study population includes subjects enrolled in a naturalistic observational registry protocol for intravenous ketamine treatment in TRD: A Naturalistic Study of Ketamine for Treatment Resistant Mood Disorders (GDKet) (NCT04226963). Detailed methodology is discussed elsewhere (19). The present study comprises a population of 41 patients (26 females) with a mean age of 48.5 years (SD 14.3), with depressive episodes without psychotic features in the course of a major depressive disorder or bipolar disorder. The diagnosis was established by a clinician psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria and certified using a Mini International Neuropsychiatric Interview (MINI). All participants exhibited treatment resistance for the current episode. For unipolar depression, for all MDD patients, it was defined as an inadequate response to two or more antidepressants used in adequate doses and time duration according to the Antidepressant Treatment Response Questionnaire ATRQ (20). TRD-BP was defined as a clinically unsatisfactory response to at least two approved dissimilar medications administered in adequate doses and for a sufficient amount of time (21).

Only medically stable adults (<65 years) were enrolled in the study. Medical stability was based on physical examination, medical history, life factors, laboratory tests, and electrocardiography (ECG). If necessary, patients continued current medications during the ketamine treatment. Exclusion criteria included pregnancy, breastfeeding, an active history of uncontrolled diseases, or previous adverse effects while on ketamine. The study protocol was approved by the institutional review board NKBBN/172-674/2019. All participants signed a consent form after confirming their understanding of the study procedures. The study was conducted in accordance with the latest version of the Declaration of Helsinki.

Study Design

The study followed an observational design; all patients continued baseline psychotropic treatment, as well as necessary treatment of chronic somatic diseases during ketamine infusions. The therapeutic intervention included eight intravenous ketamine infusions administered over 4 weeks as an add-on treatment. Ketamine was administered at a dose of 0.5 mg/kg based on the actual body weight of the patient and given as an intravenous infusion over 40 min. The preparation used for preparing infusions was Ketalar 50 (ketamine hydrochloride) 50 mg/ml; one vial contained 10 ml. The managing psychiatrist monitored safety before, during, and after the infusion every 15 min to 1.5 h after the infusion, including periodic assessment of vital signs (heart rate, body temperature, respiration rate, blood pressure, and oxygen saturation). Safety monitoring included also the Brief Psychiatric Rating Scale (BPRS) and Clinician-Administered Dissociative States Scale (CADSS) at baseline and 1 h after the infusion.

Psychometric Measures

Anhedonia was measured with the Snaith–Hamilton Pleasure Scale (SHAPS), and a 14-item self-reported measure of anhedonia was used. The items assess anhedonia on a 1–4 scale ranging from "strongly agree" to "strongly disagree." The SHAPS score can range from 0 to 14, where a score higher than 2 indicates the presence of anhedonia (22). Depressive symptoms were monitored with the 30-item Inventory for Depressive Symptomatology—Self Report (IDS-SR 30) (23). We determined the effect of the change in the level of anhedonia based on the severity of the measured depressive symptoms. The primary outcome was the change in the SHAPS score. The secondary outcomes were the effect of this change on the severity of depressive symptoms measured by IDS-SR 30 and the change in the score of item 18 in the IDS-SR 30 reflecting the intensity of suicidal thoughts. Item 18 describes "Thoughts of death or suicide," and scores from 0—I do not think of suicide or death, through 1—I feel that life is empty or wonder if it is worth living, 2—I think of suicide or death several times a week for several minutes, up to 3—I think of suicide or death several times a

day in some detail, or I have made specific plans for suicide or have actually tried to take my life. The results reported here were assessed before treatment, at the third, fifth, and seventh infusions, and 1 week after treatment.

Statistical Analysis

Data were analyzed by using the IBM SPSS Statistics package ver. 26. Demographic and clinical characteristics were presented as mean and standard deviation or frequencies. In some cases, other statistics were provided. The normality of the continuous variables was examined by the Shapiro–Wilk test. In addition, the following methods were used: (a) a one-way ANOVA with repeated measures for the results of the SHAPS and IDS-30 complemented with Tuckey's *post-hoc* tests, (b) general linear models with repeated measures for the results of the same questionnaires, adjusted for potential confounders (sex, age, BMI, benzodiazepines), (c) the Friedman's test (following Dunn's *post-hoc* tests) for analysis of IDS-30 item no. 18 scores, and (d) a moderated mediation model for the relationship between ketamine infusions and depression severity (IDS-30) with anhedonia (SHAPS) as the potential mediator and the therapy of benzodiazepines as the moderator of association between the ketamine and SHAPS scores. In order to conduct the above analysis, we used PROCESS macro (v3.5) for SPSS, following the bootstrapping procedure with 5,000 resamples. All calculations were made for a sample of $N = 41$. The significance level was set at $\alpha = 0.05$. With the assumed moderate effect for the selected methods, the analyzed sample ($N = 41$) allowed to obtain the power of the test at a level > 0.8.

RESULTS

Demographic and Clinical Analysis

Demographic and clinical analysis of the study sample is presented in **Table 1**.

We did not observe any serious adverse effects. Patients experienced a mild and transient increase in arterial blood pressure and self-limiting mild-to-moderate dissociative symptoms.

Snaith–Hamilton Pleasure Scale

At baseline, 97.5% of the patients ($n = 39$) met the criteria for clinically significant anhedonia (i.e., SHAPS ≥ 2). The simple ANOVA with repeated measures indicates a significant reduction in the SHAPS total score across infusions—$F_{(4,160)} = 13.36$, $p < 0.001$, $\eta^2 p = 0.25$; with G-G and H-F correction $p < 0.001$. Pairwise comparisons (Tuckey's *post-hoc* tests) show that there was a significant decrease in the SHAPS total score from the baseline to each infusion and the post-infusion visit (in all comparisons $p < 0.001$) (**Figure 1**). No significant differences emerged between each infusion and between infusions and the post-infusion visit.

After adjusting for potential confounders (sex, age, BMI, and treatment with benzodiazepines), there was a significant interaction between the ketamine infusion and use of benzodiazepines—$F_{(4, 144)} = 2.60$, $p = 0.039$, $\eta^2 p = 0.07$ with H-F correction $p = 0.041$. A significant reduction in the SHAPS after each infusion ($p = 0.002$ in comparison with the third infusion and $p < 0.001$ in comparison with the rest infusions) and during the post-infusion visit ($p < 0.001$) was

TABLE 1 | Demographic and clinical characteristics of the total sample.

Variables	Total sample ($N = 41$)
	Mean (SD)
Age	48.5 (14.3)
BMI	27.5 (5.6)
Episode duration (weeks)	26.9 (29.0)
Number of depressive episodes	6.1 (8.1)
Baseline results (before infusion)	
SHAPS	9.6 (3.5)
IDS-30 total	46.7 (13.1)
IDS item no. 18	1.2 (1.2)
Diagnosis	*N* (%)
MDD	28 (68.3%)
BD	13 (31.7%)
Sex	
Females	26 (63.4%)
Males	15 (36.6%)
Education	
Primary	2 (4.9%)
Secondary	4 (9.8%)
Vocational	16 (39.0%)
Higher	19 (46.3%)
Employment status	
Unemployed	8 (19.5%)
Pension	16 (39.0%)
Retirement	7 (17.1%)
Employed	9 (22.0%)
Study	1 (2.4%)
Marital status	
Single	11 (26.8%)
Informal relationship	2 (4.9%)
Married	20 (48.8%)
Divorced	5 (12.2%)
Widowed	3 (7.3%)
Concomitant meds	
TCA	MDD: 4 (14.3%), BD: 0 (0%)
SSRI	MDD: 16 (57.1%), BD: 4 (30.8%)
SNRI	MDD: 5 (17.9%), BD: 5 (38.5%)
Other	MDD: 11 (39.3%), BD: 3 (23.1%)
Antipsychotics	MDD: 8 (28.6%), BD: 8 (61.5%)
Mood stabilizers	MDD: 10 (35.7%), BD: 10 (76.9%)
Lithium	MDD: 0 (0%), BD: 3 (23.1%)
BDZ	MDD: 12 (42.9%), BD: 8 (61.5%)

SHAPS, Snaith–Hamilton Pleasure Scale; IDS-SR 30, 30-Item Inventory for Depressive Symptomatology—Self Report; SD, standard deviation; BMI, body mass index; MDD, major depressive disorder; BD, Bipolar disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and noradrenaline reuptake inhibitors; AD, antidepressants; TCA, tricyclic antidepressants; BDZ, benzodiazepines.

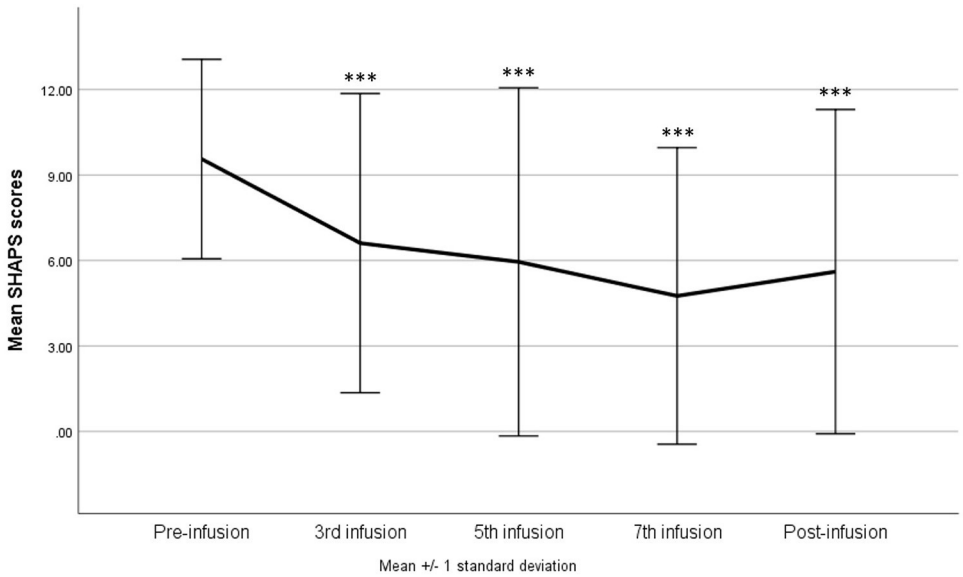

FIGURE 1 | Snaith–Hamilton Pleasure Scale (SHAPS) score change during ketamine treatment. ***$p < 0.001$ in comparison with baseline scores (pre-infusion).

observed only among patients not using benzodiazepines. In the second group, a reduction (in comparison with baseline results) was noticed only after the seventh infusion ($p = 0.036$); however, eventually, the total score did not differ between the baseline and the post-infusion visit (**Figure 2**).

30-Item Inventory for Depressive Symptomatology—Self Report

The same models as above were tested for the IDS-30 total scores as dependent variable. In the one-way repeated measures of ANOVA, the result was statistically significant—$F_{(4, 160)} = 8.86$, $p < 0.001$, $\eta^2 p = 0.18$; with G-G and H-F correction $p < 0.001$, suggesting a gradual decrease in the score as a result of the administering of ketamine. The difference between the baseline and third infusion was significant at $p = 0.013$, and between the baseline results and subsequent infusions and the post-infusion visit $p < 0.001$ (**Figure 3**). The model adjusted for confounding variables indicated a sustained statistically significant effect of the infusions—$F_{(4, 144)} = 3.28$, $p = 0.013$, $\eta^2 p = 0.08$; with G-G and H-F correction $p < 0.05$, but no significant interaction effects.

30-Item Inventory for Depressive Symptomatology—Self Report 30 Item No. 18

Due to the nature of the variable, the analysis of the changes in scores was carried out using the non-parametric Friedman test (and *post-hoc* Dunn's test), while the model taking into account confounding variables was omitted. The results showed a significant decrease in the intensity of suicidal ideation as a result of ketamine infusions [$\chi^2_{(4)} = 15.53$, $p = 0.004$, $W = 0.09$], but this change was observed only after the fifth ($p = 0.047$) and the seventh ($p = 0.028$) infusions in comparison with the pre-infusion measurement. At the same time, the results obtained during the post-infusion visit did not differ from the baseline. Instead of a graph, a table with descriptive statistics is presented for better readability.

Mediation Model

Mediation analysis with moderation (model 7. in macro PROCESS v3.5.) was conducted in order to determine if there was an indirect effect of anhedonia on the relationship between the number of infusions and the severity of depression. Taking benzodiazepines was included as a moderator of the relationship between infusions and the SHAPS total scores. Due to the lack of significance of the interaction between infusions and benzodiazepines in the overall model, the mediation model without a moderator was finally analyzed (model 4. in macro PROCESS v3.5) (**Figure 4**). The obtained results indicate a significant unstandardized indirect effect of anhedonia in the relationship between infusions and the severity of depression: −1.90 (95% CI bootstrap method: −2.83 to −0.91). The whole model was significant—$F_{(2, 202)} = 74.42$, $p < 0.001$ and explained 42% of the variance of the dependent variable.

DISCUSSION

A primary finding in this study is a statistically significant decrease in the level of anhedonia during ketamine treatment. It was also found that significant reduction in SHAPS after each infusion and 1 week post-treatment was observed only among patients not using benzodiazepines. The IDS-SR 30 score reduced significantly during treatment. We observed

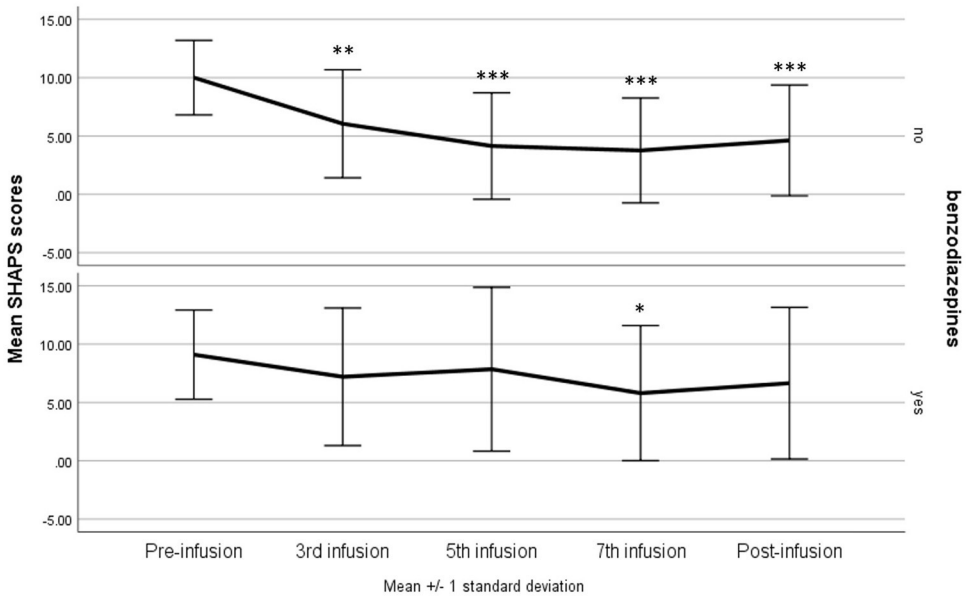

FIGURE 2 | Snaith–Hamilton Pleasure Scale (SHAPS) score change during ketamine treatment in patients using benzodiazepines compared with the rest of the study group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ in comparison with baseline scores (pre-infusion).

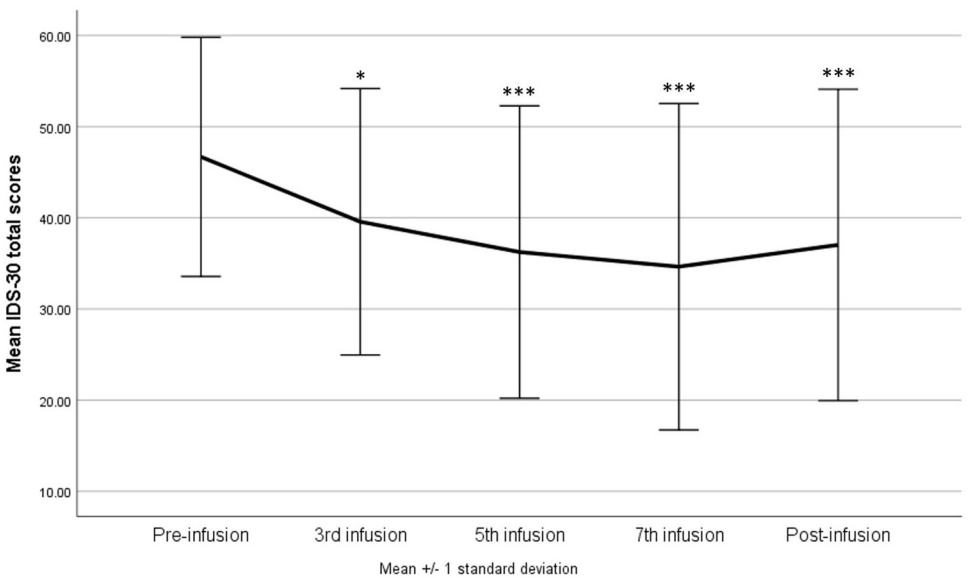

FIGURE 3 | The 30-item inventory for Depressive Symptomatology—Self Report (IDS-SR 30) score during ketamine treatment. *$p < 0.05$, ***$p < 0.001$ in comparison with baseline scores (pre-infusion).

a significant decrease in the intensity of suicidal ideation reflected in the score of item 18 after the fifth and the seventh infusions. The indirect effect of anhedonia on the severity of the depression was investigated in a mediation model, which confirmed that reduction in depressive symptoms was mediated by the antianhedonic effect, meaning that the general level of depression is reduced due to a decrease in the symptoms of anhedonia. The change in the level of anhedonia explained 42% of the variance of the IDS-SR 30 score improvement.

The results are in line with the existing evidence, although data on the effect of ketamine on anhedonia are scarce.

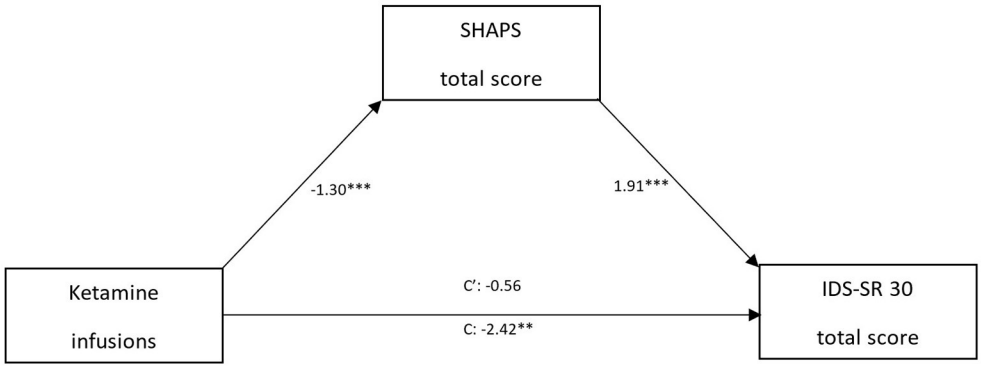

FIGURE 4 | The mediating effect of anhedonia in the relationship between ketamine treatment and the 30-item Inventory for Depressive Symptomatology—Self Report (IDS-SR 30) score. Snaith–Hamilton Pleasure Scale (SHAPS). #The model presents unstandardized effects.

One study has shown a rapid antianhedonic effect after a single infusion of ketamine in 36 patients with treatment-resistant bipolar depression (16). A subsequent open label study by the same group included 52 participants with TRD who received one infusion of 0.5 mg/kg ketamine after a 2-week washout period, which also confirmed a rapid antianhedonic effect of ketamine (17). In a study investigating the clinical correlates of suicidal thoughts, the authors found that after a single infusion of ketamine, TRD patients with MDD and BD significantly reduced their SHAPS scores. The authors also observed that improvements on the SHAPS accounted for an additional 13% of the variance in suicidal thought reduction, beyond the influence of depressive symptoms (24). A recent retrospective *post-hoc* analysis of over 200 participants with treatment-resistant depression in the course of MDD or BD revealed a significant reduction in the SHAPS score during and after four ketamine infusions. The authors also found that improvements in depressive symptoms, suicidal ideation, and anxiety symptoms were mediated by a reduction in anhedonic symptoms since anhedonia accounted for 26% of the variance in depressive score improvements measured with QIDS 16 (18).

Our secondary finding was that there appeared to be no significant effect of ketamine on anhedonia in the subgroup of patients using benzodiazepines compared with the rest of patients. There is some evidence on the attenuation of the antidepressant effect of ketamine by concomitant BDZ. One case report describes a patient with bipolar depression treated with 10 infusions of ketamine as an add on to lithium, fluoxetine, quetiapine, and 3.5 mg of lorazepam. During lorazepam administration, the response to ketamine was limited to 24 h, but when lorazepam was withdrawn, the response extended to 10–14 days. No other changes in medications were made (25). A *post-hoc* analysis of data of 10 TRD patients treated with ketamine has shown that the responder group had a significantly smaller dose of BDZ used than a non-responder group (26). Another *post-hoc* analysis of the effect of six ketamine infusions on 13 TRD patients has shown that BDZ users had a longer time to response and remission as well as a shorter time to relapse compared with the rest of the group. A recent *post-hoc* analysis of data from 47 MDD patients treated with a single infusion of ketamine has shown significantly worse outcomes in the subgroup receiving BDZ, and this effect depended on the dose of the BDZ. Moreover, the BDZ attenuating effect was present only on days 3 and 7, not at 24 h post infusion, which suggests that it may be related to the neurotrophic effect of ketamine treatment (27). Our results stand in line with the aforementioned reports, although in the cited papers, the investigators focused on the severity of depression, and our objective was to study this effect on anhedonia. The process of interference of BDZ on the ketamine effect can be hypothetically explained as follows: ketamine blocks NMDA receptors causing disinhibition of GABAergic interneurons and a subsequent increase in glutamatergic activity with a following BDNF increase. Benzodiazepines act as agonists against GABA-A receptors and, therefore, counteract the effect on the GABAergic neurons stimulating them.

Ketamine and benzodiazepines have a common target, which is the reward system. Dysregulation of the reward system function has been described in depression, anhedonia, but also in addictions (28). Despite being very useful in short-term treatment for anxiety, there is evidence that benzodiazepines might worsen depressive symptoms (29). In a study including over 900 TRD patients, the authors found that regular benzodiazepine use was a strong correlate of treatment resistance. The suggested reason is the possible coexistence of anxiety disorder, suppression of feelings as an effect of BDZ, which can deepen depression and undermine the effectiveness of psychotherapy as well as the negative influence of BDZ on cognitive functions (30). The same group conducted a study on 1,034 (128 BP I, 906 BP II) patients with treatment for bipolar depression, dividing them into three groups: low, medium, and high resistance, based on the number of medications they used. The authors found that regular BDZ use was significantly more common in the last group,

defined as the TRBD group using five or more psychotropic medications (31).

Similar to benzodiazepines, ketamine has abuse potential (32); therefore, it is particularly important to follow-up patients on ketamine treatment, especially on long-term use as this regimen seems to be the most effective (33).

Several limitations of the study should be taken into consideration. The study was conducted without a placebo control, randomization, and blinding. Thus, the results apply to the naturalistic observational design. Apart from these obvious shortcomings, the registry design has also benefits and can help to study the effect of medication in a real-life setting (34). There were no measurements of ketamine and its metabolites as well as the concentrations of benzodiazepines in the blood of patients. Another limitation is that unipolar and bipolar patients were included in the same group due to the relatively small number of participants. This was also the reason why we did not analyze different benzodiazepines separately. Observational studies provide an overall low quality of evidence, and the true effect might be markedly different from the estimated effect due to the risk of bias, imprecision, inconsistency, and indirectness, and the present level C of evidence that is insufficient for scientific recommendation. However, our report aims at contributing to the literature with regard to the matters of safety and tolerability, which may be useful for future research with a more rigorous design.

In summary, our study results suggest that there is an antianhedonic effect of intravenous ketamine in patients with treatment-resistant depression in the course of unipolar and bipolar disorder in an open label naturalistic study.

This effect was attenuated by the use of benzodiazepines. The use of ketamine needs to be monitored in order to prevent the development of substance use disorder. Our findings need replication in a large placebo controlled RCT.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Ethics Committee of Medical University of Gdańsk (NKBBN/172-674/2019). The patients/participants provided their written informed consent to participate in this study after confirming their understanding of the study procedures. The study was conducted in accordance with the latest version of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

WC and MW: conceptualization. WC: methodology and funding acquisition. MW, AWi, and AWł: software. MW and AWł: formal analysis. MG-W and AWł: investigation. MW: resources. AWi and AWł: data curation. AWi: writing—original draft preparation. AWi and WC: writing—review and editing. MG-W and MW: project administration. All authors have read and agreed to the published version of the manuscript.

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ORIGINAL RESEARCH
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Oxidative Stress Biomarkers as a Predictor of Stage Illness and Clinical Course of Schizophrenia

Dariusz Juchnowicz[1], Michał Dzikowski[2], Joanna Rog[2], Napoleon Waszkiewicz[3], Anna Zalewska[4], Mateusz Maciejczyk[5] and Hanna Karakuła-Juchnowicz[2]*

[1] Department of Psychiatric Nursing, Medical University of Lublin, Lublin, Poland, [2] Department of Psychiatry, Psychotherapy and Early Intervention, Medical University of Lublin, Lublin, Poland, [3] Department of Psychiatry, Medical University of Bialystok, Choroszcz, Poland, [4] Experimental Dentistry Laboratory and Department of Restorative Dentistry, Medical University of Bialystok, Bialystok, Poland, [5] Department of Hygiene, Epidemiology and Ergonomics, Medical University of Bialystok, Bialystok, Poland

Pro/antioxidant imbalance has been reported in schizophrenia (SZ). However, the results of studies are inconsistent and usually do not include other factors that are highly affected by oxidative stress (OS).This cross-sectional study aimed to determine the serum levels of OS markers and their potential connection with schizophrenia. The total sample comprised 147: 98 individuals with SZ −47 first-episode (FS) and 49 chronic patients (CS)—and 49 healthy individuals (HC) as a control group. The examination included clinical variables and serum levels of antioxidants and oxidative damage products. The significant changes were observed in concentrations of all examined markers, without any specific direction of the pro/antioxidant balance shift between SZ and HC. In the regression model adjusted for cofounders, catalase: OR = 0.81 (95%CI: 0.74–0.88); glutathione peroxidase: OR = 1.06 (95%CI: 1.02–1.10); total antioxidant capacity: OR = 0.85 (95%CI: 0.75–0.98); oxidative stress index: OR = 1.25 (95%CI: 1.03–1.52); ferric reducing ability of plasma: OR = 0.79 (95%CI: 0.69–0.89); advanced glycation end products: OR = 1.03 (95%CI: 1.01–1.04); and advanced oxidation protein products (AOPP): OR = 1.05 (95%CI: 1.03–1.07) turned out to be significant predictors of schizophrenia. In the multiple stepwise regression model, pro/antioxidant status and their interaction with the duration of illness-related factors affected schizophrenia symptoms: positive symptoms (FRAPxKYN), negative (DITYR, FRAP, CAT), general (KYN), and over-all psychopathology (KYNxNFK). The results confirm differences in serum levels of oxidative biomarkers between SZ patients and healthy individuals. The pro/antioxidant status could be considered a predictor of schizophrenia and the factor affects patients' symptom severity.

Keywords: schizophrenia, oxidative stress, antioxidant, psychosis, biomarkers

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****Correspondence:***
Joanna Rog
rog.joann@gmail.com

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INTRODUCTION

Schizophrenia (SZ) affected ∼ 1% around the world and, according to the World Health Organization (WHO), was ranked as one of the top 10 illnesses contributing to the global burden of disease (1). Despite the growing knowledge of the disease, the mechanisms underlying them are still poorly understood, but more and more evidence confirms no one contributory cause.

To an increasing extent, SZ has been seen as a manifestation of the interplay between many pathophysiological processes affecting not only the brain but also other organs (2, 3).

One of the factors involved in the pathophysiology of SZ is oxidative stress (OS). OS is an imbalance between oxidative and reductive reactions, increasing reactive oxygen species (ROS), and decreasing antioxidant levels. Brain cells are highly vulnerable to OS due to a high metabolic rate (use of oxygen) and modest levels of antioxidants following a high abundance of peroxide substrates (4). ROS can come from the inactivation of monoaminergic neurotransmitters, as by-products of adrenaline, noradrenaline, dopamine, and serotonin (5). On the other hand, ROS are the secondary messengers, fundamental in many brain-connected processes, including cell growth, differentiation, and proliferation; signaling; and immune response. There is also some evidence, stating that ROS are engaged in human adult neurogenesis (5). Therefore, ROS has both pro-survival and pro-death effects, and their excess leads to OS and inflammation promotion. The imbalance between antioxidant and pro-oxidant could negatively affect neural growth, differentiation, regeneration, and synaptic plasticity. OS may play a role in the neuroprogression of SZ *via* DNA damage and immune-inflammatory pathways (6). Experimental evidence confirms that OS is involved in apoptotic pathways mediating the inflammatory response of CNS. Indicators of OS could be released by activation of immune cells and vice versa—OS can activate an immune-inflammatory pathway (7).

Consequently, SZ should be considered in the context of CNS dysfunction and other organ changes, including the interplay between the imbalance of pro/antioxidant state. Some of the oxidative-related factors have been proposed as potential biomarkers of SZ (8, 9). Although there are failures to replicate results, both observational and intervention studies support the association between redox imbalance and SZ. Most studies assessing OS in SZ populations point to an increase of toxic by-products due to both increased pro-oxidants and decreased antioxidants (10–12). Several hypotheses concerning the oxidative pathophysiology of SZ have been postulated. However, the source of abnormalities remains unclear (13). Despite the extensive studies focusing on indicators of OS, there is no clear consensus of the interplay between oxidation markers and SZ.

Considering the aforementioned, our study aimed to quantify the serum levels of OS markers and their potential connection with SZ.

MATERIALS AND METHODS

Study Population

The study included 147 participants aged 18–65 years: 98 patients that met the criteria of SZ according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (14) and 49 healthy individuals (HC) as a control group. Among the SZ group, 49 were the first-episode patients (FS, up to 24 months after first treatment contact), and 49 were chronic patients (CS).

Exclusion criteria were as follows: co-occurrence of neurological diseases, intellectual disability, organic brain dysfunction, autoimmune diseases or other diseases in unstable phase (including metabolic diseases) or addiction (except nicotine and caffeine), the present clinical signs of inflammation (hsCRP $\geqq 5\,\mu g/ml$) and/or leukocytosis (>10.000 G/I) during entry to the study, and having psychiatric diagnosis (in the past or current) in HC group.

All participants gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Medical University of Lublin, Poland (project identification code: KE-0254/231/2013).

Blood Collection

Venous blood (20 ml) samples were collected after overnight (12-h) fasting and centrifugation (at 2,000 × g, 10 min at room temperature). The obtained serum has been stored at −80°C and thawed only once to further analysis.

Laboratory Tests

OS Biomarkers

The pro/antioxidant balance assessment included the following: 1) enzymatic and non-enzymatic antioxidants: catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase-1 (SOD-1), glutathione reductase (GR), reduced glutathione (GSH), total antioxidant capacity (TAC), and ferric reducing ability of plasma (FRAP) and 2) oxidative damage products: advanced glycation end products (AGEs), advanced oxidation protein products (AOPP), dityrosine (DITYR), kynurenine (KYN), N-formylkynurenine (NFK), tryptophan (TRY), and total oxidant status (TOS), as well as concentrations of nitric oxide (NO) and total protein. All reagents for the biochemical assays (unless otherwise specified) were obtained from Sigma-Aldrich, Germany. The absorbance/fluorescence was measured using Infinite M200 PRO Multimode Microplate Reader (Tecan, Mannedorf, Switzerland). All determinations were estimated in duplicate samples and standardized to 100 mg of total protein.

Enzymatic and Non-enzymatic Antioxidants

Seven indicators of antioxidant defense were assessed:

1. The activity of CAT (EC 1.11.1.6) was determined colorimetrically by measuring the decomposition rate of hydrogen peroxide in a 50-mM phosphate buffer (pH 7.0) at 240 nm (15). One unit of CAT activity was defined as the amount of enzyme that decomposes 1 mmol hydrogen peroxide for 1 min.
2. The activity of SOD-1 (E.C. 1.15.1.1) was assayed colorimetrically by measuring the cytosolic activity of SOD by inhibiting the oxidation of adrenaline to adrenochrome in pH 10.2 at 480 nm (16). It was assumed that one unit of SOD activity inhibits the oxidation of adrenaline by 50%.
3. The activity of GPx (EC 1.11.1.9) was measured colorimetrically based on the reduction of organic peroxides by GPx in the presence of NADPH and glutathione reductase (GR) at 340 nm (17). One unit of GPx activity was assumed to catalyze oxidation of 1 μmol of NADPH for 1 min.

4. The activity of GR (EC 1.6.4.2.) was determined colorimetrically by measuring the decrease in absorbance of NADPH at 340 nm (18). One unit of GR activity was defined as that quantity of enzyme which catalyzes the oxidation of 1 μmol of NADPH for 1 min.
5. The concentration of GSH was analyzed colorimetrically by reaction with 5,5′-dithiobis-2-nitrobenzoic acid (DTNB) in a 0.2-M phosphate buffer (pH 8.0) to give a complex that absorbs at 412 nm (19).
6. TAC was estimated colorimetrically using two, 2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid radical cation ($ABTS^{*+}$) (20). Changes in the absorbance were determined at 660 nm, and the TAC level was calculated from the calibration curve for 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox).
7. FRAP was determined colorimetrically by measuring the ferric reducing ability of samples with TPTZ (2, 4, 6-tripyridyl-s-triazine) (21). Changes in the absorbance were determined at 593 nm, and FRAP level was calculated from the calibration curve for iron sulfate ($FeSO_4$).

Oxidative Damage Products

We chose six biomarkers related to oxidative damage in SZ for examination:

1. The content of AGEs was analyzed fluorimetrically by measuring AGE-specific fluorescence emission/excitation at 350 nm/440 nm (22). For AGE determination, serum samples were diluted 1:50 (*v:v*) in phosphate-buffered saline (PBS, pH 7.2).
2. The concentration of AOPP was assayed colorimetrically by measuring the oxidative capacity of the iodine ion at 340 nm (22). For AOPP determination, serum samples were diluted in PBS (pH 7.2) 1:50 (*v:v*).
3. To detect DITYR, KYN, NFK, and TRY, samples were diluted 1:10 (*v:v*), in 0.1 M H_2SO_4, and fluorescence at 330/415, 365/480, 325/434, and 95/340 nm, respectively, was measured (23). The results were normalized to fluorescence of 0.1 mg/ml quinine sulfate in 0.1 M H_2SO_4 (24).
4. The concentration of TOS was estimated colorimetrically based on the oxidation of Fe^{2+} to Fe^{3+} ions in the presence of the oxidants contained in the sample (25). The absorbance was measured bichromatically at 560/800 nm. The oxidative stress index (OSI) was calculated using the formula: OSI = TOS/TAC *x* 100 (23).
5. The level of NO was determined colorimetrically by measuring its stable decomposition products NO_3^- and NO_2^- by the Griess reaction (26). Changes in the optical density were analyzed at 543 nm.
6. The concentration of total protein was measured by the bicinchoninic acid (BCA) method (27) using commercial kit Thermo Scientific Pierce BCA Protein Assay (Rockford, IL, USA) following the manufacturer's instructions.

Sociodemographic and Clinical Data

The characteristics of the study sample were determined using a self-constructed questionnaire including sociodemographic/lifestyle information, including duration of illness (DoI), number of episodes (NoE), medication, comorbidity, number of hospitalizations (NoH), and number of smoking cigarettes daily. The clinical data on patients were obtained from a supervising physician during the blood collection day. The doses of antipsychotic medication were calculated based on defined daily doses (DDDs) to 1 mg olanzapine (28). The severity of SZ symptoms was assessed by a well-trained physician (M.D.) using the Polish adaptation of the Positive and Negative Symptom Scale (PANSS) (29).

Statistical Analysis

We used Statistica 13 software (TIBCO Software Inc., Palo Alto, CA, USA) to analyze obtained results. To determine the distribution of variables, the Shapiro–Wilk test was applied. Due to non-Gaussian distribution in most of the factors, non-parametric tests were used: Man–Whitney U to determine the differences between two groups and Kruskal–Wallis test in three groups for continuous variables. To establish the differences between categorical variables across the group, a chi-square test was applied. We used Spearman's rho correlation to determine the magnitude and direction of the correlation. For all analyses, $p < 0.05$ was considered statistically significant. We used Bonferroni correction for *post hoc* correction to control for type I error.

We performed univariable logistic regression to assess the potential odds of SZ depending on OS. The odds ratio and 95% confidence interval for markers which was statistically significant were determined. We also adjusted the obtained models of potential cofounders in the multiple analysis with interactions.

To assess the possible effect of oxidative status on psychopathological symptoms, multiple stepwise regression analysis with automatic selection of variables was conducted. The obtained models were verified by determination of the adjusted *R*-squared. We included the following variables as potential predictors: age, number of hospitalization, duration of illness, olanzapine equivalents (OE), gender, body mass index (BMI), and number of smoking cigarettes were included in the model as possible confounders.

RESULTS

Characteristics of the Study Population

The characteristics of the examined population are shown in **Table 1**. The study group included 147 participants: 98 individuals with SZ (SZ group) divided into two subgroups—chronic (CS; $n = 49$) and first-episode patients (FS; $n = 47$)—and 49 healthy individuals constituting the control group (HC). There was a difference in the age of chronic and first-episode patients ($p < 0.001$). The CS group had a higher BMI than the SZ group ($p = 0.03$) and HC ($p < 0.001$). Not surprisingly, chronic patients had a longer length of illness, more psychotic episodes ($p < 0.001$), and lower severity of SZ symptoms ($p < 0.001$) compared to the FS group. The median of smoking cigarettes per day was 0 across all examined groups ($p > 0.05$). Fifteen participants from the CS group (30.61%) and two participants from the FS group (4.08%) received typical antipsychotic drugs. Fifteen FS (30.61%) and

TABLE 1 | Characteristic of examined population.

Variable	SZ	FS	CS	HC	*p*-value
Age, years [M]	29	21[1]	40[1]	28[1]	[1] <0.001
Gender (male) [%]	52 (53.06)	26 (53.06)	26 (53.06)	21 (42.86)	NS
BMI, kg/m^2 [M]	24.5	21.3[2]	25.9 [1/2]	22.9[1]	[1]0.03 [2] <0.001
Smoking cigarettes per day [M]	0	0	0	0	NS
Duration of illness, months [M]	24	3[1]	241[1]	NA	[1] <0.001
Number of episodes [M]	3	1[1]	7[1]	NA	[1] <0.001
PANSS total [M]	87	104[1]	72[1]	NA	[1] <0.001

SZ, schizophrenia; FS, first episode; CS, chronic schizophrenia; HC, healthy control; BMI, body mass index; PANSS, Positive and Negative Symptoms Scale. [1,2]*indicate groups with differences. M, median.*

TABLE 2 | The differences in oxidative stress between examined groups.

Variables	SZ	FS	CS	HC	*p*-value
Antioxidant defense biomarkers					
CAT	26.77[1]	30.14[2]	25.23[3]	41.21 [1/2/3]	[1/2/3] <0.001
GPx	36.94[1]	36.21	37.632[2]	33.07 [1/2]	[1]0.018 [2]0.012
SOD	203.75	289.38 [1/2]	145.16 [1/3]	217.39 [2/3]	[1] <0.001 [2]0.036 [3] <0.006
GR	1.11	1.04[1]	1.33[1]	1.08	[1]0.003
GSH	0.17[1]	0.17[2]	0.17[3]	0.38 [1/2/3]	[1/2/3] <0.001
TAC	53.67[1]	47.90[2]	60.20 [2/3]	46.82 [1/3]	[1/2/3] <0.001
TOS	1777.48[1]	1680.57[2]	1826.37[3]	189.41 [1/2/3]	[1/2/3] <0.001
OSI	32.02[1]	33.07[2]	30.93[3]	4.44 [1/2/3]	[1/2/3] <0.001
FRAP	11.96[1]	13.90[2]	11.27[3]	15.79 [1/2/3]	[1/3] <0.001 [2]0.004
Oxidative damage products					
AGEs	420.84[1]	414.98[2]	424.32[3]	379.15 [1/2/3]	[1/2/3] <0.001
AOPP	1.15[1]	1.01 [2/3]	1.23 [3/4]	0.53 [1/2/4]	[1/2/4] <0.001 [3]0.025
DITYR	851.68	895.47[1]	822.86 [1/2]	892.86[2]	[1]0.001 [2]0.002
KYN	715.63[1]	785.94[2]	452.53 [2/3]	793.64 [1/3]	[1]0.002 [2/3] <0.001
NFK	307.45[1]	330.65[2]	226.90 [2/3]	343.35 [1/3]	[1]0.003 [2]0.001 [3] <0.001
TRY	2754.19	2765.01	2713.05	2785.31	NS
NO	1.79	1.49 [1/2]	2.40[1]	2.12[2]	[1]0.013 [2]0.046

SZ, schizophrenia; FS, first episode; CS, chronic schizophrenia; HC, healthy control; CAT, catalase; GPx, glutathione peroxidase; SOD-1, superoxide dismutase-1; GR, glutathione reductase; GSH, reduced glutathione; TAC, total antioxidant capacity; TOS, total oxidant status; OSI, oxidative stress index; FRAP, ferric reducing ability of plasma; AGEs, advanced glycation end products; AOPP, advanced oxidation protein products; DITYR, dityrosine; KYN, kynurenine; NFK, N-formylkynurenine; TRY, tryptophan; NO, nitric oxide. [1,2,3,4]*indicate groups with differences. Data are presented as median.*

43 CS (87.76%) patients received atypical antipsychotics drugs. Other individuals from the FS group were drug-naive.

The Differences in OS Biomarkers Between Patients With SZ and Healthy Individuals

The obtained results confirm substantial differences in redox state between individuals who have SZ and healthy persons (see **Table 2**). The significant changes were observed in concentrations of CAT [higher in HC and lower in FS group ($p < 0.001$)], SOD which was the lowest in chronic patients and the highest in healthy control ($p < 0.006$), and GSH (which was substantially higher in healthy persons compared to the all-patient group $p < 0.001$). Compared to healthy individuals, the changes in GPx concentrations were confirmed in the CS ($p = 0.012$) and SZ ($p = 0.018$) groups but not in the FS group. The GR reduction was noted in FS patients compared to CS ($p = 0.003$). The TAC (SZ>HC; FS<CS; CS>HC) was higher in the CS group

($p < 0.001$), and TOS, OSI, FRAP, and AGEs differed in healthy individuals compared to the all-examined-patients group (lower levels of TOS, OSI, AGEs, and AOPP) and higher levels of FRAP in the HC group ($p < 0.001$). AOPP also had a different concentration in serum of first-episode and chronic patients (FS < CS; $p = 0.025$). The greater levels characterized FS and HC groups compared to CS ($p = 0.001$ and $p = 0.002$, respectively). A higher concentration of KYN was noted in the HC group compared to SZ ($p = 0.002$) and the FS group ($p < 0.001$). KYN was also higher in first-episode patients compared to the chronic group ($p < 0.001$). NFK differentiated SZ ($p = 0.003$) and CS patients ($p < 0.001$) compared to HC (lower in patients groups) but was also lower in CS compared to FS patients ($p = 0.001$). The lower concentration of NO was noted in the FS group compared to CS ($p = 0.013$) and HC groups ($p = 0.046$).

Some of the indicated results turned out to be not significant after Bonferroni correction (GPx between all patients with SZ and HC, SOD-1 between FS and HC, AOPP between FS and CS, NO between FS and HC).

In the analysis of gender effect on OS status, we found higher TOS in CS males compared to females ($p < 0.05$) and higher SOD in HC males compared to females ($p < 0.05$).

The Relationship Between OS and Lifestyle/Clinical Features Across Study Groups

We found many correlations between OS and health- and illness-related parameters. However, most of them were weak (see **Supplementary Table 1**). A strong association was only seen between BMI and SOD-1 concentration in the HC group ($R = -0.55$; $p < 0.05$). It is worth mentioning that the relationships between SOD-1, age ($R = -0.49$; $p < 0.05$), DoI ($R = -0.47$; $p < 0.05$); TAC, DoI ($R = 0.47$; $p < 0.05$); and KYN, age ($R = -0.50$; $p < 0.05$), DoI ($R = -0.48$; $p < 0.05$) in the SZ group were achieved between moderate to large difference effects.

The pro/Antioxidant Imbalance and Odds of SZ

Univariate Analysis

The results of the univariate analysis are shown in **Table 3**. Higher concentrations of GPx, TAC, OSI, AGEs, and AOPP had increased odds of SZ. Lower concentrations of CAT, GSG, and FRAP were also positively connected with a SZ diagnosis.

Multivariable Analysis

In the model adjusted for BMI, number of cigarettes and age CAT: OR = 0.81 (95%CI: 0.74–0.88); GPx: OR = 1.06 (95%CI: 1.02–1.10); TAC: OR = 0.85 (95%CI: 0.75–0.98); OSI: OR = 1.25 (95%CI: 1.03–1.52); FRAP: OR = 0.79 (95%CI: 0.69–0.89), AGEs: OR = 1.03 (95%CI: 1.01–1.04); and AOPP: OR = 1.05 (95%CI: 1.03–1.07) remained significant predictors of SZ.

The Effect of Pro/Antioxidant Imbalance on SZ Symptoms

In the forward multiple stepwise regression model, the positive symptoms were lowered with the DoI and were increased with simultaneous FRAP and KYN rising (see **Table 4**). The following model was adjusted for FRAP and KYN concentration and explained the 24.55% variability of positive symptoms in the SZ group.

With NoH, DITYR concentration, and interaction between FRAP and CAT, their concentrations turned out to be factors that affect negative symptoms in the backward multiple stepwise regression model. The following model explained 28.73% variability of negative symptoms in the SZ group.

The general symptoms were positively affected by the NoH and negatively affected by the higher concentration of KYN and longer DoI as one in the model adjusted for OE, NFK, and interaction between them, and KYN and interaction between KYN and NFK, DoI. This forward multiple-step regression model explained the 45.78% variability of general symptoms in the SZ group.

TABLE 3 | Odds ratio between schizophrenia and oxidative stress: crude results.

	OR	95% CI	*p*-value
CAT	0.84	0.79–0.90	<0.0001
GPx	1.06	1.02–1.10	0.002
GSH	0.84	0.78–0.89	<0.0001
TAC	1.06	1.03–1.10	0.0004
OSI	1.11	1.06–1.15	<0.0001
FRAP	0.76	0.67–0.86	<0.0001
AGEs	1.03	1.01–1.04	<0.0001
AOPP	1.05	1.03–1.06	<0.0001

CAT, catalase; GPx, glutathione peroxidase; GSH, reduced glutathione; TAC, total antioxidant capacity; OSI, oxidative stress index; FRAP, ferric reducing ability of plasma; AGEs, advanced glycation end products; AOPP, advanced oxidation protein products; OR, odds ratio; CI, confidence interval.

TABLE 4 | The oxidation-related predictors of psychopathological symptoms in schizophrenia: multiple models.

Positive symptoms	R^2	*p*-value	β
FRAPxKYN	24.55%	0.03	0.93
DoI		0.002	−0.36
Negative symptoms	R^2	*p*-value	**B**
NoH	28.73%	0.006	2.33
DITYR		<0.001	0.50
NoHxDITYR		0.01	−2.09
FRAP		0.04	−0.20
CAT		0.004	−0.28
General symptoms	R^2	*p*-value	**B**
NoH	45.78%	0.03	0.28
DoIxKYN		0.006	−0.63
Psychopathological symptoms (total PANSS)	R^2	*p*-value	**B**
KYNxNFK	34.42%	0.03	1.22

CAT, catalase; FRAP, ferric reducing ability of plasma; KYN, kynurenine; NFK, N-formylkynurenine; DoI, duration of illness; NoH, number of hospitalization; R^2, coefficient of determination; ?, standardized regression coefficients beta; x, interaction between variables.

In the multiple stepwise forward regression, simultaneous increases in KYN and NFK concentrations affected psychopathological symptoms (total PANSS score) in the model adjusted for DoI and interaction between it and KYN, KYN, and NFK. The following model explained the 34.42% variability of symptoms in the SZ group.

In the FES group, the higher severity negative symptoms were related to lower CAT concentration in the model adjusted for DITYR, NFK, and interaction between them (multiple stepwise forward regression model). The following model explained 24.56% of the variability of negative symptoms in the FS group.

DISCUSSION

The role of OS in psychiatric disorders and SZ remains unclear. The meta-analysis published in 2019 confirmed that some of the markers were different in the patients' group than healthy individuals. Nevertheless, CAT (blood cells), GPx (blood cells, serum/plasma), GSH (serum/plasma), SOD (blood cells), SOD (serum/plasma) concentrations were unaffected, while TAS was the only marker that was lower in FES (11). Nevertheless, the authors did not adjust the results for many important disease-related factors, including the type or dose of antipsychotics. It should be pointed out that the definition of FEP varied across studied populations, patients on a different stage of illness may be assigned to this group, and diagnostic classification is not well-designed to facilitate biological and biochemical differentiation (11).

We found many indicators of redox imbalance in SZ patients. Some of the antioxidants were raised, while others decreased compared to healthy individuals. These ambiguous results may be the effect of other mechanisms that strongly affect OS and antioxidant defense of cells or psychotropic drugs and biological adaptation to illness.

In our study, the CAT concentration was negatively linked to the duration of illness ($R = -0.29$, $p < 0.05$) and the number of episodes ($R = -0.31$, $p < 0.05$). What is more, higher levels were related to a lower chance of SZ and negative symptoms. Taken together, as the disease progresses, the antioxidant enzyme stores are likely to run out. In two meta-analyses, CAT was not different between healthy individuals and the first-episode SZ patients (11, 12). CAT converts H_2O_2 into H_2O and O_2. There was also the hypothesis that polymorphism of the CAT gene could be engaged in earlier SZ development in males (30).

According to our results, the GPx concentration increased in chronic and first-episode patients compared to healthy individuals. Moreover, higher GPx was related with higher SZ chance (OR = 1.06; 95% CI: 1.02–1.10, $p = 0.002$). GPx levels may rise in the adaptive mechanism due to increased OS at the first episode of psychosis. Still, differences between HC and FS in GPx concentrations were not noted. In the meta-analysis, FEP was also no different from CAT from healthy individuals and patients with different SZ subtypes (11, 12). GPx is an antioxidant that, together with CAT, converts H_2O_2 into H_2O and O_2. Based on two meta-analysis results, differences in GPx concentration between SZ and healthy individuals were not seen (12). However, it was shown that in acutely relapsed and chronic inpatients subgroups GPx in RBC and serum were significantly decreased (10). The results in FEP individuals were discordant (10, 11).

The SOD-1 concentration was lower in chronic SZ but not in the first episode compared to healthy individuals. The potential SOD-1 role in SZ chance was not noted. In our study, the concentration of SOD-1 turned out to be related to psychopathological symptoms. These results suggest the role of SOD-1 in diminished OS by the interaction with peroxidation compounds. The meta-analysis indicated that SOD-1 activity significantly decreased in the disorganized type of SZ (12). The SOD-1 role is to catalyze the conversion of superoxide radicals to hydrogen peroxide. SOD-1 was to shown to be decreased in acutely relapsed inpatients (RBC), stable medicated out (RBC) patients, and FEP (RBC) (10). SOD-1 increased in stable medicated outpatients (serum) and chronic inpatients (RBC). In one meta-analysis in FEP, levels of SOD were increased in plasma but decreased in RBC, and in a Turkish study, the polymorphism of gene SOD was related to an increased risk of SZ. The observed reduced SOD activity should increase superoxide radicals (10), but a later meta-analysis did not support this (11).

In our study, the GR concentration was lower only in FS patients compared to the CS group. The GR fall with the time since diagnosis was confirmed by the correlation between GR and both the duration of illness ($R = 0.35$; $p < 0.05$) and the number of episodes ($R = 0.31$; $p < 0.05$) in SZ patients. However, we did not see the directly GR effect on symptoms or SZ chance.

GSH concentration was lower across all patients' groups, independent of illness stage. Their level was related to lower SZ chance, but this was not significant after adjusting for health-related factors. In the meta-analysis from 2019, there were no changes in GSH in FEP group serum and plasma (11).

It is well-known that assessment of redox homeostasis cannot be based solely on single biomarkers. Much more information about the efficiency of the antioxidant barrier is provided by the analysis of the total antioxidant potential. TAC takes into account the interactions between individual antioxidants (31, 32). TAC was different between patients and HC. The higher levels were in CS compared to both FEP and HC. The higher levels of TAC were related to SZ diagnosis chance. Surprisingly, after covariates were included, TAC was a factor inversely related to SZ odds. Some studies indicate no differences in TAC levels between patients and healthy individuals (33).

Although we did not directly assess the rate of ROS production, a shift in redox homeostasis in favor of oxidative reactions may be evidenced by elevated TOS. This parameter expresses the total content of oxidants in a biological system (25, 34). TOS was ∼ 10-fold in SZ (independent on stage disease) compared to healthy individuals, and in the multivariable analysis, higher TOS increased SZ risk. Nonetheless, the concentration was not related to psychopathological symptoms. In opposition to our results, the concentration of TAS in serum and plasma was significantly decreased during the first episode, according to two meta-analyses (10, 11).

Also, OSI was several times higher in all SZ patients than HC, and rising levels increased SZ chance by 25% [OR = 1.25

(1.03–1.52)]. Most studies supported these results in chronic patients (35–37), and OSI was found to be higher in deficit SZ and remitted SZ patients compared to non-deficit and non-remission ones (38, 39).

We found a lower concentration of FRAP in both the first-episode and chronic patients, but a more significant difference was occurring between chronic patients and healthy individuals. Other studies supported it (40, 41); one study suggests that FRAP was lower in first-episode drug-naïve patients compared to healthy control (42). According to our study, lower FRAP concentration was a predictor of SZ risk after lifestyle variable adjustment [OR = 0.79 (0.69–0.89)], and simultaneous increases of FRAP and KYN were related to higher severity of positive symptoms in the multivariable analysis. In the multiple models, higher levels of FRAP affected the lower severity of negative symptoms, which is supported by authors who had observed a trend toward an inverse correlation between negative symptoms and FRAP (42). Lower FRAP was suggested to engage in cognitive deficits (36). This indicates the role of FRAP in the interaction with other oxidative compounds and the enzyme role in attempt reduction OS during psychosis development followed by depletion with the duration of illness. The longitudinal study suggests increasing in FRAP levels during antipsychotic treatment (41).

AGEs which turned out to be a predictor of SZ was higher in the patients' group, especially chronic patients, than healthy individuals. A consequence of disruption of antioxidant systems is intensified oxidation and glycation of proteins and lipids. Therefore, the increase in oxidative and carbonyl stress biomarkers in the progression of SZ is not surprising. The review conducted in 2015 showed that AGE accumulation is enhanced in subjects with SZ (43). The longitudinal study confirmed increased AGE accumulation in the skin, implicating a growing cardiovascular risk in psychosis (44).

AOPP, the marker of protein damage induced by oxidation stress, was elevated in all patients, with the most substantial rising in the chronic group. Our results are not supported by all studies (45), but some confirm that AOPP was increased in schizophrenic patients and suggest that AOPP could be considered an independent risk factor for SZ (46). Their potential rising with the duration of illness was suggested by relationship to age ($R = -0.39$; $p < 0.05$) and duration of illness ($R = -0.35$; $p<0.05$) in chronic patients. The AOPP increased the risk for SZ, and the connection remained significant after analyzing the covariates. There was also the suggestion that deficit SZ is characterized by higher AOPP levels (47). The assessment of drug-free patients has noticed that the levels of AOPP were related to higher severity of general symptoms and total psychopathology (46), but we did not find any effect of AOPP on SZ symptoms.

The higher DITYR (product of oxidative damage) was seen in first-episode patients and healthy individuals compared to the CS group. Formulated DITYR residues can increase AOPP production. The lower DITYR in chronic patients could be the result of failure to detect them due to excessive AOPP production. In the SZ group, there was also a correlation between psychopathological symptoms and DITYR levels: positive ($R = 0.29$; $p < 0.05$), general ($R = 0.31$; $p < 0.05$), and total psychopathology ($R = 0.31$; $p < 0.05$). It should be pointed out that multivariable analysis confirmed the relationship between DITYR and negative symptoms only.

Despite the noticed relationship between KYN and age in the SZ group, the HC and SZ group did not differ in age but had different KYN and NFK concentrations. We also found the correlation between positive ($R = 0.43$; $p < 0.05$), general ($R = 0.39$ $p < 0.05$), all symptoms ($R = 0.38$; $p < 0.05$), and KYN. Our multivariable regression analysis suggests the interaction between KYN and NFK in the induction of negative symptoms and the interplay between FRAP and KYN in the severity of positive symptoms. Kynurenine metabolites can cross the blood–brain barrier. However, the relevance of metabolites within peripheral circulation is not fully understood, but the substances are involved in the inflammatory response of CNS (48).

The higher NO concentration was seen only in chronic compared to first-episode patients. The obtained results could be affected by antipsychotic treatment, confirmed by a meta-analysis showing that only patients under treatment have higher levels of plasma/serum nitric oxide than controls (49). Nitric oxide possesses properties of both pro- and antioxidants. It can also stimulate the peroxidation of lipids and mediate antioxidant reactions in cellular membranes (49). In our study, NO concentration was related to age, except in the SZ group only, which suggests that this relationship is spurious ($R = -0.35$; $p < 0.05$).

Studies on OS in SZ are still at the beginning, especially regarding state-specific factors (specific to acute phases, first episode, or early stages), and the psychiatric population results are often contradictory. Inconsistent findings might be the result of different types of collected samples (serum, whole blood, mRNA, brain tissue), method of measurement, stages of illness, patients' treatment, comorbidity, and lifestyle factors (including diet and physical activity) (7, 12, 42). OS can lead to macromolecule oxidation, disruption of cell behavior, and conditions (50). Studies suggest that peripheral OS operates in a synchronized way with central response (51).

Further studies are needed to clearly define the role of OS in individuals with psychosis regarding state-specific factors (to acute phases, first episode, or early stages) and which of them are more durable and may be a trait of the psychotic condition. Stratification of patients based on oxidative-related parameters, according to precision medicine, is a promising approach to increasing SZ therapy's effectiveness/to facilitating a new approach based on precision medicine and implementing biological/biochemical-tailored treatment to restoring redox balance (11, 52).

LIMITATIONS

The study has limitations that should be acknowledged. The assessment included only peripheral blood parameters. Further studies should concentrate on analyzing them together with neuroimaging assessment to detect the relationship between

central and peripheral oxidative status. The anthropometric values (BMI) were different between examined groups, which can strongly affect oxidative parameters (53). Nevertheless, in our analysis, BMI not affect most of the assessed biomarkers. The individuals from patients' groups had not taken the same type of antipsychotic drug. To control for patient heterogeneity, we performed analysis according to the illness stage and adjusted obtained results of potential cofounders. However, the treatment and drug interaction with intra-individual variability could change pro/antioxidative response in many different manners.

Another limitation is the lack of correlation between OS and critical biological factors specific for the SZ process, progression, or stage (54–56). Determining the relationship between them and the OS biomarkers is an urgent need. In clinical practice, based on psychopathological symptoms, severity assessment on the clinical interview is treated as a gold standard in SZ diagnosis. Some authors, based on the preclinical studies, suggest some of the SZ biomarkers. Up to date, the information and results of these studies are limited. This point needs further investigation.

It is well-known that antioxidants are very labile molecules. Only in the presence of damage initiated, for example, at the initial or terminal stage, can their activity be linked to specific directions of OS shifts. However, we did not assess these stages. In further exploration, more attention should be paid to another critical indicator of OS that we omitted (i.e., lipid peroxidation or thiobarbituric acid active products). Measurement of them would provide important information about the levels of the processes being studied.

CONCLUSIONS

The study results confirm differences in serum levels of OS biomarkers between patients suffering from SZ and healthy individuals. In patient groups, the levels of oxidation products and antioxidant depend on the stage of illness (first-episode patients vs. chronic SZ). The pro/antioxidant status could be considered a predictor of SZ (CAT, GPX, TAC, FRAP, AGEs, and AOPP) or/and factor affecting patients' symptom severity (CAT, FRAP, KYN, NFK, DITYR). Monitoring of peripheral blood level oxidative biomarkers is a promising method in the SZ approach. However, critical analysis including more confounding factors is required to confirm obtained results.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Lublin, Poland. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DJ, MD, and HK-J: conceptualization. JR: data curation and formal analysis. DJ, MD, NW, AZ, and MM: investigation and methodology. HK-J: project administration and supervision. DJ, JR, and HK-J: writing—original draft. DJ, JR, and HK-J: writing—review and editing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.728986/full#supplementary-material

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Resting-State fMRI to Identify the Brain Correlates of Treatment Response to Medications in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Lessons From the CUNMET Study

Victor Pereira-Sanchez[1,2], Alexandre R. Franco[3,4,5], Pilar de Castro-Manglano[6], Maria A. Fernandez-Seara[7], Maria Vallejo-Valdivielso[2], Azucena Díez-Suárez[2], Miguel Fernandez-Martinez[7], M. Reyes Garcia de Eulate[7], Michael Milham[3,4], Cesar A. Soutullo[8] and Francisco X. Castellanos[1,4]*

[1] Department of Child and Adolescent Psychiatry, New York University (NYU) Grossman School of Medicine, New York, NY, United States, [2] Departamento de Psiquiatría y Psicología Clínica, Clínica Universidad de Navarra, Pamplona, Spain, [3] Center for the Developing Brain, Child Mind Institute, New York, NY, United States, [4] Center for Biomedical Imaging and Neuromodulation, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, United States, [5] Department of Psychiatry, New York University Grossman School of Medicine, New York, NY, United States, [6] Departamento de Psiquiatría y Psicología Clínica, Clínica Universidad de Navarra, Madrid, Spain, [7] Departamento de Radiología, Clínica Universidad de Navarra, Pamplona, Spain, [8] Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, United States

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***Correspondence:**
Victor Pereira-Sanchez
vpereira@alumni.unav.es

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Neuroimaging research seeks to identify biomarkers to improve the diagnosis, prognosis, and treatment of attention-deficit/hyperactivity disorder (ADHD), although clinical translation of findings remains distant. Resting-state functional magnetic resonance imaging (R-fMRI) is increasingly being used to characterize functional connectivity in the brain. Despite mixed results to date and multiple methodological challenges, dominant hypotheses implicate hyperconnectivity across brain networks in patients with ADHD, which could be the target of pharmacological treatments. We describe the experience and results of the Clínica Universidad de Navarra (Spain) Metilfenidato (CUNMET) pilot study. CUNMET tested the feasibility of identifying R-fMRI markers of clinical response in children with ADHD undergoing naturalistical pharmacological treatments. We analyzed cross-sectional data from 56 patients with ADHD (18 treated with methylphenidate, 18 treated with lisdexamfetamine, and 20 treatment-naive patients). Standard preprocessing and statistical analyses with attention to control for head motion and correction for multiple comparisons were performed. The only results that survived correction were noted in contrasts of children who responded clinically to lisdexamfetamine after long-term treatment vs. treatment-naive patients. In these children, we observed stronger negative correlations (anticorrelations) across nodes in six brain networks, which is consistent with higher across-network functional segregation in patients treated with lisdexamfetamine, i.e., less inter-network interference than in treatment-naive patients.

We also note the lessons learned, which could help those pursuing clinically relevant multidisciplinary research in ADHD en route to eventual personalized medicine. To advance reproducible open science, our report is accompanied with links providing access to our data and analytic scripts.

Keywords: attention-deficit/hyperactivity disorder (ADHD), resting state, fMRI, stimulants, functional connectivity, reproducibility, feasibility, open science

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting 5–10% of children and adolescents (1) and persisting into adulthood in about half of cases (2). Pharmacological treatments address the core symptoms of ADHD; long-term benefits in functional outcomes, though questioned, are documented (3). However, predicting which medication will show the best efficacy and tolerability for any given individual is not feasible. Thus, current medication management consists of trial and error titration (4).

Neuroimaging research in mental disorders, including ADHD, aims to elucidate the pathophysiology and neuropsychopharmacology of these conditions and their treatments in a quest for personalized medicine (5). Yet, despite a growing literature and increasing methodological sophistication, neuroimaging is still unable to inform "bedside" clinical decisions (6).

Resting-state functional magnetic resonance imaging (R-fMRI) has become a mainstream brain imaging technique. It highlights the statistical properties of spontaneous fluctuations in blood oxygen level dependent (BOLD) signals to infer "functional connectivity" among spatially distant areas which represent putative brain functional networks (7).

R-fMRI research in ADHD has identified widespread brain circuitry differences between patients and typically-developing control individuals (TDCs) and their possible normalization with medications; however, results have been inconsistent across studies (8, 9). Challenges to the validity and reproducibility of neuroimaging findings include insufficient control of in-scanner head motion, excessive false positive rates from inadequate control for multiple statistical comparisons, small sample size, lack of thorough reporting of methods and results and lack of open sharing of study data (10). Furthermore, research in neuroimaging and medication in ADHD has frequently used experimental treatment designs which are less relevant to finding the brain correlates of real-life treatment patterns (9).

THE CUNMET STUDY

The "Clínica Universidad de Navarra Metilfenidato" (CUNMET) study was designed as a proof-of-concept study in partial fulfillment of the requirements for a Ph.D. [see also (6, 9)]. The study was based at the child and adolescent psychiatry outpatient service at Clínica Universidad de Navarra, a tertiary university hospital in the north of Spain.

CUNMET's overarching objective was to evaluate the feasibility of conducting a naturalistic neuroimaging study with a clinical sample of children and adolescents with ADHD, with the aim of exploring putative R-fMRI correlates of differential symptomatic response to stimulant medications. Specific objectives were: (1) To obtain phenotypic (i.e., demographic, clinical), neuropsychological, and R-fMRI data from a cross-sectional sample of children and adolescents with ADHD with differential pharmacological responses to stimulants and a longitudinal subsample of treatment-naive patients evaluated pre- and post-treatment; (2) to conduct rigorous and transparent methods to minimize the effects of imaging artifacts, in particular, head motion and false-positive rates, in the exploration of neural correlates of treatment response; (3) to explore reliable R-fMRI differences in whole-brain network correlations across treatment-response groups and treatment-naive patients, as well as the modulation of these correlations after treatment with methylphenidate in treatment-naive patients; (4) to transparently describe the challenges encountered and the limitations of the study; and (5) to contribute to open-science efforts through best practices in reporting and data sharing.

Detailed information on methods is available in **Supplementary Material**. Our study included boys and girls aged 7–17 years with a diagnosis of ADHD based on DSM-5 criteria (11), falling into one of four groups: (1) patients who responded well to an extended-release formulation of methylphenidate (MPH) as the first-line treatment and were taking MPH; (2) patients who had not responded to MPH and responded to extended-release lisdexamfetamine (LDX) as second-line treatment and were taking LDX; (3) patients who had not responded to either MPH or LDX and responded to extended-release guanfacine (GFC) as the third treatment; and (4) patients who had not started medications when recruited (NAIVE). A subset of patients in the NAIVE group were invited into a longitudinal prospective pre- vs. post-treatment analysis after undergoing treatment with MPH. Clinical response was defined by either a reduction of at least 30% in parent-reported ADHD rating scale (12) or substantial improvement in Clinical Global Impression (13) after at least 3 months of the corresponding treatment. Main exclusion criteria were diagnosis of comorbid neuropsychiatric disorders and/or use of medication for symptoms of such disorders (with the exception of oppositional defiant disorder, headaches, and insomnia) and contraindications for MRI. The study had the corresponding ethical approvals, and participation was voluntary and required a written informed consent from the parents and assent from the patients.

After consent and assent were obtained along with clinical assessments that confirmed inclusion/exclusion criteria were met, R-fMRI data were acquired with a Siemens MAGNETOM 3.0 Tesla Skyra (Siemens; Erlangen, Germany) with a Siemens 32-channel head coil. Each scan session lasted around 20 min and consisted of a R-fMRI echo planar imaging BOLD sequence (total duration = 8.41 min, eyes open, TR = 2,020 ms, TE = 30 ms, 36 slices, voxel size = 3 × 3 × 3.5 mm, Field of View = 192 mm, flip angle = 80°, 250 volumes, matrix = 64 × 64), a perfusion-weighted ASL sequence (not further described here) and an anatomical T1-weighted magnetization-prepared rapid gradient-echo sequence (total duration = 5:12 min, TR = 2,300 ms, TE = 2.96 ms, number of blocks = 1, voxel size = 1.0 × 1.0 × 1.1 mm, field of view = 256 mm, flip angle = 9°, slices per block = 176, imaging matrix = 256 × 256).

Briefly, preprocessing and quality control of images used the Configurable Pipeline for Analysis of Connectomes (C-PAC, v.1.6.2a) (14) which included skullstripping, segmentation, spatial normalization of anatomical images, slice timing correction, functional-to-anatomical registration, spatial normalization, nuisance signal correction (with CompCor (15), ICA-AROMA (16) and scrubbing of volumes with more than 0.3 mm of framewise displacement, independent component analysis denoising, and median angle correction), band-pass filtering (0.01–0.1 Hz), spatial smoothing [full width at half maximum (FWHM) Gaussian kernel of 6 mm], and Z-scoring of functional image time series.

Analyses were conducted at two levels of spatial resolution. Dual regression of the Smith et al. 10-network parcellation (medial visual, occipital pole visual, lateral visual, default mode, cerebellum, sensorimotor, auditory, executive control, and right and left frontoparietal) (17) were used to extract time series of preprocessed data; we also used regions-of-interest from the Schaefer et al. 200-node parcellation (18) which overlap with the Yeo et al. 17-network parcellation (visual A&B, somatomotor A&B, temporal-parietal, dorsal attention A&B, salience-ventral attention A&B, frontoparietal control A-C, default mode A-C, limbic A&B) (19). Connectivity graphs were calculated for each individual and later used for group statistical analyses.

Descriptive and comparative statistics of relevant phenotypic data consisted of across-group tests, conducted with STATA v.12.0 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP., https://www.stata.com). Group comparisons of neuroimaging graphs were performed using the Network-Based Statistic (NBS) Toolbox (https://sites.google.com/site/bctnet/comparison/nbs) (20). Multiple comparisons were corrected through False Discovery Rate (FDR). Statistical significance was set at $p < 0.05$, corrected for multiple comparisons. The contrasts were:

(a) Stimulant-treated vs. untreated (merged MPH + LDX groups vs. naive).
(b) MPH-treated vs. untreated (MPH vs. naive).
(c) LDX-treated vs. untreated (LDX vs. naive).
(d) MPH-treated vs. LDX-treated (MPH vs. naive).

We recruited a sample of 68 participants, who provided a total of 76 scans (21 MPH patients, 21 LDX, 3 GFC, and 23 naive; 8 Treatment-naive patients were scanned pre- and post-MPH treatment). This distribution deviated from the original plan ($N = 80$; 20/group): first, GFC participants were difficult to recruit, due to the relative paucity of non-responders to stimulants in our clinic and their higher likelihood of presenting exclusion criteria; second, we were only able to obtain a post-treatment scan and evaluation in eight naive patients prior to the termination of the study at the end of the principal investigator's residency. Due to insufficient recruitment, the three GFC participants were excluded from analyses. Similarly, the eight post-treatment scans from the subgroup of naive participants who were assessed pre- and post-MPH were also excluded; instead, resources were shifted to slightly increase the samples in the MPH, LDX, and naive groups. Difficulties encountered in the recruitment process, in general, were: (a) logistical, such as scheduling issues for MRI scans due to limited scanner availability and scheduling difficulties for patients and families, many of whom lived far from the hospital; (b) constraints related to the research design, such as exclusion criteria and the challenges of complying with complex procedures on the day of scanning.

In addition, 9 participants were excluded from analyses after image quality control (7 due to excessive head motion, 1 due to a marked acquisition artifact, and 1 due to large anatomical anomalies). This led to a final sample of 56 retained participants, relatively evenly distributed across the MPH, LDX, and naive groups.

Table 1 shows the key sociodemographic and clinical characteristics of the analyzed sample, and two quality control metrics: head motion data and amount of imaging data removed per group.

Across-group comparisons of functional connectivity between pairs of the ten brain networks extracted through dual regression based on Smith et al. (17) yielded no statistically significant results after adjustment for multiple statistical comparisons.

Across-group comparisons of functional connectivity between pairs of the 200 brain nodes extracted based on Schaefer et al. (18) detected 30 pairs of functional connectivity which exceeded the 5% FDR threshold in at least one of the 859 simulations. All of these occurred exclusively in the contrast between LDX and NAIVE groups. Assuming that many of these nominally significant results likely represent false positives, we focus on the eight correlations that emerged in at least 5% of the simulations. **Figure 1** displays the 12 brain nodes involved in these eight pairs. They represented 10 distinct brain regions, identified with their corresponding Yeo et al. (19) networks. The nodes were predominantly located in the right hemisphere and mainly involved the frontoparietal control, attention, and default mode networks, although the somatomotor and visual networks were also represented. The box plots of average functional connectivity show that the LDX group had lower average functional connectivity in each pair than the NAIVE group; specifically, while the average functional connectivity values in these eight pairs in the NAIVE group were around zero, they were negative (i.e., anticorrelated) in the LDX group. Detailed information on results is available in **Supplementary Material**.

TABLE 1 | CUNMET included sample - key phenotypic characteristics.

Group	MPH	LDX	Naive	Total	F/X^2	*p*
n included (*n* excluded)	18 (3)	18 (3)	20 (3)	56 (9)		
Age (SD) in years	14.4 (2.9)	13.3 (2.9)	12.3 (2.3)	13.3 (2.8)	2.87	0.06
Range	8.2–17.97	9.0–17.93	7.4–16.4	7.4–17.97		
Sex: boys/girls (*n*)	8/10	13/5	14/6	35/21	3.7	0.16
ADHD presentation: Combined/inattentive	10/8	12/6	10/10	32/24	1.1	0.58
Handedness^X ($n = 42$): Right/left handed	9/3	13/0	14/3	36/6	3.45	0.18
Comorbid ODD, *n* (%)	1 (5.6)	3 (16.7)	1 (5)	5 (8.9)	1.95	0.38
Median treatment duration in months	25	22.5	N/A	23.5	0.315	0.57
Range	3–120	6–59		3–120		
Mean framewise displacement pre-scrubbing in mm	0.089 (0.059)	0.08 (0.042)	0.09 (0.057)	0.087 (0.053)	0.2	0.82
%Retained BOLD volumes after scrubbing /total 250 (SD)	89.7% (10.5)	89.7% (10.5)	86.4% (13.8)	88.5% (11.7)	0.51	0.60

Table of key phenotypic (sociodemographic, clinical) and imaging quality control characteristics across groups, in the sample of participants included in the imaging analyses. Results are means (with standard deviations) except for absolute numbers (n), ranges and proportions (%). Statistical differences among groups are given with their corresponding statistical test value [ANOVA F for comparison of means, Pearson's Chi-square (X^2) for comparison of proportions and Kruskal-Wallis's Chi-square for comparison of medians] and p-values. P-values are rounded to two decimals. For continuous variables, we conducted descriptive and comparative analyses of means and ranks with both ANOVA and Kruskal-Wallis tests, as the groups were small and heterogeneous. As results were similar, ANOVA results are presented for simplicity. Framewise displacement (FD) measures head motion. Intellectual Quotients (IQ) reported here are for the full-scale.

A full table with all the relevant recorded data can be found on ***Supplementary Material****.*

^{X}Variables with missing data.

MPH, group 1, on methylphenidate; LDX, group 2, on lisdexamfetamine; ADHD, Attention-deficit/hyperactivity disorder; 15q, Edinburgh Handedness Questionnaire, 15-item version; ADHD-RS.es, ADHD rating scale, Spanish version; ODD, oppositional-defiant disorder; N/A, not applicable; SD, standard deviation.

DISCUSSION

In this exploratory study primarily designed to assess feasibility, within the constraints of a training program and with limited resources, we confirmed that it is feasible to conduct a complex brain imaging effort within a naturalistic clinical practice setting, albeit with multiple limitations. Conducting this study was an explicit learning process. The research team was aware of the main methodological threats of R-fMRI research: small sample sizes, poor data quality due to signal artifacts [in particular, head motion (21), which is greater in children with ADHD], high false positive rates [reflecting insufficiently stringent correction for multiple comparisons (22)], excessive analytic flexibility (23), and lack of replicability of published research due to deficiencies in reporting (24). As the field has started to confront these problems, best practices in study reporting and transparency have been developed (25). In response, publicly-funded multicenter endeavors [such as ENIGMA (26) and ABCD (27)] are creating large sample sizes. In this admittedly small pilot study, we opted for stringent quality control (especially in terms of head motion corrections and exclusions), conservative statistical analyses, and transparent reporting.

Given the limitations of this study, all of our results have to be considered preliminary. In particular, we cannot be confident regarding the null results in the comparisons involving the MPH group. The greater similarity in functional connectivity patterns between the MPH group and the NAIVE group than the LDX group is surprising, as the neuropharmacological and clinical effects of MPH and LDX, both stimulants, are similar. We note a lack of R-fMRI research comparing methylphenidate vs. amphetamines (9) so cannot comment further.

Our preliminary results showed strengthened negative correlations (anticorrelations) across pairs of brain regions corresponding to different networks in children with ADHD who responded clinically to LDX after long-term treatment, when contrasted to treatment-naive patients. This finding is consistent with higher across-network functional segregation in patients treated with LDX, suggesting that distinct brain networks were operating with less interference from other networks than in treatment-naive patients. Such an increase in across-network functional segregation could be a neural correlate of positive clinical response to LDX in patients with ADHD. Due to the cross-sectional design and the lack of a healthy comparison sample, we cannot ascertain whether these differences between groups reflected pre-post medication changes, were markers of medication intake, mediators between medication intake and clinical response, or rather adaptive changes after clinical response.

The overall tentative findings, involving diverse combinations of nodes from six different networks, are compatible with systems neuroscience approaches that highlight the role of functional network segregation in health and disease. In these models,

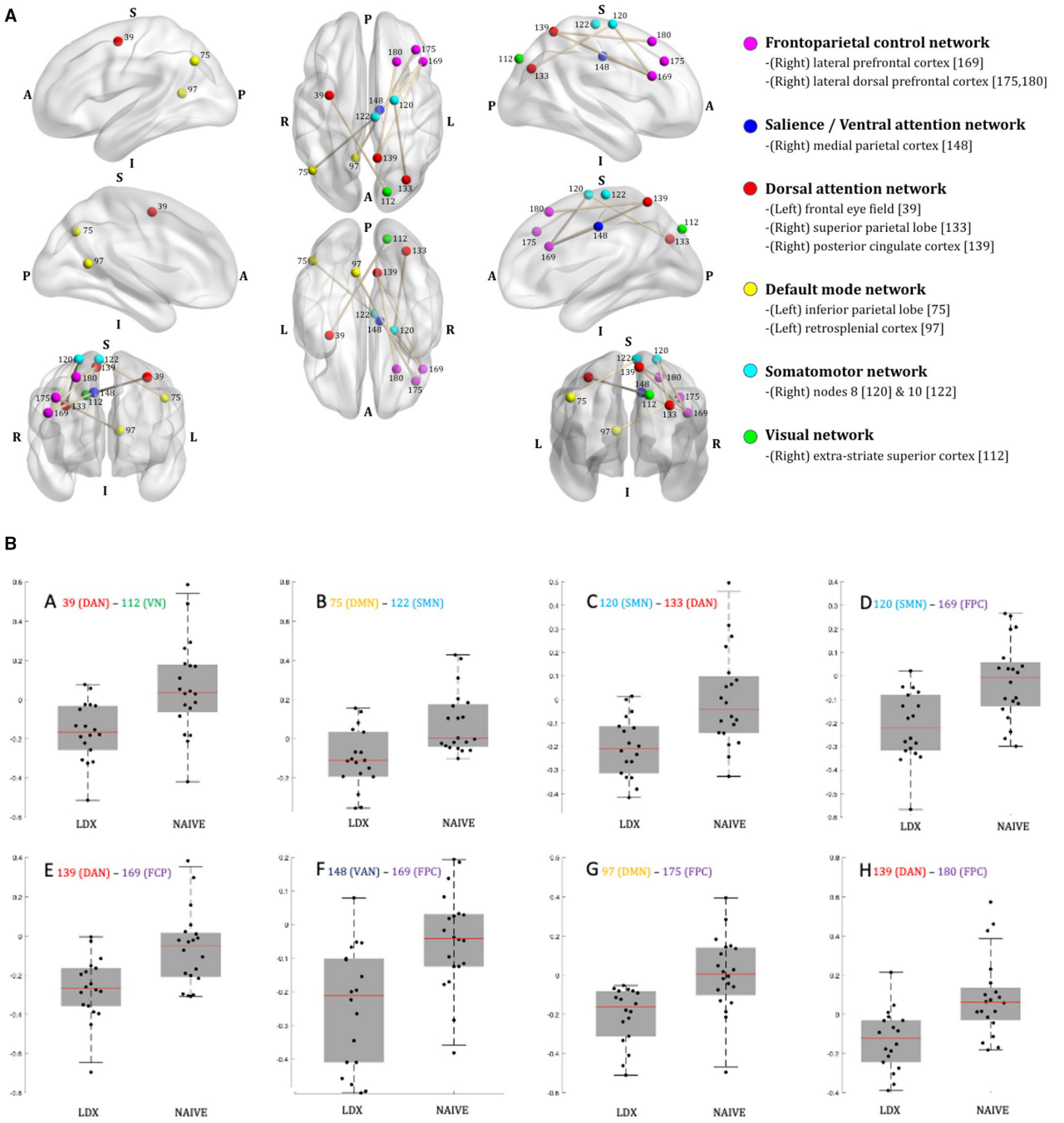

FIGURE 1 | CUNMET neuroimaging results. **(A)** Projections of the hubs and edges of the pairs of brain nodes [numbered per the Schaefer et al. (18) atlas] that differed significantly on at least 5% of simulations between children treated with lisdexamfetamine vs. medication-naive patients overlaid on semi-transparent brains. The correspondence between Schaefer's numbers and node names, as well as between the colors of the edges (nodes) and the brain network they belong to [per Yeo et al. (19) brain atlas] are indicated to the right. A, anterior; P, posterior; L, left; R, right; S, superior; I, inferior. For correspondence between the Schaefer nodes and Montreal Neurological Institute brain coordinates see **Supplementary Material**. Graphs generated with BrainNet Viewer software (https://journals.plos.org/plosone/article?id = 10.1371/journal.pone.0068910). **(B)** Box plots of between-group differences in average functional connectivity across the eight pairs of brain nodes [numbered per Schaefer et al. (18)]. LDX = study group 2, patients treated with lisdexamfetamine; naive = study group 4, treatment naive-patients. MPH group (group 1) is not presented here as it did not yield reliable statistically-significant differences in comparisons with LDX and naive, although its average functional connectivities were similar to the connectivities in the naive group. The corresponding brain networks for each node [as per Yeo et al. (19) brain atlas] are indicated by the color codes provided in the right side of **(A)**. DAN (red) = Dorsal attention network; VN (green) = Visual network; DMN (yellow) = Default mode network; SMN (light blue) = Somatomotor network; FCP (purple-fuchsia) = Frontoparietal control network; VAN (dark blue) = Salience/Ventral attention network. Graphs generated with MATLAB.

increasing segregation reflects efficient network functioning and excessive integration can be a correlate of brain dysfunction (28). If excessive cross-network functional integration were confirmed to be a consistent feature of ADHD and related neuropsychiatric disorders, it could represent a therapeutic target of medications.

LESSONS LEARNED

In terms of study design, the naturalistic approach, further constrained by difficulties encountered during its execution, has a limited ability to differentiate true pharmacological effects from other potential confounders, and in this sense is inferior to randomized controlled trials (9). However, this design is better suited for examining "real world" treatment responses. In addition, our cross-sectional analyses did not allow us to confirm whether across-group differences reflected true medication-induced changes. Finally, the lack of TDC individuals prevented us from formulating any tentative conclusions about the potential "normalizing" effect of medications reported in some previous studies (9) (i.e., disappearance of neuroimaging statistical differences between patients with ADHD and TDC when patients are on treatment). Nevertheless, as noted elsewhere, claims of "normalization" should be considered with caution (9).

Another major limitation was the limited sample size, even if it was in line with that of most previous studies (9). Small sizes have been endemic in neuroimaging research of ADHD (6, 8), and medication studies present further logistical complications for recruitment and retention of participants. This is partially offset by the within-subject analyses which increase statistical power relative to cross-sectional designs (29).

We adopted a naturalistic design with relatively broad inclusion criteria reflecting the patients with ADHD seen in our clinic. Thus, we recruited a sample encompassing a wide age range (7–17 years), both sexes, right and left-handed individuals, and allowed certain comorbidities (learning disabilities, oppositional defiant disorder, anxiety and mood symptoms and sub-diagnostic threshold autistic traits). This approach contrasts with previous studies which had narrower age ranges and/or excluded females (9). The down-side of our more inclusive approach is greater heterogeneity, which also decreases statistical power.

Other study limitations included inconsistencies in demographic and clinical data collected, the specific naturalistic medication scheme (which reflected clinical practice in one center), lack of mock-scanning training sessions, lack of real time monitoring of wakefulness and head motion, and flexibility of analytic pipelines (outlined in **Supplementary Material**) due to the exploratory nature of this study and PhD candidate training purposes.

The analytic approach was robust to limit the effects of head motion and false-positive rates, two key issues in neuroimaging research of ADHD (9), and the whole-brain network-based analyses afforded a big-picture perspective of brain functioning that transcends the study of isolated regions or networks. The statistically-salient results, along with the statistical uncertainty of their robustness, are transparently reported.

Our experience conducting the CUNMET study, with its successes, shortcomings, and preliminary results may be relevant for the design of future research in this area. We provide specific recommendations in five domains:

1 *Study design:* Design prospective naturalistic studies to assess pre vs. post-treatment changes in medication-naive patients with ADHD, optimally with a comparison group of TDC individuals scanned twice. Account for the potential effects of age/development on treatment responses and its brain correlates (30). Sample sizes of at least 50/group would improve statistical power and reproducibility (29).
2 *Participant assessment and data collection:* Ensure systematic collection of clinical, sociodemographic, and neuropsychological data in naturalistic settings. Use standard clinical assessments in initial visits and follow-ups. Conduct a thorough medication history for each patient.
3 *Image acquisition:* Include training (mock) scanning sessions to habituate participants to the experience. Optimize head immobilization tools. Monitor real-time wakefulness and head motion. Record any incidents during the session. Increase the total duration of BOLD sequence data to at least 25 min (31), by combining movie watching or tasks.
4 *Imaging and statistical analyses:* Conduct thorough quality control soon after obtaining each image. Perform rigorous nuisance and head motion corrections, and include whole-brain metrics. Consistently correct for multiple comparisons. Discuss the rationale and potential limitations of the selected methods.
5 *Transparency and reporting, and open science:* Prospectively register the study protocol, including the data analysis plan, in online platforms such as the Open Science Framework (www.osf.io), and report relevant changes from the initial protocol. Follow the Organization for the Human Brain Mapping - Best Practices in data analysis and sharing in neuroimaging using MRI (OHBM-COBIDAS) (25) to thoroughly report methods and results. Ask prospectively for permission from participants to share their deidentified data with the scientific community. Share deidentified data and full analytic scripts in online repositories.

In conclusion, the CUNMET study constituted a fruitful proof-of-concept of state-of-the-art neuropsychopharmacological research in ADHD. Despite substantial shortcomings, we demonstrated the feasibility of a naturalistic design within the constraints of real-time clinical practice and a training program, and our findings suggest that potential brain correlates of clinical response to lisdexamfetamine in children and adolescents are based in across-network segregation. The lessons learned from CUNMET are offered to inform future research and to encourage prospective investigators to undertake transparent, open-science collaborative efforts. While similar individual small studies will not advance the field on their own, their aggregation may offer frameworks for efficient exploration of designs, methods, and

potential biomarkers (32) in the quest for personalized medicine in ADHD.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: The CUNMET Study team supports open science and is sharing de-identified patient data and analytic scripts to allow other researchers to carry out independent analyses, providing they acknowledge the source of the data and its funding in their reports. Deidentified and defaced brain imaging and phenotypic data from the patients for whom we received permission for sharing are available at INDI (http://fcon_1000.projects.nitrc.org/indi/retro/CUNMET.html). Our analytic codes are available at GitHub (https://github.com/victorpsanchez/cunmetstudy).

ETHICS STATEMENT

The CUNMET study was registered by the Spanish Agency of Drugs and Medical Products on March 27, 2017, with the registration code CUN-MET-2017-01. The statistical group analysis plan was registered at Open Science Framework (https://osf.io/2dfs8) on September 24, 2019, after data collection and pilot preprocessing and before conducting group analysis. The study was ethically reviewed and approved by the Ethics Committee for Medications Research of Navarra (Spain) (Comité de Ética de la Investigación con medicamentos, CEIm de Navarra) on June 21, 2017, with the codes CUNMET-2017-01 EO17/11, which also approved an amended protocol on May 22, 2019. This study was compliant with the research ethics principles of the Declaration of Helsinki (seventh revision, 2013), taking into account the specific principles for research with children and adolescents. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

VP-S led the study design, data collection and analysis, reporting of results, and prepared the manuscript. AF assisted with data analysis, reporting of results, and manuscript preparation. PC-M and CS supervised the study design, data collection, and reporting of results, and reviewed the manuscript. MF-S, MV-V, AD-S, and MG assisted in the study design, data collection and analysis, and reviewed the manuscript. MF-M assisted in the data analysis and reviewed the manuscript. MM assisted in the study design, supervised the data analysis, and reviewed the manuscript. FC supervised the study design, data collection and analysis, reporting of results, and reviewed the manuscript. All authors approved the final version of the manuscript and assumed their responsibility as coauthors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.759696/full#supplementary-material

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REVIEW
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Physiotherapy and Physical Activity as Factors Improving the Psychological State of Patients With Cancer

Ewelina Zyzniewska-Banaszak[1]*, *Jolanta Kucharska-Mazur*[2] and *Aleksandra Mazur*[3]

[1] Department of Rehabilitation Musculoskeletal System, Pomeranian Medical University, Szczecin, Poland, [2] Department of Psychiatry, Pomeranian Medical University, Szczecin, Poland, [3] Department of Social Sciences, Institute of Psychology, University of Gdańsk, Gdańsk, Poland

Physiotherapy in oncology is a process closely related to cancer treatment methods. Rehabilitation is based on physical activity in various forms involving the musculoskeletal system but also affects the emotional state. Physical activity influences physical and psychological well-being of people undergoing oncological treatment, in the course of which the most common psychiatric disorders are depression, substance use disorder, sleep disorders, fatigue syndrome, resulting in worsening of the quality of life. Difficulties in implementing physical exercise in cancer patients pose a challenge to treatment teams.

Keywords: physiotherapy, physical activity, cancer, mental disorders, rehabilitation

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Tadeusz Pienkowski, Medical Centre for Postgraduate Education, Poland

***Correspondence:**
Ewelina Zyzniewska-Banaszak
banaszak@pum.edu.pl

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INTRODUCTION

Physiotherapy in oncology is a process closely related to cancer treatment methods. The main tool for the improvement of people with cancer is physical activity in all possible forms, both in passive and active involvement of the motor system. The term "motor activity," is used in the world information system as "physical activity." It is a component of a healthy lifestyle. Without it, any health strategy, its maintenance and multiplication is impossible, and in case of children, moreover, a proper development. Physical activity is a basic determinant of fitness and physical efficiency, which are also measures of health.

Both in healthy and sick people, physical activity significantly influences the level of physical performance and is an integral component of a healthy lifestyle, therefore it must be included in the strategy of maintaining health, understood not only as the absence of disease, but full physical, mental and social well-being. This fits in with the WHO (1) definition of mental health, according to which it is a state in which a person realizes their abilities and is able to cope with a variety of life situations, can participate in social life and is able to work productively.

We know that physical activity improves not only the somatic state but also the mental state of patients. Epidemiological studies (2) show that people who start exercising or stay active are less likely to develop depression. Paffenbarger et al. observed in male alumni from Harvard College, aged 35–74 years, a reduced risk of being susceptible to depression in those with high physical activity, e.g., >2,500 kcal burned per week (relative risk of depression 0.72) and in those doing moderate physical activity e.g., 1,000–2,000 kcal burned per week (relative risk of depression 0.83), compared to those with low physical activity, considered as energy expenditure below 4.5 MET metabolic equivalent of task (relative risk of depression 1.0) (3).

Farmer et al. in an 8-year follow-up, found a 2-fold increased risk of clinical depression in women with low physical activity. Furthermore, physical activity not only

reduces the risk of illness/relapse, but can also be considered a form of therapy for depression (4). This is supported by Biddle and Mutrie's (5), Stanton and Reaburn (6) review article and Craft et al. meta-analysis (7). Results from 30 studies showed that people who exercise were less depressed than individuals who did not exercise (overall mean effect–0.72). Experimental studies show that both aerobic and resistance exercise are effective in treating depression, and the effect of aerobic training is comparable to psychotherapeutic interventions (5).

The use of various supportive forms of therapy is particularly important in oncology. Cancer treatment methods—conservative, surgical and radiotherapy—are the cause of complications such as scars that limit tissue mobility, contractures, joint mobility disorders, statics disorders, swelling and a number of other complaints related to the course of therapy. These limitations affect functional impairment, reduce quality of life, and consequently the psychological state. Patients experience depression, grief, anger, rage, feelings of inferiority, guilt, and anxiety. At the root of these reactions is severe stress created by the diagnosis of the disease, uncertainty about the prognosis, inadequate social support, poor relationships with medical staff, and the impact of traumatizing life events. Young age, loss of independence, coherence disorders, sense of life threat, physical pain, medical interventions, lack of control over the course of the disease, hospitalizations, changes in physical appearance additionally increase the risk of developing depression in oncology patients and influence its course (8, 9).

The mere suspicion of cancer is a difficult fact for patients to accept. Also the highly stressful process of diagnosis, implementation of treatment and the course of therapy may be the reason for mental disorders. The most frequent mental disorders occurring in the course of cancer treatment are depressive and anxiety disorders, sleep disorders, fatigue syndrome and reduced quality of life. Therefore, it seems significant to diagnose them early in oncological patients and to provide psychological support while taking into account the necessity of comprehensive oncological rehabilitation. Psychophysical aspects of patients' improvement at every stage of oncological treatment should be carried out in cooperation between a psychologist and a physiotherapist, and implementation of broadly defined rehabilitation in patients during chemotherapy, radiotherapy and surgical treatment at all stages of cancer is a standard of treatment management. As already mentioned, a significant role can be played by physical activity already at the stage of cancer prevention and, above all, supporting the process of cancer treatment. The use of movement during rehabilitation supports cured patients in returning to normal functioning.

DIFFICULTIES IN INCORPORATING PHYSICAL ACTIVITY IN PATIENTS WITH CANCER

With numerous counter-indications to the use of physical methods in cancer, physical activity is the recommended form of physiotherapy in various types of cancer, including advanced stages of the diseases (10).

However, it is often difficult to implement and accept systematic physical activity in treated patients. This problem was described by Frawley et al. (11) in patients who underwent surgery for abdominal and pelvic cancers (including colorectal cancer, prostate cancer, and genital cancers) and were not very willing to engage in rehabilitation programs (of 84% people who were qualified to participate in the program, only 24% completed it). On the other hand, those who decided to participate in rehabilitation programs achieved beneficial therapeutic effects assessed in terms of satisfaction with participation in the program, improvement in functional ability and muscle strength, reduction in pelvic floor complaints, and level of physical activity. This group also had reduced levels of anxiety and depression and improved quality of life ($p < 0.05$).

In general, poor physical health, depressive symptoms, and lower health-related quality of life (HRQL) are associated with decreased physical activity. It is sometimes difficult to determine whether poor general health causes aversion to physical activity or whether lack of physical activity is the cause of poor general health (12).

Among the reasons for difficulty in engaging in physical activity, we can mention poor well-being associated with side effects of cancer treatment and cancer-related fatigue (CRF) syndrome. CRF, defined as the inability to exert both physical and intellectual effort, has a multifactorial etiology and considerable individual variability. It differs from typical fatigue in its degree of severity. It is described as weakness and lack of energy, impaired attention, causes difficulty in performing even a small physical effort. It is usually accompanied by apathy, which is characterized by an inability to engage in mental activity and a rapidly occurring feeling of fatigue and discouragement. Unlike typical fatigue, it does not subside with rest and sleep. Despite some similarities to depression, it is experienced as a separate condition, causing a drop in mood. It persists during treatment, but in some cases also after treatment has ended. Although no gold standard treatment is currently available for this syndrome, randomized controlled trials have shown beneficial effects of physical activity compared with control in reducing fatigue, with a mean effect size of −0.27 (13, 14).

Although physiotherapy has a documented positive effect on both the somatic and psychological recovery of people treated for cancer (15, 16) difficulties with exercise tolerance, including on the cardiovascular side, must be anticipated.

Mikkelsen et al. (17) describe that despite positive perceptions of physical activity among older cancer patients, there were problems with maintaining physical activity during cancer treatment. Factors related to cancer and aging were identified as barriers, with overwhelming feelings of fatigue being the most difficult to overcome. Improved overall physical and mental well-being, a set rhythm of activities (e.g., exercise and group supervision), and social support were identified as motivators and facilitators of activity. Preferences for forms of physical activity varied, but familiar activities increased motivation. Exercise programs for patients with cancer must be tailored to each patient's limitations, needs, and personal resources (18).

A similar study by Frikkel et al. (19) noted that weakness due to cancer therapy was the most commonly reported barrier to physical activity among both physically active and inactive patients. They examined 141 of 440 eligible patients (32.0%) with various oncologic diagnoses. The most common barriers to physical activity cited by patients were weakness due to cancer therapy (76.6% of individuals), fatigue/insomnia (71.6%), and functional impairment due to cancer therapy-related fatigue as measured by the Functional Assessment of Cancer Therapy Fatigue (FACT-F) questionnaire (70.2%). After statistical analysis, fatigue and clinically significant depression were found to be negative predictors of exercise motivation. Patients who were physically active prior to their illness and those who were interested in exercise and who believed that exercise would improve their quality of life were more motivated to exercise. Motivated patients were 5.6 times more likely to be physically active ($p < 0.001$).

It is worth noticing that the mental state is closely related to the motivation of patients to engage in therapy, including physiotherapeutic activities. Experiencing the fact of a potentially life-threatening disease may become the cause of adaptation disorders of a depressive-anxiety type. Insomnia, anxiety, fatigue caused by cancer are risk factors for depression, but on the other hand they may already be symptoms of depression. A meta-analysis of 27 studies on sleep disorders in women with breast cancer indicates that the frequency of these disorders (insomnia, problems falling asleep and waking up during the night) showed a pooled estimate of 0.40 [95% confidence interval (CI) = [0.29–0.52], $I^2 = 100\%$, $p < 0.00001$] and ranged from 0.14 (95% CI = [0.04–0.24]) to 0.93 (95% CI = [0.91–0.95]). Pain, hot flashes, non-Caucasian race and menopausal period, especially depressive symptoms and fatigue, were statistically significantly associated with the occurrence of sleep disorders (20).

Motivating to be active during and after cancer treatment is an interdisciplinary task for both medical staff and patients' families. Non-medical predictors such as the location of the rehabilitation center, experiences with previous physical activity, and the level of difficulty of the applied physical tasks are also mobilizing factors. These factors should be considered when developing and implementing exercise interventions (21, 22).

BENEFITS OF PHYSICAL ACTIVITY ON THE MENTAL HEALTH OF ONCOLOGY PATIENTS

Planned and deliberate physical activity affects psychological well-being because it is inherently oriented toward health and high quality of life (23).

In particular, physical activity, understood as any kind of body movement induced by working muscles and causing an energy expenditure exceeding the resting energy level, plays a significant role in primary prevention and is a complement to therapy based on established and traditional methods of treating depressive disorders. In cancer, prevention and effective treatment of depression can significantly affect the prognosis of the underlying disease (24).

The most common side effects of oncological treatment are disorders of the locomotor system (reduced joint mobility, paresis and muscle paralysis), reduced efficiency of the circulatory system, lymphedema, reduced efficiency of the respiratory system, e.g., due to impaired lung ventilation. The range of physiotherapeutic actions in such cases can be preventive, curative or palliative. These activities include preventing complications and functional consequences of treatment, alleviating symptoms of terminal illness and improving quality of life. Physical activity can potentially counteract a number of side effects of chemotherapy or hormonal therapy, such as fatigue syndrome, weight gain, muscle atrophy, hot flashes, nausea, or increased susceptibility to infection.

We know that physical activity can be therapeutic for individuals with severe mental illness who generally have sedentary lifestyles and experience numerous lifestyle-related medical complications. On a physiological level, regular exercise can potentially increase levels of serotonin, brain-derived neurotrophic factor (BDNF), and endothelial growth factor (VEGF) (25).

Appropriately selected regular physical activity can be a form of prevention of depressive disorders. It should be treated as a technique supplementing pharmacological and psychotherapeutic treatment of depressive disorders, including those occurring in the course of cancer. This is the opinion of the European Psychiatric Association supported by the International Organization of Physical Therapists in Mental Health (IOPTMH) concerning physical activity as a method of treating serious mental illnesses (26).

On a psychological level, physical training can improve mood, self-esteem, and reduce anxiety and pain in patients. The relationship between improvements in self-reported physical status and improvements in overall self-esteem, depression, and anxiety confirms the role of the physical concept of self in the recovery of psychiatric patients with depression and anxiety and other syndromes (26–33). In depressed adults, compared to control group, sensitivity analyses revealed a moderate to large effect in favor of endurance exercise [SMD: −0.79 (90% CI: −1.10, −0.48); $p < 0.00001$, $I^2 = 84\%$] and a large effect size in favor of neuromuscular exercise [SMD: −1.14 (90 CI: −1.50, −0.78); $p < 0.00001$, $I^2 = 80\%$] (33).

When recommending physical activity to people suffering from depression, it is essential to consider that inadequate motivation may activate feelings of guilt, suicidal thoughts and behaviors. Therefore, both as a form of primary prevention and as a method complementary to pharmacotherapy and psychotherapy, it should be tailored to the individual capabilities and health status of the trainees in terms of intensity, duration, and frequency (24).

Despite ongoing research, there are no clear recommendations for the use of different forms of physiotherapy and physical activity in different types of cancer.

Physical treatments (massage, electrotherapy, hydrotherapy, and others) in oncology patients are one of the most controversial topics in rehabilitation planning. Cancer is cited as a counter-indication to their use. The development of imaging techniques

puts this issue in a new light. Based on the evidence, most articles (34) report beneficial effects of physiotherapy in oncology patients, and only a few list it as harmful. Of course, each patient requires individual assessment, but if we exclude the possibility of relapse and metastasis then most physiotherapy interventions can be used safely.

The relationship between physical activity, psychological well-being and better cancer treatment is very clear. For example, among the recommended non-pharmacological treatments for depression in breast cancer patients, yoga with meditation is mentioned alongside psychotherapy as reducing depressive symptoms in these patients. However, more research is needed to determine the magnitude of this effect, depending on the severity of depression and the presence of co-existing diseases (35).

Grégoire et al. (36) compared the effectiveness of interventions based on cognitive behavioral therapy (CBT), self-hypnosis, and yoga in people with breast cancer. Nine months after the intervention, a decrease in anxiety ($p = 0.000$), depression ($p = 0.000$), and fatigue ($p = 0.002$) was observed in the hypnosis group and a decrease in anxiety ($p = 0.024$) in the yoga group, while no change in the studied parameters was found in the CBT group and the control group without any of these interventions. The combination of different physiotherapeutic approaches seems to be an interesting psychological approach to improve the well-being of patients with breast cancer. However, further research is needed to better understand the mechanisms of such interventions and their long-term impact on quality of life.

Exercises based on yoga, can be used as a form of physical activity. The work of the musculoskeletal, circulatory and respiratory organs during practice is evident. Studies (37–39) confirm the positive effects of dynamic yoga (hatha yoga) and related meditation or pranayama practices on health, including the treatment of depression, insomnia, and psychosomatic disorders. Chronic inflammation may fuel declines in physical function leading to frailty and disability.

Although the mechanisms of the observed improvements in mental health are not yet fully understood, yoga techniques can be used as an addition to pharmacotherapy. Given the growing awareness of the impact of lifestyle, stress reduction, and the importance of moderate exercise for health, various relaxation and movement techniques may complement therapies used for most psychiatric disorders. No negative side effects of supplementing standard therapies with exercises based on various forms of yoga have been demonstrated. If yoga dampens or limits both fatigue and inflammation, then regular practice could have substantial health benefits (40).

Another study compared five areas of rehabilitation after breast cancer treatment, including exercise and physical activity, complementary and alternative medicine, yoga, lymphedema management, and psychosocial interventions. Clear evidence of effectiveness was found for exercise and yoga. Exercise interventions improved shoulder mobility, reduced lymphedema, pain, fatigue, and improved quality of life. In contrast, yoga improved quality of life, reduced anxiety, depression, sleep disturbances, fatigue, and gastrointestinal symptoms. The effects of complementary and alternative medicine on nausea, pain, fatigue, anger, and anxiety were demonstrated, but these results should be interpreted with caution due to the poor methodological quality of the studies included in the evaluation (35). Physical activity also improves the overall health of people with cancer, thereby facilitating treatment. This is evidenced by the Leach et al. (41) study, which showed that physical inactivity was associated with more comorbidities following a cancer diagnosis.

According to a meta-analysis by Zeng et al. (42) (10 studies, 838 participants), in cancer patients undergoing chemotherapy, exercise has beneficial effects on physical performance and reduces depression.

One of the problems affecting people undergoing cancer treatment is an aversion to social interaction due to poor psychological well-being. Brand et al. (43) showed that in 129 people with psychiatric disorders, even one session of exercise increased interest in social contact and interaction.

The attractiveness of forms of exercise seems to be a key factor in encouraging people to undertake it. Nordic walking (NW) seems to be an interesting rehabilitation method for women with breast cancer. Sánchez-Lastra et al. (44) conducted a study that analyzed the effects of NW on women with breast cancer. The results of the studies analyzed indicated that NW had a significant and positive effect on a number of breast cancer symptoms, including lymphedema, physical performance, disability, and sense of illness. No side effects were reported.

Another form of exercise worth recommending is Pilates. It is a system of harmonious, slow exercises involving all muscle groups, combined with breathing exercises. Eyigor et al. (45) conducted a study on the effects of Pilates on functional capacity, fatigue, depression, and quality of life in 60 women, ages 18 to 75, with breast cancer. Patients who performed Pilates and home exercises (group 1) and patients who performed only home exercises (group 2) were compared. Subjects were evaluated before and after the rehabilitation program and it was found that in group 1, scores on the 6-minute walk test (6MWT), Beck Depression Inventory (BDI), and quality of life as measured by the EORTC QLQ-C30 and EORTC QLQ BR23 improved ($P < 0.05$). In group 2, there was no significant improvement in the parameters compared with the pre-exercise period. When the two exercise groups were compared, there were significant differences in 6MWT in the pilates exercise group ($p < 0.05$).

Physical activity is not only important in post-treatment rehabilitation, but is also part of the process of cancer therapy and prevention of cancer reoccurrence. In fact, physical activity after treatment for breast cancer, colorectal cancer and prostate cancer has been shown to reduce the risk of recurrence of the disease (46).

Movement is a manifestation of human physical and mental health. Therefore, activating patients only in illness is a bad strategy. The concept of lifelong activity should also include the period after recovery from cancer. Successful cancer treatment and longer life of cured patients require maintenance of physical fitness and quality of life. Physical activity is a good and inexpensive way to address physical and psychological problems. A meta-analysis by Saskija et al. (47) examined the results of 56 studies evaluating the effects of behavioral techniques and exercise on fatigue, depression, anxiety, body image, stress, and quality of life in breast cancer patients during treatment and after

recovery. Statistically significant results were found for the effects of behavioral techniques on fatigue ($p < 0.001$), depression ($p < 0.001$), anxiety ($p < 0.001$), and stress ($p = 0.038$). Statistically significant results were found for the effects of exercise on fatigue ($p = 0.004$), depression ($p = 0.016$), body image ($p = 0.007$), and quality of life ($p = 0.001$).

This is supported by the results of the multicenter, randomized phase III BREX (48) study on the effectiveness of exercise in preventing long-term side effects of complementary treatment and breast cancer reoccurrence in women ($n = 444$). The purpose of the study was to investigate whether regular exercise can reduce the long-term side effects of complementary treatment for breast cancer and improve quality of life. Women aged 35–68 years who had completed complementary chemotherapy or started hormonal therapy for breast cancer within the previous 4 months participated in the study. Physical activity levels were assessed by diary, physical fitness by a 2-km walk test, quality of life by the EORTC QLQC30 and BR-23 questionnaires, fatigue by the FACIT-fatigue scale, and depression by the Beck Depression Inventory (BDI) 13-item scale. Participants who improved their level of physical activity over the 5-year follow-up were more likely to improve their global health score ($p = 0.016$), physical ($p = 0.009$), social ($p = 0.013$), role functioning ($p = 0.005$), and fatigue ($p = 0.002$). Better performance on the 2-km walk test was associated with improvements in global health, physical and role functioning, body image, future outlook, and fatigue ($p = 0.011$, $p < 0.001$, $p = 0.001$, $p = 0.021$, $p = 0.012$, $p = 0.003$).

The results obtained allow us to claim that improving the level of physical activity or physical fitness causes a positive change in the quality of life of patients with breast cancer.

A study conducted by Adams et al. (49, 50) on 63 male testicular cancer survivors (TCS) confirmed the importance of physical training in improving the mental state of patients diagnosed with cancer. These subjects were treated with 12 weeks of high-intensity interval training (HIIT). Participant-reported changes including cancer-related fatigue CRF, depression, anxiety, stress, self-esteem, sleep quality, and health-related quality of life were observed. Status was assessed at the beginning, after the intervention, and at 3-month follow-up. Cardiorespiratory fitness was also examined as a mediator of intervention effects. This effect size is larger than the 0.22–0.30 reported in recent meta-analyses of aerobic exercise and fatigue in cancer survivors (50). Statistical analysis revealed that training significantly reduced CRF ($p = 0.003$), improved self-esteem ($p = 0.029$) and multiple HRQoL domains ($p \leq 0.05$) compared to subjects without such training. Effects on CRF ($p = 0.031$) and vitality ($p = 0.015$) persisted after 3 months of follow-up. Changes in cardiorespiratory fitness mediated improvements in CRF and HRQoL. Improvements in CRF were greater for TCS with inactive lifestyles, lower fitness, higher testosterone, and clinical fatigue at the beginning (49, 50).

Great problem in physiotherapy is the inconsistency of physical parameters applied such as doses of stimuli used, frequency and duration of treatments. In contrast to the various recommendations for physiotherapy interventions in patients with cancer, physical activity is a commonly recommended factor that is not questionable and affects mental and physical well-being. So how can such activity best be tailored to the patient's condition, taking into account their mental health? Future research should incorporate mediator analysis, biomarker testing, use appropriate control and comparison groups, evaluate outcomes using psychometric measures, and prioritize pragmatic trials toward moving into routine practice. Schuch et al. (51) makes a point to consider the relationship between potential biological mediators (e.g., BDNF) and exercise intensity as well as duration when designing exercise interventions. Therefore, developing a typology to match the most appropriate exercise prescription to the "type" of depression would both help advance research and facilitate clinical application. In studying the effectiveness of exercise programs, it is important to remember that the use of alternative exercise methods as a "control" creates a serious difficulty—usually these alternative methods also have antidepressant effects.

Psychometric scales that can accurately reflect changes in mild to moderate levels of depressive symptomatology should be favored in assessing outcomes, as these are likely to be the most common levels of symptom severity in selected samples. Although, when assessing the effects of rehabilitation in everyday physiotherapy practice, it is worth noting that in people with mild to moderate depression, a small change in symptom severity may be difficult to discern without the use of objective methods such as psychometric scales.

Further research will allow specific methods for combining non-pharmacological therapies to promote restoration of lost function during cancer and cancer prevention to be devised (52).

PHYSICAL ACTIVITY IN CANCER PREVENTION

In order to maintain health, systematic activity and appropriate levels of activity are essential. Determining the optimal level of physical activity is completely individualized. It depends on living conditions, gender, health status, fitness level and genetic factors. The optimum of activity to maintain health is different from that to improve health. AF directly or indirectly affects the other components of lifestyle. People who exercise regularly tend to smoke less, consume less alcohol, sleep better and eat better, which reduces the risk of cancer and increases life expectancy (53).

Associations of low physical activity with increased risk of many types of cancer are documented. This is especially true for breast, colorectal, and endometrial cancers. Physical activity also likely contributes to a lower risk of prostate and lung cancer. The largest body of research, however, concerns breast cancer. A meta-analysis of 47 out of 62 studies found that physical activity reduces breast cancer risk by 25–30% in pre- and postmenopausal women (54).

Many scientific societies and organizations from the Center for Disease Control, the National Cancer Institute, and the American Cancer Society (ACS) dedicated to cancer prevention and treatment have reported[1] (55, 56) that physical activity is

[1]Division of Cancer Prevention and Control. Available online at: http://www.cdc.gov (accessed July 31, 2021).

associated with or may be associated with a lower risk of cancer. Whether this is due to physical activity alone is unknown, but it undoubtedly has beneficial effects on other cancer risk factors.

The American Cancer Society has published guidelines (57) on diet and physical activity in cancer prevention in 2020.

Physical activity levels for adults should be 150–300 min of moderate-intensity physical activity per week or 75–150 min of high-intensity physical activity or an equivalent combination; reaching or exceeding the upper limit of 300 min is optimal. Children and adolescents should do at least 1 h each day of moderate to vigorous activity per week.

According to the ACS, it is important for cancer prevention to reduce sedentary lifestyle, lying down and watching TV and other forms of screen entertainment.

Recommended activities include exercise and recreational activities such as walking, dancing, recreational cycling, skating and roller skating, horseback riding, kayaking, yoga, jogging and running, fast cycling, strength training, swimming, skipping, aerobics, and martial arts. Recommended sports include downhill skiing, golf, volleyball, basketball, badminton, tennis, soccer, field hockey, lacrosse, and singles tennis (58). Daily activities and household chores such as mowing the lawn, working around the house and in the garden, and repair work are also mentioned as possible forms of physical activity. This also applies to activities related to professional work[2].

[2]Available online at: https://www.cancer.org/healthy/eat-healthy-get-active/acs-guidelines-nutrition-physical-activity-cancer-prevention/guidelines.html.

SUMMARY

The presented information proves that physical activity is an effective method of supporting cancer treatment and plays an important role in its prevention. Individualization of physiotherapy programmes has a positive effect on patient co-operation. In order to overcome barriers, patients in advanced stages of cancer should be offered programmes that include information, motivational counseling and individualized exercise training. Collaboration with mental health professionals can also have a significant impact on patients' motivation to engage in physical activity.

It is clear that more than one intervention can have a positive effect on a particular symptom and that the effects depend not only on the type of intervention but also on how and when the intervention is delivered. Further research is needed to develop specific guidelines for the use of physical activity according to the somatic and psychological status of patients with cancer.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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CONCEPTUAL ANALYSIS
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Neurocognition and Social Cognition— Possibilities for Diagnosis and Treatment in Ultra-High Risk for Psychosis State

Katarzyna Rek-Owodziń[1], Ernest Tyburski[1], Katarzyna Waszczuk[2], Jerzy Samochowiec[2] and Monika Mak[1]*

[1] Department of Health Psychology, Pomeranian Medical University in Szczecin, Szczecin, Poland, [2] Department of Psychiatry, Pomeranian Medical University in Szczecin, Szczecin, Poland

In recent decades, clinicians have developed the construct of ultra-high risk (UHR) for psychosis to characterize the prodromal phase of psychosis or classify people with weakly expressed psychotic symptoms. In this conceptual analysis, we have gathered up-to-date data about the clinical picture of neurocognition and social cognition in people at UHR for psychosis. We also discuss treatment options. A well-chosen therapeutic approach can help to deal with difficulties and delay or even prevent the development of full-blown psychotic disorders in the UHR group. Despite much evidence supporting the benefits of therapy, early interventions are still not as widely used as they should be. Thus, a better understanding of the UHR state is very important for all healthcare workers.

Keywords: neurocognition, social cognition, ultra-high risk for psychosis, schizophrenia prodrome, schizophrenia spectrum, diagnosis, treatment

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Geert Dom,
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University of Brescia, Italy

****Correspondence:***
Ernest Tyburski
ernest.tyburski@gmail.com

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INTRODUCTION

In recent decades, clinicians have developed the construct of ultra-high risk (UHR) for psychosis states. This condition is associated with the risk of a diagnosis of schizophrenia or other psychotic disorder within 1-3 years of manifestation of symptoms and is sometimes considered the prodromal phase of psychosis (1). Some people at UHR will not develop a full-blown illness, but their symptoms can cause distress and affect every day functioning (2, 3).

Specific deficits in cognitive functioning in schizophrenia were reported a long time ago by the pioneers Kraepelin (4) and Bleuler (5). Furthermore, they are recognized as core features of this severe psychotic disorder (6). A number of studies have shown that subjects in the prodromal phase of psychosis show overall impairments in cognitive functioning, but these are substantially less severe than in first-episode psychosis (FP) and chronic schizophrenia (CHS) (6, 7). Some findings even suggest that cognitive deficits may already exist before the development of symptoms of UHR (8). However, it is not clear whether deterioration of cognitive functions always co-occurs with the increasing severity of psychotic symptoms during the transition from UHR to FP (8). Neurocognitive deficits are not only characteristic of the UHR condition—studies indicate that patients in the prodromal phase of psychosis present also deficits in social cognition (9). Specific dysfunctions in neuro- and social cognition lead to difficulties in various areas of life, such as education, work, social life, mood.

Detailed study of the UHR state is important not only from the perspective of clinical knowledge, but also for the planning of interventions for people with early psychotic states. Fast diagnosis and

well-chosen therapy can reduce suffering and slow down or even prevent the development of full-blown psychosis or other disorders in the UHR group. This group of patients requires an extremely delicate approach because of the risk of stigmatization and its negative consequences. Knowledge about different aspects of UHR for psychosis should be widespread among healthcare workers, as this would improve outcomes for people affected by this condition.

Therefore, this article aims to present the primary characteristics of the UHR state, the associated neurocognition and social cognition, and possibilities for treatment, taking into consideration the controversy in this field. There is a need to set an unambiguous direction in thinking about people with the UHR state.

CLINICAL CHARACTERISTICS OF UHR FOR PSYCHOSIS

Psychotic disorders are not binary conditions, but rather they occur on a spectrum. In the 19th and 20th centuries, clinicians and researchers focused on establishing proper criteria and treatment recommendations for people with severe and long-lasting psychotic symptoms. Detailed analysis of the medical history of many patients showed that specific prodromal symptoms occurred before the development of a full picture of the disease. Furthermore, young people with concurrent psychotic symptoms who did not fit in any particular unit in an institution were increasingly referred to specialists. Following the need to fully understand different stages of psychotic spectrum disorders, clinicians developed the construct of UHR for psychosis. Other definitions of UHR exist, though with some theoretical differences (10).

For over 20 years, the criteria for UHR for psychosis have been used worldwide due to their predictive validity (11). However, this state is not described in any leading classifications such as ICD-10 or DSM V. It was used by clinical practitioners and researchers to catch people in very early phases of the psychotic spectrum. To meet the criteria of UHR, one or more of the following must be present: attenuated psychotic symptoms (APS), a brief limited intermittent psychotic episode (BLIPS), trait vulnerability plus a marked decline in psychosocial functioning, known as genetic risk and deterioration syndrome (GRD), or unspecified prodromal symptoms (UPS) (10). APS must be present at least several times a week within the past year (but no longer than 5 years) and must include psychotic symptoms of sufficient severity and frequency as ideas of reference, perceptual disturbances, odd beliefs or magical thinking, paranoid ideation, odd thinking and speech, and odd behavior and appearance (12, 13). BLIPS—understood as frank, transient psychotic symptoms—must be present for at least several minutes a day, but cannot last longer than a week, at a frequency of at least once per month, and cannot be described by another disorder (12). BLIPS symptoms resolve spontaneously (13). GRD can be diagnosed when a person meets the criteria for a schizotypal personality disorder or when one has a first-degree relative with a psychotic disorder and significant decline in mental state or functioning have been present for at least 1 month (13).

Prodromal symptoms may also include neurocognitive dysfunctions, but their presence is not necessary for the diagnosis. UHR criteria may be measured by different scales, most of which are based on detailed interviews, as for example: the Structured Interview for Prodromal Symptoms (SIPS), the Comprehensive Assessment of At-Risk Mental States (CAARMS), the Basel Screening Instrument for Psychosis (BSIP), and short screening methods such as the Prodromal Questionnaire - Brief version (PQ-B) or Prime Screen—Revised (PRIME) (10, 12, 14).

Several studies have been conducted to estimate the risk of transition to psychosis in the UHR group. Different results have been obtained. Fusar-Poli et al. (1) in their meta-analysis, showed that individuals with a UHR diagnosis have a 15-30% risk of developing a psychotic disorder within 12 months and after 3 years this grows to over 36%. Earlier studies tended to show higher rates of transition than later studies. This may be an instance of the decline effect - the phenomenon of fewer new studies supporting a hypothesis as time progresses (15).

Despite meeting the criteria for UHR, an individual may never meet the criteria of any psychotic disorder or other psychiatric diagnosis. It is very important to be extra careful making a diagnosis to avoid stigmatization and iatrogenic effects in such a sensitive population. A recent study indicates that 43% of patients in the UHR sample recover or go into remission from UHR and 57% have no remission, transition, or relapse over 1 year (16). Some help-seekers diagnosed with UHR ultimately get a diagnosis of another (not psychotic) disorder, such as depression, bipolar disorder, personality disorder, or substance abuse (16). On the other hand, after diagnosis of the prodromal phase of psychosis, frequent evaluation of symptoms is needed to catch a potential transition to psychosis.

The criteria for transition are not clearly defined. Some of authors define them as the occurrence of at least 1 fully positive psychotic symptom which is present at least several times a week for more than 1 week or the presence of at least 1 full psychotic symptom for at least 1 day if this symptom is seriously disorganizing or dangerous (10, 16, 17). The differences between UHR, schizophrenia, acute psychotic disorder, and other psychotic disorders mostly concern the severity, duration, and frequency of psychotic symptoms (**Table 1**). In some cases, mental states can change rapidly, otherwise the process of transition may last years and be gradual.

The precise prevalence of UHR for psychosis in populations is unknown because the diagnostic criteria were established based on research conducted on samples of people who had sought help (10). Data obtained in various studies estimates the prevalence of psychotic symptoms or psychotic-like experiences to be around 4-8%—the results varied depending on the method of diagnosis (structured interviews, questionnaires, or clinical interviews) (10, 19). Children and adolescents may report psychotic symptoms which do not cause significant distress and go into remission without any medical interventions (for example: suspiciousness, bizarre behavior or appearance, magical thinking). The highest risk of developing psychosis is

TABLE 1 | Diagnostic criteria of ultra-high risk (12), schizophrenia (18) and acute transient disorder (18).

	Ultra-high risk	Schizophrenia	Acute and transient psychotic disorders
Symptoms	- At least one of the following: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, odd thinking or speech, or Trait and state risk factors and significant decline in mental state or functioning	- At least one of the following: (a) Thought echo, thought insertion or withdrawal, or thought broadcasting; (b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception; (c) Hallucinatory voices giving a running commentary on the patient's behavior, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body; (d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g. being able to control the weather, or being in communication with aliens from another world), or - At least two of the following: (e) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas; (f) Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech; (g) Catatonic behavior, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor; (h) "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication)	- Delusions, hallucinations, and perceptual disturbances, and severe disruption of ordinary behavior
Duration of symptoms	- At least 1 week and no longer than 5 years for APS - <1 week for BLIPS - At least 1 month and not longer than 5 years for GRD	- At least 1 month	- Acute onset, 2 weeks or less
Frequency of symptoms	- At least several times a week	- Most of the time during 1 month	- Most of the time during episode

APS, attenuated psychotic symptoms. BLIPS, brief limited intermittent psychotic episode. GD, genetic risk and deterioration syndrome.

from ages 15-30, but prodromal symptoms can appear earlier (10, 13).

NEUROCOGNITION

During the course of schizophrenia, psychological testing or observation of the patient can reveal deficits in neurocognitive functions, varying in degrees of severity and range. Impairments in neurocognitive functions may be considered to be an indication of vulnerability for psychotic disorder (5). Neurodevelopmental and neurodegenerative models try to explain the pathomechanism of these changes in cognitive efficiency. Many studies have shown that deficits in cognitive functions are specific not only to full-blown schizophrenia, but also to UHR.

A large longitudinal study conducted in America (NAPLS) on a UHR group and patients with FP suggested that people with prodromal symptoms are already dealing with neurocognitive difficulties, but they are less severe than in people with a diagnosis of FP (20). People in the prodromal phase of schizophrenia generally show levels of impairments intermediate between schizophrenia patients and healthy controls (6).

A study conducted by a team from Switzerland found evidence of impairment in auditory working memory, verbal fluency, processing speed, and declarative verbal memory in a UHR group (21). A meta-analysis of 19 studies, comprising a total of 1,188 UHR subjects, found that prodromal symptoms of schizophrenia are associated with small to moderate neurocognitive deficits in general intelligence, executive functions, verbal fluency, attention, visual and verbal memory, and working memory (1).

Individuals who transitioned to full-blown psychosis had worse scores in verbal fluency, verbal and visual memory, and working memory (22). A general tendency in the severity of cognitive impairments in the schizophrenia spectrum is that if psychopathological symptoms last longer, the impairments are deeper.

It should be noted that impairments in general intelligence, attention, and visual and verbal memory are small to moderate in UHR, while they are moderate in FP, and deep in CHS (22, 23). Executive functions, verbal fluency, and working memory tend to get worse in the prodromal phase of psychosis and present in the form of small to moderate impairments, but then in FP and CHS these impairments last on a moderate level (23).

Processing speed index, measured in neurocognitive tests by symbol or digit coding speed, is the most differentiating factor between a healthy control group and schizophrenia spectrum patients (24, 25). These difficulties are considered to be the core neurocognitive impairments in schizophrenia (24). Deficits in processing speed appear at the very beginning of the psychotic process. Data have shown that there are significant differences in symbol coding speed between siblings at UHR of psychosis

who later develop psychotic symptoms and those who do not (25).

The relationship between the onset of symptoms and the presence of different cognitive deficits can be two-sided. In the neurodegenerative model, psychotic symptoms cause typical brain dysfunctions. In this model, the severity and extent of cognitive impairments will increase with the duration and severity of clinical symptoms of UHR for psychosis. This also explains why we observe greater cognitive deficits at each stage of the schizophrenia continuum. But on the other hand, impairments in individual cognitive functions may have a significant impact on the development of psychotic and quasi-psychotic symptoms in UHR people. For example, impairments in attention and processing speed lead to an unrealistic perception of one's surroundings and strengthen the delusional attitude. Disturbances in cognitive functions can also have a negative impact on self-esteem and social relations. This can lead to social isolation and the development of negative symptoms.

The findings of Bora et al. (7) suggest that neurocognitive impairments are already established before the development of the UHR condition, which supports the neurodevelopmental model of schizophrenia. This theory implies that specific pathological processes disturb the developmental trajectory which, in the future, causes functional disorders and increased risk of developing a psychotic disorder. Results of the longitudinal population-based cohort study conducted by Mollon et al. (26) indicate that patients with psychotic disorder, unlike patients with psychosis with depression, psychotic experiences, or depression, present progressive deficits in IQ. Cognitive impairments in this group are already present in the first two decades of life. These findings suggest that cognitive deficits associated with psychosis may be the product of increasing lags across different critical developmental periods. Another longitudinal study confirming the neurodevelopmental model indicates that baseline cognitive impairment is a significant factor differentiating UHR individuals who present more severe symptoms from healthy controls and people who were diagnosed with UHR but whose symptoms are in remission (27).

In order to thoroughly investigate the cause of cognitive deficits in the UHR group, numerous neuroimaging studies have been conducted. A systematic review and meta-analysis performed in 2018 by a research group from China showed that data collected in different studies reveals a specific neurophysiology in UHR people (28). Structural abnormalities, such as in gray matter volume and cortical thickness of the thalamocortical circuit, are characteristic of UHR people and can be considered to be a marker of transition to psychosis (28). The very important role of prefrontal volume loss in the development of structural and functional brain changes has been demonstrated by a team from Melbourne University (29). Their research also found that UHR patients who developed a full psychotic episode had increased brain contraction in the right prefrontal region (29). Further discoveries regarding cognitive functioning and neurophysiological changes in individuals at ultra-high risk of psychosis would be beneficial, especially regarding the relation between neurocognitive functions and responses to treatment.

SOCIAL COGNITION

In trying to understand the relationship between social cognition and UHR, we shall first briefly look at the specifics of psychotic disorders with particular attention devoted to schizophrenia. Studies indicate that patients with a diagnosis of schizophrenia score worse on tasks assessing emotion perception, theory of mind (ToM), adaptive attributional styles, social perception, and social knowledge (30). In addition to social cognitive deficits, negative symptoms of psychosis such as lack of desire to form relationships, poverty of speech, and lack of motivation may impact social interactions. Various types of training in social skills have been created to help people with schizophrenia deal with their limitations (31, 32).

Researchers, based on their knowledge of relationships between social cognition and psychotic disorders, have conducted several studies focused on social cognition in UHR. A meta-analysis of 17 studies showed that general impairments in social cognition are typical in the UHR group (30). They discuss a study conducted by Addington and his team in which they proved that patients identified as UHR get significantly worse results on tasks involving emotion recognition (30). A study performed by a team from Korea confirmed these results and found that people in an at-risk state processed facial configuration at a lower level than the healthy control group, as do schizophrenia patients (33). This effect did not extend to processing facial features (33). Overall, research confirms mild impairments in emotion recognition in UHR people. The abilities to recognize emotions based on faces and voice are similarly impaired in FP, but these skills are significantly worse in CHS. There is evidence that, like schizophrenia patients, people in a UHR state have greater difficulty recognizing negative facial affect, for example emotions such as fear, disgust, or anger (34).

The inspiration to look for a relationship between social cognition deficits and UHR was reports suggesting that patients with autism spectrum disorders (ASD) are at greater risk of developing affective and nonaffective psychoses (35). ASD and different disorders from the schizophrenia spectrum are related to similar levels of social cognition impairments (36, 37). Despite the fact that the co-diagnosis of ASD and schizophrenia is controversial and is still a topic of debate, researchers are studying the relationship between ASD symptoms and psychotic symptoms because of some commonalities between these disorders. Research on the role of ASD symptoms in the context of psychotic symptoms has also been conducted with UHR groups (37, 38). Although the results of the study conducted by Foss-Feig et al. suggest that there are no differences between patients with UHR with and without ASD in baseline psychosis symptoms and conversion rates, further research on this topic could furnish significant insights because of the similar social cognition deficits in both groups (38).

Another skill which is very important in social functioning is mentalizing, described in Theory of Mind (ToM) as the ability to be aware of the mental states of other people, such as moods or emotions, and their impact on behavior. There is evidence that impairments in metalizing are present at every stage of psychotic spectrum disorders, but it is still unknown whether the severity

of these impairments increases at each stage (39). However, Debbané et al. suggest that ideas of reference and odd beliefs, understood as disturbances in the process of mentalization, are more likely to be present in early stages of psychosis (39). On the other hand, a lack of changes to the ability to metalize is recognized as a protective factor against vulnerability for psychosis (39).

It has also been shown that there is a correlation between atypical brain activation patterns during tasks involving monitoring the reality and perception of self and others and manifestation of sociotype in adolescence (39). Regarding ToM, a meta-analysis of 17 studies showed that there are significant moderate deficits in verbal ToM in UHR samples (9). A study conducted in Denmark showed that people in the UHR phase scored significantly worse than healthy controls on a ToM measure and a global measure of emotion recognition (34). Ayesa-Arriola et al. (40) showed that deficits in ToM are a trait of schizophrenia. These difficulties are present from the onset of psychosis, remain throughout the illness, and are not associated with clinical symptoms (40). There is some evidence that there are differences in measures of attributional bias between UHR groups and healthy controls, but other studies did not find such differences (9, 30, 34). Specific attributional biases are characteristic of schizophrenia patients, but further research is needed to identify whether there is a correlation between frequency and types of attributional bias on each psychotic disorder spectrum.

An interesting issue is the impact of UHR symptoms on social cognition. A study conducted by a team from the Netherlands found data suggesting that adolescents in a UHR state have problems identifying and verbalizing their own emotions and, furthermore, the level of difficulty was related to the severity of high risk symptoms (41). A study by Shim et al. indicated that the duration of prodromal symptoms was correlated with impaired social skills and general symptoms were significantly related to lower levels of "independence-competence" (42). Intensification of positive and negative symptoms did not affect social competences (42). Another study showed that negative symptoms are a significant predictor of impairments in social skills (34). Moreover, negative symptoms, especially experiential ones such as avolition and anhedonia, tend to have a strong impact on functioning in UHR individuals (34). There is evidence that anhedonia may be a predictor of transition to full-blown psychosis (34). The severity and type of social cognition impairments are not themselves correlated with frequency and time of transition from UHR to psychosis during adolescence (39). However, data about relationships between social cognition and different stages of psychotic disorders are still limited and further research needs to be conducted to understand this topic more thoroughly.

POSSIBILITIES FOR TREATMENT

Diagnostic criteria, evidence from research, brain mechanism models, case studies and other methods of gathering knowledge about specific psychiatric conditions are investigated, among other reasons, to find effective methods of treating people who seek help. As the prodromal phase of psychosis is not recognized as a disorder in ICD or DSM criteria, therapeutic interactions should be focused on prevention of conversion to psychosis or other disorders and should include actions which aim to improve quality of functioning.

Taking into consideration the guidance for early detection, the European Psychiatric Association (EPA) has developed evidence-based recommendations for interventions for individuals at UHR for psychosis (43). Much research indicates that both psychological and pharmacological interventions can be beneficial in the UHR group (43). The EPA recommends cognitive-behavioral therapy (CBT) as the first-choice intervention in the prodromal phase of psychosis; this can be complemented by pharmacological interventions with low dose second-generation antipsychotic drugs (43). The decision to add pharmacology to a treatment should be considered when the severity of symptoms limits the efficacy of CBT (43). Antipsychotic medications should only be given in exceptional circumstances because of, inter alia, their side-effects. Proper selection and implementation of therapy can postpone or even prevent the development of full-blown disorders.

Many studies indicate that CBT is the most effective method of providing help to people at risk of psychosis. A study conducted in 2012 in the Netherlands indicated that CBT can reduce the transition to psychosis by about 50% (44). Another study showed that after 4 years of follow-up, CBT is still effective at preventing transition from UHR to FP (45). Moritz et al. (15) highlight the controversy regarding the effectiveness of interventions in the UHR state. Despite the fact that there are studies showing the effectiveness of CBT and CBT combined with pharmacotherapy in UHR state, there are also other data suggesting that these forms of intervention cannot prevent transition to psychosis (15). There are also data suggesting that there are no advantages of specialized treatment over need-based treatment in the UHR state (15). Specialized treatment for people in the UHR state, especially when it is so named, is itself controversial because of the risk of stigmatization. Stigma—fear of becoming psychotic—may lead to depression and increase a risk of suicide (15). Interventions for people at UHR should rather focus on current problems and provide knowledge about mental health in general, not only about psychotic disorders.

The risk of transition to psychosis is highest in the first year after diagnosis of UHR (45). Therapeutic intervention should be offered in the first half year of prodromal symptoms, as it increases the effectiveness of therapy (45). Cognitive-behavioral therapy may be effective in the treatment of the UHR because, inter alia, during the therapy a person learns how to monitor emotions, test their own thoughts, control behavior, and see the interactions between these three elements. Therapy offers the opportunity to share, find understanding, and become able to challenge cognitive biases in a safe environment. In UHR for psychosis, we can observe some specific elements in cognition: e.g., the presence of dysfunctional metacognitive beliefs that can lead to misjudging reality and others' intentions as well as cause difficulty in dealing with stressful life events (11). Young people in the prodromal phase of psychosis tend to worry about

the condition of their memory and attention and view their thoughts as uncontrollable and dangerous (46). In the treatment of patients who deal with dysfunctional beliefs, metacognitive training—a form of CBT—or other cognitive techniques may be beneficial (11).

Despite the fact that the EPA recommendations indicate the use of CBT or CBT combined with pharmacotherapy, other treatment opportunities have been offered and tested for effectiveness in the UHR group. One such promising method is cognitive remediation (CR). CR is an intervention based on behavioral training composed of various tasks focused on improving cognitive functioning (47, 48). It is an evidenced-based intervention in schizophrenia which can improve cognitive functioning and, with it, the quality of everyday functioning (47). The previously mentioned neurodegenerative and neurodevelopmental model of psychosis suggests that such interventions could also be effective in the UHR group. There are studies indicating that CR may improve different domains of cognitive functions, such as verbal memory, visual memory, attention, processing speed, facial emotion recognition, executive functioning, and social functioning in people at UHR. However, it has not been confirmed that this form of intervention influences global measures of cognition, clinical symptoms, or functioning (49, 50). More research on the effectiveness of CR in UHR is needed, but it may be a promising intervention option.

DISCUSSION

In modern psychiatry, more and more time is being devoted to developing a detailed understanding of the different stages of the spectrum of mental disorders. There have been many reports on the ultra high risk (UHR) for psychosis state in recent years, giving us a better understanding of the cognitive and social functioning of people in this group. Knowledge about the difficulties faced by people at UHR enables us to tailor therapies appropriately. Due to the specificity and variability of prodromal symptoms and the sensitivity of patients, this issue should be treated with exceptional dedication and caution at the same time.

Impairments in cognitive functions are described in the UHR state and some studies suggest their presence even before the onset of prodromal symptoms. From a clinical perspective, it seems appropriate to use cognitive training or remediation in patients with prodromal symptoms. This form of intervention can not only improve patients' quality of life, but also slow or prevent the development of symptoms. Based on the neurodegenerative model of psychotic disorders, future research should focus on the relationship between therapeutic interactions and the severity of cognitive deficits. When assessing cognitive functions in patients from the UHR group, it is worthwhile to conduct follow-up research.

Some studies have suggested that social cognition impairments are characteristic of the UHR state, but data on specific skills are still limited. Research in this area should be continued. It seems particularly interesting to identify the specific relationships between difficulties in social cognition and global functioning. Knowledge about impairments in social cognition in the UHR state implies that therapeutic interactions should also address strengthening social competences.

The UHR state is not included in any leading classification of psychiatric disorders. Nevertheless, the diagnostic criteria for UHR were chosen to identify people who are more likely to develop a psychotic disorder. On the one hand, early detection of UHR enables the monitoring of the patient's condition and the implementation of appropriate interventions to stop or slow down the development of symptoms. On the other hand, all clinicians should keep in mind the risk of stigmatization of UHR patients, which may have fatal consequences. The effects of stigmatization may include a decrease in self-esteem, social isolation, hopelessness, increased use of avoidance strategies, as well as depression and anxiety symptoms (13, 51). Path analysis indicates that self-labeling and stress related to stigma is a valuable predictor of suicide (51). Clinicians must both treat mental illness and help maintain good mental health; therefore, when planning interventions in the UHR group, both the positive and negative consequences of diagnosis should be taken into account. It should be considered whether the use of the term UHR for psychosis should be applied directly to the patient at all. Perhaps a better approach would be to address the patient's current problems and symptoms without predicting the development of severe mental illness. Even though one study of 55 patients and 50 professionals found that patients were less likely than professionals to believe that the terms UHR and APS were at risk of stigmatization, due to, inter alia, the small size of the study group; further research on the topic is needed to draw firm conclusions on this point (52). It is also important to note that patients with a family history of psychosis were more likely to associate the term UHR with stigma and agreed that this term should be changed (52). Certainly the stigmatization effect in UHR should be taken into account in the process of diagnosis and therapy to avoid iatrogenic effects.

Evidence-based therapeutic methods, such as CBT or CBT combined with pharmacotherapy, are recommended by the EPA as the interventions for the UHR state. Research results suggest that this intervention might be effective in preventing transition to full-blown psychosis. However, it is worth mentioning that there is no clear agreement on these recommendations. Research in this area should definitely be continued. Clinical experience and a holistic view of people suggest a direction of research that focuses not on creating therapies specifically for UHR patients, but rather on adjusting interventions to the current needs of the patient. Therapy should focus on reducing subjective discomfort, teaching adaptive techniques for managing stress, improving social skills, and undermining cognitive biases. Even if it might sometimes be impossible to fully prevent the development of an illness, any delay could be very beneficial from the perspective of brain mechanisms, social functioning, and relations with others. Furthermore, early interventions include psychoeducation and provide the abilities necessary to deal with the disease, so they can ensure a milder course of the disorder.

The efficacy of different methods and therapeutic techniques still needs to be tested in UHR patients. Current evidence is promising, but it is still worthwhile to investigate the

effectiveness of other methods. Young people in an at-risk state can probably respond well to group therapy or modern forms of treatment using techniques such as computer training, virtual reality, or mobile applications. Despite the recommendations and evidence from research, early interventions are not as widely used as they should be. A study conducted in England showed that only 53% of 50 medical teams included these treatments in their service and provided them for at least 12 months (53).

Despite knowledge about the UHR condition and the effectiveness of therapy, early interventions are still not as widely used as they should be. There is a pressing need to raise awareness about UHR symptoms and possible methods of treatment.

CONCLUSION

To conclude, UHR for psychosis is the condition of being at risk of developing a psychotic disorder in which attenuated psychotic symptoms, frank, transient psychotic symptoms, or genetic risk and deterioration syndrome are present. It most often affects young people, and even when it does not lead to a transition to full-blown psychosis or some other psychiatric disorder, it impairs neurocognitive functions and social cognitive functioning. Deficits in cognitive functions such as general intelligence, memory, processing speed, attention, executive functions, and verbal fluency have been demonstrated by different studies. These impairments tend to be established before the appearance of prodromal symptoms, which supports the neurodevelopmental model of psychotic disorders. Structural and functional changes in brain activity in the prodromal phase of psychosis, such as gray matter volume, cortical thickness of the thalamocortical circuit, and prefrontal volume loss, have been shown by neuroimaging studies. UHR is also associated with difficulties in emotion perception based on face and voice recognition, mentalizing, and theory of mind. Early diagnosis, symptom monitoring, and early therapeutic interventions are key in people experiencing UHR. Avoiding stigmatization is extremely important during the diagnosis and treatment of people from the UHR group.

AUTHOR CONTRIBUTIONS

KR-O and ET was involved in the paper design, managed literature searches and analyses, and wrote the first draft of the manuscript. JS and MM was a supervisor and corrected the manuscript. KW corrected the manuscript. All authors contributed to and have approved the final manuscript.

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A Randomized Controlled Trial of Attentional Control Training for Treating Alcohol Use Disorder

Angelina Isabella Mellentin[1,2,3], W. Miles Cox[4], Javad S. Fadardi[5], Laila Martinussen[1], Nicolaj Mistarz[1], Lotte Skøt[1], Kristine Rømer Thomsen[6], Kim Mathiasen[3], Mia Lichtenstein[3] and Anette Søgaard Nielsen[1,2]*

[1] Unit for Psychiatric Research, Department of Clinical Research, University of Southern Denmark, Odense, Denmark, [2] Brain Research-Inter-Disciplinary Guided Excellence (BRIDGE), Department of Clinical Research, University of Southern Denmark, Odense, Denmark, [3] Centre for Telepsychiatry, Mental Health Services in the Region of Southern Denmark, Odense, Denmark, [4] School of Human and Behavioral Sciences, Bangor University, Bangor, United Kingdom, [5] Cognitive Health Laboratory, Department of Psychology, Ferdowsi University of Mashhad, Mashhad, Iran, [6] Centre for Alcohol and Drug Research, Department of Psychology and Behavioral Sciences, Aarhus University, Aarhus, Denmark

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Walter Roberts, Yale University, United States

***Correspondence:**
Angelina Isabella Mellentin
amellentin@health.sdu.dk

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Background: There is consistent evidence that community and clinical samples of individuals with an alcohol use disorder (AUD) have attentional biases toward alcohol cues. The alcohol attentional control training program (AACTP) has shown promise for retraining these biases and decreasing alcohol consumption in community samples of excessive drinkers. However, there is a lack of evidence regarding the effectiveness of ACTP in clinical AUD samples. The main aim of the present study is to investigate whether primary pharmacological and psychological, evidence-based alcohol treatment can be enhanced by the addition of a gamified AACTP smartphone application for patients with an AUD.

Design and Methods: The study will be implemented as a randomized controlled trial. A total of 317 consecutively enrolled patients with AUD will be recruited from alcohol outpatient clinics in Denmark. Patients will be randomized to one of three groups upon initiation of primary alcohol treatment: Group A: a gamified AACTP smartphone application + treatment as usual (TAU); Group B: a gamified AACTP sham-control application + TAU; or Group C: only TAU. Treatment outcomes will be assessed at baseline, post-treatment, and at 3- and 6-month follow-ups. Repeated measures MANOVA will be used to compare the trajectories of the groups over time on alcohol attentional bias, alcohol craving, and drinking reductions. It is hypothesized that Group A will achieve better treatment outcomes than either Group B or Group C.

Perspectives: Because attentional bias for alcohol cues is proportional to the amount of alcohol consumed, and these biases are not addressed within current evidence-based treatment programs, this study is expected to provide new evidence regarding the effectiveness of the gamified AACTP in a clinical population. Furthermore, due to promising results found using AACTP in community samples of excessive drinkers, there is a high probability that the AACTP treatment in this study will also be effective, thereby

allowing AACTP to be readily implemented in clinical settings. Finally, we expect that this study will increase the effectiveness of evidence-based AUD treatment and introduce a new, low-cost gamified treatment targeting patients with an AUD. Overall, this study is likely to have an impact at the scientific, clinical, and societal levels.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT05102942?term=NCT05102942&draw=2&rank=1, identifier: NCT05102942.

Keywords: alcohol use disorder, attentional bias, Stroop task, cognitive bias modification, add-on treatment, randomized clinical trial

BACKGROUND

Alcohol-use disorder (AUD), as defined by DSM-5 criteria, is very common in the Western world, with a 12-month prevalence of 14% and a lifetime prevalence of 29% (1). Furthermore, AUD is the most prevalent and most harmful of all substance-use disorders (2, 3) and is among the leading causes of illness, disability, and mortality (4, 5). The high prevalence and severity of AUD underscore the importance of having easily available and effective treatments.

Overall, evidence-based psychological treatments, such as cognitive-behavioral therapy (CBT), have shown to be effective in the short term (6). During CBT, patients with an AUD are taught methods to help them identify high-risk situations for relapse. They also learn coping strategies for avoiding alcohol in high-risk situations. Patients are, however, supposed to learn these strategies by applying explicit and controlled cognitive techniques rather than practicing the strategies while being exposed to alcohol *in vivo* (7–9). Recovering patients often experience a relapse when they are exposed to alcohol and related stimuli in real-life, and they can only later analyze the consequences of their behavior. Patients with an AUD initially respond well to evidence-based psychological treatments, but as many as 50% of them relapse within 6 months after treatment discharge (10–12). This indicates that CBT and other evidence-based psychological treatments do not address all the crucial cognitive dysfunctions associated with maintaining an addiction; thus, they may not prepare patients to deal with their inevitable confrontation with alcohol cues in real life in Western societies.

One shortcoming of current psychological treatments is that they mainly target explicit and controlled cognitive dysfunctions. However, according to dual process models of addictive behaviors, confrontation with alcohol cues *in vivo* is influenced by two semi-independent cognitive systems: (1) a fast associative *impulsive* system, which is involved in the automatic evaluation of alcohol-related stimuli in the environment in terms of their emotional and motivational significance and which initiates approach or avoidance responses; and (2) a slow and controlled *reflective* system, which is involved in the regulation of the automatic and implicit responses elicited by the impulsive system, and which is responsible for explicit and controlled, higher-order cognitive processes (13–16).

Addictive behaviors, such as AUD, can be conceptualized as a dysfunction of these systems, whereby an over-activated impulsive system becomes sensitized and triggers approach behaviors toward alcohol cues, whereas a relatively under-activated reflective system is unable to regulate the behavior. Because the impulsive system is partly automatic and implicit, approach behaviors targeting alcohol cues in the environment allow the self-destructive drinking behavior to be maintained, even though the drinker might have explicit knowledge about the consequences generated by the reflective system (15, 16). Corroborating evidence from functional neuroimaging studies suggest that patients with AUD exhibit aberrant activation in dorsolateral prefrontal cortex, insular cortex, and anterior cingulate cortex, which are structures that act as a critical part of the reflective system (17–21). In addition to the of hypoactivation of the neural correlates for the reflective system, hyperactivation of subcortical structures such as ventral striatum and nucleus accumbens have also been found in AUD, which underlines the notion of a dysfunctional interaction between the reflective and impulsive systems (19–22). Although standard evidence-based psychological treatments for AUD target and attempt to modify dysfunctions in one of the cognitive systems that influence the maintenance of an AUD, the impulsive cognitive dysfunctions are addressed to a much lesser extent.

A cognitive dysfunction in the impulsive system that has consistently been identified as a crucial component in the maintenance of an AUD is alcohol attentional bias (AB). An AB for alcohol cues refers to the implicit and automatic cognitive process of selectively focusing attention on alcohol-related stimuli in the environment at the expense of processing other relevant stimuli (23, 24). AB for alcohol cues has been measured by using a variety of experimental paradigms (25). Among the most widely used paradigm is the alcohol variant of the experimental Stroop task (24, 26, 27). The alcohol Stroop consists of two categories of stimuli: alcohol-related (e.g., beer, wine, tavern) and neutral (e.g., chair, envelop, juice). During the task participants are asked to name the color (i.e., red, yellow, blue, or green) in which each stimulus appears as fast and accurately as possible while ignoring their content and

Abbreviations: AASE, alcohol abstinence self-efficacy scale; AAT, Alcohol approach-avoidance task; AB, attentional bias; A-GNG, Alcohol Go/No-Go; ACTP, attention control training program; AUD, alcohol use disorder; CBT, cognitive behavior therapy; ETG, ethyl glucuronide; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MSFVT, Multi-stimulus free-viewing task; MoCA, Montreal Cognitive Assessment.; PANAS, Positive and Negative Affect Schedule; RTCQ-TV, Readiness-to-Change Questionnaire Treatment Version; RT, reaction time; TAU, treatment as usual; TLFB, timeline follow-back; VAS, Visual Analog Scale.

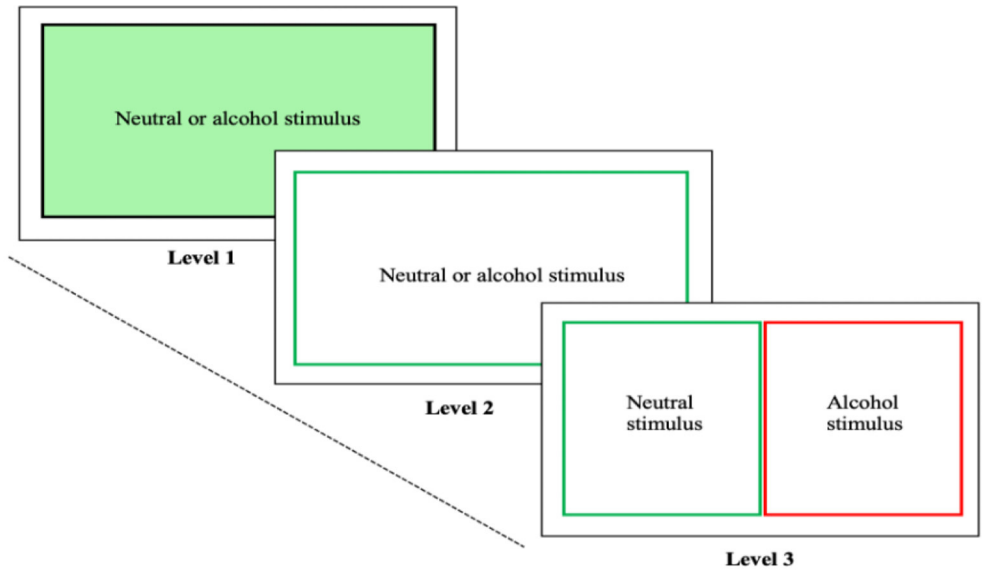

FIGURE 1 | Alcohol attention control training program: In Level 1, neutral or alcohol stimuli are successively presented on the screen, while the colored background of the screen needs to be identified. In Level 2, instead of the background, a colored outline needs to be identified. In Level 3, neutral and alcohol stimuli appear simultaneously of which the neutral stimulus needs to be identified.

meaning. The degree of AB is indicated by slower mean reaction times to alcohol cues compared to neutral cues and is calculated as an interference score. The alcohol-related meaning of the stimuli is presumably either capturing the person's attention more readily or maintaining the attentional focus for a longer period of time than the neutral cues (24). AB as measured by the alcohol Stroop task has consistently been found in both community and clinical samples of excessive drinkers (28–31), and the degree of AB is proportional to the amount of alcohol that participants habitually consume (24). For example, clinical AUD samples exhibit greater AB than sub-clinical samples of heavy drinkers (24, 29, 32). In addition, the degree of AB is inversely related to drinkers' ability to control their drinking (31, 33–35). Finally, it has been shown that clinical samples of AUD patients who have stronger alcohol AB at treatment admission are more likely to have an unsuccessful treatment outcome compared to patients with less AB, and the degree of AB of the unsuccessful patients increased during the course of treatment, suggesting that abstinence increases attentional awareness of alcohol cues (28). Taken together, the research suggests that AB is of utmost importance in maintaining an AUD and if not corrected, it might impede the effectiveness of other treatments and cause the patient to relapse.

The principles underlying the experimental alcohol Stroop task have recently been applied in the Alcohol Attention Control Training Program (AACTP), which is a computerized training program aimed at increasing drinkers' cognitive control over their alcohol AB. As illustrated in **Figure 1**, the AACTP consists of three different levels of training.

At Level 1, individual pictorial stimuli with a colored background (e.g., red, or green) are shown one at a time on a computer screen. Each stimulus is either alcohol-related or neutral. The participant is instructed to ignore the content of the stimuli while naming the color of the background. At Level 2, again an alcohol-related and a neutral stimulus is presented successively on the computer screen one at a time. In contrast to Level 1 in which the pictures have a colored background, the pictures now have only a colored outline whose color the participant is supposed to identify, thus making the task more difficult than at Level 1. At Level 3, two stimuli (an alcohol-related one and a neutral one) are presented simultaneously on the computer screen. The participant is asked to identify as quickly and accurately as possible the outline color of the neutral stimulus, while ignoring the alcohol-related stimulus.

The AACTP uses a variety of pictorial alcohol-related stimuli to train participants to progressively divert their attention away from alcohol-stimuli, with increasing levels of difficulty across the training. The alcohol AACTP has been evaluated in community samples of excessive drinkers who have shown reductions in both AB and alcohol consumption at post-treatment and follow-up (32, 36, 37). Recent reviews and meta-analyses do point to methodological shortcomings and conflicting evidence on the effects of training programs targeting AB across patients with various addictive disorders, including AUD (38–40). Despite the need for more well-designed studies, there is, however, also evidence suggesting that AACTP may be more promising for targeting alcohol consumption when compared to other AB training programs (40). Furthermore, the ACTP has been studied as an add-on treatment among clinical populations with food- and opiate addictions. In both cases, the addition of the ACTP in the experimental group led to a greater reduction in disease-specific AB and the accompanying

unhealthy behavior than in the control groups (41, 42). This evidence suggests that AACTP might be a promising tool for ameliorating AB in clinical samples of patients with an AUD, especially when used in conjunction with a conventional treatment for AUDs.

In contrast to many other psychological treatments, clinical neuropsychological treatments building on experimental laboratory tasks are particularly suitable for alternative delivery pathways, such as tablets and mobile applications. These delivery pathways make it possible to use gamification elements, which would increase patients' motivation to participate. Gamification is defined as the use of game-design features in a non-gaming context, such as in a psychological treatment setting. Gamification would make the intervention more engaging, enjoyable, and motivating for participants (43), and using gamification elements is likely to enhance compliance with neuropsychological treatments. Commonly used gaming techniques include time-pressure, sound effects, feedback, progression in level of difficulty, achievement rankings, and competition (43–45). Although the AACTP have shown great promise in treating cognitive dysfunctions not targeted by conventional psychological treatments, the use of gamification elements may enhance compliance with and the effectiveness of these interventions.

Taken together, the results of prior studies are promising in terms of the clinical relevance of AB training. However, the small number of studies with small sample sizes conducted to date highlights the need for future research to verify the robustness of these mostly positive findings in actual clinical AUD settings (40). Further, adding gamification elements may increase compliance and hence the effectiveness of the intervention.

Aims

The main aim of the study is to determine whether a gamified version of the AACTP when used as an add-on to a primary evidence-based treatment will increase the treatment's effectiveness. Based on the available evidence, it is hypothesized that the experimental group (Group A) will achieve a better treatment outcome than either the active control group (Group B) or the treatment-as-usual group (Group C). Additionally, we hypothesize that there will be a dose-response effect in Group A: the more that the patients use the AACTP, the better their outcome will be. Full descriptions of the experimental and control groups are provided in Section 2.5 below.

METHODS

The study (a) will be registered in ClinicalTrials.gov, which is the largest registry of clinical trials and is administered by the United States National Library of Medicine (NLM) at the National Institutes of Health, and (b) will be conducted and reported according to CONSORT guidelines (46).

Design and Setting

The study will be conducted as a parallel randomized controlled study in various outpatient alcohol treatment clinics in Denmark. Most individuals with AUD who present themselves for treatment at these clinics are offered outpatient treatment. This outpatient treatment is financed through public funds. It accepts self-referrals, and patients can remain anonymous during treatment. Only treatment for alcohol problems is provided at the outpatient clinics.

Primary Treatment at the Outpatient Alcohol Clinics

At treatment entry, patients will be offered detoxification, if needed, before their primary treatment at one of the outpatient clinics is initiated. The primary treatment lasts 3 months and consists of both a pharmacological and a psychological treatment. The pharmacological treatment includes treatment with disulfiram and acamprosate. Naltrexone or nalmefene is also offered when deemed appropriate. The psychological treatment consists of cognitive-behavioral therapy (CBT), which is provided during hour-long individual or group sessions and typically includes eight sessions. The therapist and patient jointly plan the course of the patient's treatment. The treatment typically includes psychoeducation, functional analysis of drinking situations, and the development of coping strategies. The strategies include waiting out until an urge passes rather than acting on it, thinking about the negative consequences of drinking, thinking about the positive consequences of sobriety, consuming healthy alternative foods and beverages, problem-solving, and homework assignments between sessions. Therapists conduct the psychological treatment; they include nurses and social workers who have been specifically trained to deliver the range of therapies. Supervision takes place frequently, and psychiatrists regularly monitor patients' progress during the treatment (47).

Recruitment

Based on a power calculation (see Section 2.7.), a total of 317 patients will be required for the data analysis. On the basis of data from the Danish National Alcohol Treatment Register (48) and prior studies conducted at this clinic (49–52) and prior studies of AACTP (32, 36, 42), it seems feasible that at least 317 eligible patients (see Section 2.4.) can be recruited from January 2021 to July 2022.

After completing detoxification and prior to starting primary treatment, each patient will be briefly informed about the project and asked whether he or she is willing to meet with a research assistant who will provide further information about the study. If the patient agrees, the research assistant will provide the patient with oral and written information about the details of the study. After informed consent has been provided, a baseline interview will be conducted, and each patient meeting the eligibility criteria will be randomized. To minimize the risk of bias and to overcome potential group imbalances, the current study will utilize an urn technique that will randomize the patients to one of the three treatment groups.

Eligibility Criteria

To be eligible to participate, patients must fulfill the following criteria. They must (1) sign written informed consent, (2) be between 18 and 65 years old (because the intervention is web-based), (3) be fluent in Danish, (4) have completed detoxification (if deemed appropriate), (5) have been admitted to primary treatment within the past 8 weeks, (6) not be color-blind, (7)

not have a severe psychiatric or neurological illness (e.g., a psychotic disorder, intellectual disability, dementia) or terminal physical illness.

Experimental and Control Groups

The 317 patients (see power analysis below) fulfilling the eligibility criteria will be randomized to one of the three groups: Group A: AACTP delivered *via* a smartphone application + treatment as usual (TAU; $n = 106$), Group B: ACTP sham training delivered *via* a smartphone application + TAU ($n = 106$), or Group C: TAU only ($n = 106$). Patients in Group A will receive seven sessions of AACTP (one session per week for 7 weeks). Patients in Group B will receive seven sessions of sham training (one session per week for 7 weeks). Patients in Group C will receive only the primary treatment for AUD. Patients in the AACTP and sham control groups will start the primary treatment within the 1st month of their admission, so that the add-on treatment will not extend beyond the 3-month treatment period.

Attentional Control Training Program *via* a Smartphone Application

The AACTP, which is delivered *via* a smartphone application and based on an Android application, was designed in accordance with the conventional AACTP to help drinkers become aware of the automatic cognitive aspects of their alcohol use. The stimuli comprise alcohol-related pictures and non-alcohol-related pictures and are individually presented on a computer screen in a random order. If patients need it, a research assistant in the treatment facility will assist them with the installation of the application on their smartphone. The installation of the application on patients' personal smartphone will allow them to complete the training program at home. Thus, they will not be constrained by having to use the application in the outpatient facility.

The AATCP training will consist of seven sessions, each of which takes 10–15 min to complete. Each session will start with practice with individual stimuli (i.e., Levels 1 and 2 in the original AACTP) and proceed to Level 3, in which the patient will be asked to either (a) identify the green outline color of a non-alcohol-related picture, while ignoring the red outline color of the alcohol-related picture presented adjacent to it (stimulus-irrelevant version), or (b) identify the picture with non-alcohol-related content, while ignoring the picture with alcohol-related content presented adjacent to it (stimulus-relevant version). Level 3 is the most difficult and most effective level in the conventional AACTP. It is defined as the level in which the patient is trained to divert his or her attention away from alcohol cues when both an alcoholic and a non-alcoholic stimulus is present, and they compete for the patient's attentional resources. The patient should respond by touching the non-alcohol stimulus on the screen as fast and accurately as possible. During the sessions, the speed at which the stimuli are presented systematically increases, while the width of the outlines decreases and gradually fades away in the final sessions. This increases the difficulty of the task and trains the person's attentional system so that the alcohol-related stimuli are ignored even when there is no color cue. In case the patient makes a mistake and touches the incorrect stimulus, the tablet will provide an auditory-visual alert.

The training, therefore, occurs in seven hierarchical steps, which are arranged according to an increasing level of difficulty. Prior to each session, the patient will be encouraged to set a goal for decreasing his or her reaction times (RTs) to the neutral, non-alcohol-related stimuli, which requires increasing efficiency for the distracting cues to be ignored. The goal will be for each participant to improve his or her attentional control until a performance plateau has been reached (RTs $< 1{,}000$ ms with a response accuracy $> 90\%$).

After completing each session, the participant will be given numerical/graphical feedback on (a) the number of errors made and the mean RTs to the non-alcohol-related stimuli, and (b) a brief auditory/written interpretation of the results. The aim of the training will be to motivate patients to actively take part in the program in a meaningful and goal-directed way. Although the conventional AACTP includes some gamification elements, the smartphone application includes additional gamification elements, such as time-pressure, sound-effects, hierarchical levels, feedback, achievement ranking, and competition. These elements serve to increase the patient's engagement and compliance. Also, to increase engagement and the chances of obtaining a dose-response effect across participants, the application can control for the number of practice sessions that each trainee can complete in each period, and it can automatically save and securely encrypt and send the training data to the research server *via* an internet connection.

Attentional Control Training Program Sham Training *via* a Smartphone Application

The AACTP sham control training is like the AACTP in that it is delivered *via* a smartphone application based on an Android or iOS application and is designed in accordance with the conventional program. Patients receiving the sham control program will also have the application installed on their personal smartphone. They, therefore, will be able to use the program in any location that they wish. However, different from the AACTP, patients in the active control group will be trained to direct their attention toward the non-alcohol-related stimuli on only 50% of the trials. On the remaining trials, their attention will be directed toward the alcohol-related stimuli. Thus, the sham training should counteract the induction of AB with AB re-training because the allocation of the participant's attention will distribute equally between the alcohol-related and the non-alcohol-related stimuli. The patient will respond by touching the circle displayed on the computer screen as quickly and accurately as possible. Like the ACTP training, a red outline will signal a stimulus that should be ignored, and a green outline will signal a neutral stimulus, which should be responded to, but the alcoholic or non-alcoholic stimuli will appear equally often with the red or green outline. Also, throughout each session, the speed at which the stimuli are presented will systematically increase, and the width of the outlines will decrease and gradually fade away in the final sessions, thereby increasing the difficulty of the task. In case the patient makes an error and touches an incorrect stimulus, the tablet will provide an auditory-visual alert. As in the smartphone version of the alcohol ACTP, prior to each session the participant will be encouraged to set a goal for the speed of the reaction times and the number of errors made

until his or her performance plateau has been reached. After completing each session, the patient will be given both graphical and auditory feedback. Hence, the program will contain all the same features as the smartphone version of the alcohol ACTP. The only difference is that the patient's attention will be equally guided toward non-alcohol-related and alcohol-related stimuli in the sham control version. Selected practice data will be sent to the server to control for dose-response effects. Having the sham condition is important for ensuring that effects obtained with the smartphone version of the alcohol ACTP result from the re-training of the patients' alcohol attentional bias and not from the additional attention that they receive or from some other unintended effect, such as the Hawthorne effect (53).

Treatment as Usual

Patients in the Treatment-As-Usual (TAU) (see Section 2.2.) control group will not receive any kind of additional treatment, because we aim to determine whether the smartphone version of the alcohol ACTP will increase the effectiveness of a well-established, evidence-based pharmacological and psychological treatment.

Measures

Upon admission to the study, patients in all three or the groups will be assessed in a baseline interview. Details about patients' socio-demographic characteristics, AUD diagnosis, treatment goals, and pharmacological treatment will be obtained from their clinical records (54–56). At baseline, the general premorbid intelligence level and cognitive functioning will be assessed. Experimental measures of patients' cue-induced cravings, alcohol AB, action-tendency bias, inhibition bias, and cognitive flexibility (24, 26, 27, 57, 58) will be administered at baseline and post-treatment. Clinical measures of patients' alcohol consumption (the primary outcome measure), cravings, self-efficacy, and affective states (the secondary outcome measures) (57–62) will be taken at the baseline, post-treatment, and follow-up assessments. The follow-ups will be given at 3- and 6-months post-treatment.

Baseline Measures of General Cognitive Functioning

National Adult Reading Task. The Danish version of the National Adult Reading Task (DART/NART) (63) assesses verbal crystalized intelligence, which is indicative of general premorbid cognitive functioning. Respondents are asked to read 50 incongruent words in Danish (i.e., the pronunciation does not correspond with how the word is spelled). The total DART score can be converted to an intelligence quotient score (IQ score).

Montreal Cognitive Assessment. The Montreal Cognitive Assessment (MOCA) is a short screening tool that is sensitive to mild cognitive impairment. It assesses six cognitive domains: attention, orientation, executive functioning, visuospatial construction, memory, and language (64). The MOCA consists of short cognitive tasks that can be administered in 10 min.

Experimental Measures

Cue-Induced Cravings

Cravings for alcohol will be assessed by exposing patients to 14 alcohol-related pictures from the AACTP and 14 alcohol-related pictures that were not included in the AACTP. The aim is to determine whether cue-induced cravings will decrease in the experimental AACTP group and whether the decrease is generalized to alcohol-related stimuli not included in the AACTP. Cue-induced cravings in response to the pictures will be measured using (a) self-report by means of a visual-analog scale (see Section 2.6.2.2. for a description) (57, 58) and (b) physiological reactivity by means of skin conductance response using Imotions, which is a computerized system that has been used in various experimental studies.

Cognitive Flexibility

The classic Stroop task will be used to measure patients' degree of general attentional control. Task stimuli consisting of two types of words are used: (1) Congruent words comprise the names of four colors (i.e., red, yellow, blue, and green) that are written in a color that is congruent with the name of the color (e.g., the word *red* in red letters); (2) Incongruent words consist of the same four names of colors, but they are presented in a font color that is incongruent with the name of the color (e.g., the word *red* in blue letters). The patient's task is to name the color in which the words are presented while attempting to ignore the meaning of the word. Both the mean reaction time for correctly naming the color of the words and the number of correct responses (mean accuracy) will be recorded. Subtracting mean reaction time to the congruent words from the mean reaction time to the incongruent words gives a measure of the participant's cognitive interference (26).

Alcohol Attentional Bias

Patients' AB for alcohol cues will be assessed using the alcohol Stroop task. The task consists of two categories of words presented in different font colors (i.e., red, yellow, blue, and green): (1) alcohol-related words (e.g., bar, beer, rum, scotch, tequila, vodka, whisky), and (2) neutral words (e.g., ceiling, cupboard, fence, gate, shed, tap, chair). The two categories of words are matched for word frequency and length, number of syllables, and semantic relatedness. As in the classic Stroop task, the patient's task will be to name the color in which the words are presented while attempting to ignore the meaning of the words. AB is indicated by longer reaction times to the alcohol-related words relative to the neutral words (27, 32).

In this study, the alcohol Stroop task with pictures will also be used to measure patients' AB for alcohol cues, thereby indicating whether patients have benefitted from the AACTP training. To determine this, the task will consist of pictures of alcoholic and non-alcoholic beverages, each presented with colored outlines (i.e., red, yellow, blue, or green): (1) pictures of alcoholic beverages (e.g., beer, wine, spirits), and (2) pictures of non-alcoholic beverages (e.g., water, orange juice, smoothie). Alcohol AB is indicated by longer reaction times to the alcohol cues than to the non-alcoholic cues (24).

Attentional Bias Measured With Eye Tracker

Multi-stimulus free-viewing task (MSFVT). The MSFVT will be used to also measure patients' AB for alcohol cues. The task consists of 54 matrices, each containing pictures of eight alcoholic and eight non-alcoholic drinks. Each matrix will be presented for 6 s. The task consists of three blocks of 18 trials. Unlike the

alcohol Stroop task, this task is not based on reaction times; instead, it involves eye tracking. For each matrix, the patient is required to gaze at a fixation dot in the center of the screen for 100 ms for the matrix to appear. After a further 2,000 ms interval, the next fixation dot appears (65, 66). Tracking of the patient's eyes will, like the other physiological measure (skin conductance response), be recorded using Imotions.

Alcohol Action Tendency and Inhibition Bias

Alcohol approach-avoidance task (AAT): The AAT measures the degree of alcohol approach bias. During the AAT, patients are requested to react to pictures of the alcoholic drinks by using avoidance responses (i.e., by pushing a joystick away from themselves) and to react to the pictures of non-alcoholic drinks using approach responses (i.e., by pulling a joystick toward themselves). The mean reaction time and the number of correct approach and avoidance responses will be recorded. Similar to AB, approach bias is indicated when reaction times are faster for approaching alcohol cues than for avoiding them, whereas the opposite indicates an avoidance bias (67, 68).

Alcohol Go/No-Go (A-GNG) task: Patients' response inhibition for alcohol cues will be recorded with the A-GNG (69, 70). Here, the patient must respond to pictures of non-alcoholic drinks (e.g.., a bottle of coke or of water; the Go stimuli) and inhibit their responses to alcoholic stimuli (e.g., a bottle of beer; the No-Go stimuli). The following indices will be recorded: Number of commission errors (i.e., *false alarms* or erroneously responding to no-go stimuli), omission errors (i.e.., *misses* or failing to react on go-stimuli), accuracy (i.e., *hits* or the number of correct responses for go-stimuli), and the reaction times for the trials with correct response on go-trials. A high rate of commission errors would indicate that the patient has reduced inhibitory control, whereas a large number of omission errors would indicate lapses in attention (71). To avoid potential practice effects from the baseline to the post-treatment assessments of the experimental tasks, two parallel versions of the experimental tasks will be used.

Clinical Outcomes

Primary Outcome Measures

Alcohol consumption will be measured with the Alcohol Timeline Follow-back (TLFB) method. It involves using a calendar to help the patient retrospectively recall the number of drinks that he/she consumed on each day during the previous 3 months (59, 72). The results will be used to calculate various alcohol consumption measures, including weekly mean drinking, which will be the primary outcome measure.

To validate the TLFB, hair samples from the patients will be tested for ethyl glucuronide (ETG) by liquid chromatography-tandem mass spectrometry (LC-MS/MS). This biological marker of alcohol consumption will be collected and analyzed according to the Society for Hair Testing (73, 74).

Secondary Outcome Measures

A visual analog scale (VAS) will be used to measure patients' alcohol cravings on a scale ranging from *0* to *10*, with *0* indicating no craving at all and *10* indicating extreme craving. The scale will be presented visually on a ruler, and patients will be asked to indicate their mean and peak level of craving during the past 30 days (57, 58).

The Alcohol Abstinence Self-Efficacy Scale is a 40-item measure of patients' temptation to drink and their perceived self-efficacy in abstaining from drinking in 20 different situations that represent typical cues for drinking. Twenty items pertain to temptation, and 20 items pertain to self-efficacy. Patients will rate each item on a scale ranging from *not at all* (0) to *extremely* (4). The measure comprises the following sub-scales: (1) negative affect; (2) social interaction and positive states; (3) physical and other concerns; and (4) withdrawal and urges to drink. Both the temptation and perceived efficacy total score can range from 0 to 80 (60).

The Readiness-to-Change Questionnaire Treatment Version (RTCQ-TV) is a 12-item measure of patients' stated intentions to change their drinking, which includes the following sub-scales: (1) pre-contemplation, (2) contemplation, and (3) action stages. Four items pertain to each sub-scale, and each item is rated on a 5-point Likert Scale ranging from strongly agree (−2) to strongly disagree (+2). The total score can range from −24 to +24 (61, 75).

The Positive and Negative Affect Schedule (PANAS) is a 20-item measure of the patient's affective states, which includes two sub-scales: (1) positive affect and (2) negative affect. Ten items pertain to each sub-scale, and each item is rated on a 5-point scale ranging from *1* (*not at all*) to *5* (*very much*). The total score can range from 20 to 100 (62).

Statistical Analysis

The intent-to-treat principle will be followed in the analyses to evaluate the intervention. A repeated-measures MANOVA with groups as the between-participants factor and assessment time-point as the within-participants factor will be used to test the efficacy of the intervention across the assessment points. Efficacy would be indicated by a significant Time X Study Group interaction. Each of the significant interactions will be followed up with *post-hoc* tests to identify the source of the interaction. Potential demographic covariates (e.g., age, education, income) will also be considered by using MANCOVA. Further, attrition rate at each follow-up time point will be evaluated. Baseline characteristics of participants who remain in the study will be compared with those who have been lost to follow-up. A multiple imputation (MI) approach that adjusts for uncertainty arising from missing data (76, 77) will also be conducted to evaluate the main findings.

Based on MacKinnon (78) mediational procedures, a series of regression analyses will be conducted to test the hypothesized mediational relationships among the outcome variables, i.e., that reductions in *alcohol AB* and *cravings* will partially mediate improvements in the outcome measures. Several ancillary interaction effects will also be evaluated, although they are not hypothesized to be significant. They include potential interactions between the intervention received and patients' drinking history, affective states, and cognitive flexibility. Although the intervention is intended to be effective for all AUD patients, it is important to test this assumption by evaluating

whether the intervention is effective for specific sub-groups of patients.

A power analysis (79, 80) was conducted using G*Power for a repeated-measures MANOVA with $\alpha = 0.05$; effect size (ES) of f =0.20; power = 0.90; groups $k = 3$; and time-points measurements = 4. It showed that 88 participants will be required for the final analyses in each of the four cells (total $N = 264$). Prior evaluations identified fs of 0.30 (AB) and 0.37 (weekly mean drinking) and an f of 0.42 (situational confidence to resist drinking) on outcome measures for sub-clinical excessive drinkers (36). Further, in a study that used the intervention as an add-on treatment for clinical participants with a substance-use disorders other than AUD, effect sizes of fs = 0.33 (drug-specific AB), 0.34 (number of relapses), 0.32 (temptation to use) and 0.37 (self-confidence to resist temptation) were identified (42). Also, an unpublished study conducted with detoxified drug-abusers found fs of 0.39 (drug-specific AB), 0.18 (number of relapses), and 0.35 (temptation to use) (81). A second power analysis for a MANOVA with special effects and interactions was conducted to test the dosage-effect across groups ($\alpha = 0.05$; EF $f^2(v) = 0.06$; power = 0.90; $k = 3$; predictors = 3; and response variables = 8), which yielded an N of 220. Attrition in similar studies has usually ranged from 10 to 15% (41, 42). Assuming a somewhat higher attrition rate (20%), which is not unlikely (82, 83), indicates that 317 (264 + [264·0.20]) participants should be tested at baseline for an analysis using listwise deletion of missing cases, although a multiple imputation (MI) analysis will also be conducted to verify that results converge across missing data assumptions. The projected sample size is sufficient for the planned data analyses, including mediational analyses based on Fitz and MacKinnon's guidelines (84).

Ethics

The patients in this study will undergo primary treatment in the outpatient clinics. Although 66% of them will not receive additional treatment, all patients will be treated with the standard evidence-based AUD treatment. Thus, we find no ethical problems with not offering the add-on intervention to the entire sample. However, a critical ethical question is whether use of the ACTP would encourage patients randomized to the experimental group to consume alcohol instead of discouraging them for doing so. This concern relates to the fact that ACTP involves *in vivo* exposure to alcohol through the alcohol-related pictures. However, in Western cultures, all patients will be continuously exposed to alcohol cues, both during and after treatment, and they will be unable to avoid this because large-scale alcohol advertisements are continuously on public display in magazines and on television. Also, in Denmark alcohol is readily available, highly visible, and easy to buy around the clock in supermarkets, delicatessens, kiosks, and service stations. We, therefore, consider exposure to the alcohol pictures in the experimental group to be no riskier for patients than exposure to them in everyday life. By contrast, in the experimental group, the patients will be trained to focus less on alcohol cues and more on non-alcoholic drinks than in real life. Furthermore, the ACTP will be available only during the opening hours of the alcohol outpatient clinics, and patients in the experimental groups will be provided with a direct telephone number of a therapist in case they experience uncontrollable cravings. Patients in all three of the groups will have the option to call a therapist. All attempts will be taken to intervene in case a patient relapse. The protocol has been approved by the Regional Scientific Ethical Committees for Southern Denmark (Project ID: S-20200200).

DISCUSSION

The present study will investigate whether (1) the AACTP as an add-on intervention increases the effectiveness of a primary evidence-based treatment, and (2) a gamified version of AACTP can be successfully delivered *via* a smartphone application as an add-on. As mentioned in the introduction, the alcohol ACTP has been evaluated in community samples of excessive drinkers, for whom reductions in AB and alcohol consumption were observed post-treatment and at follow-up (32, 36, 37). In the first experimental study, it was found that individuals with harmful alcohol use (drinking > 50 units per week for men and > 35 units per week for women) showed reductions in both AB and alcohol consumption at post-treatment, and these reductions were maintained at a 3-month follow-up (32). In this initial study, the participants served as their own controls, which is a commonly used method in an initial evaluation of a new intervention (85). Hence, after recruitment and assessment, there was, in accordance with this alternative tradition, a waiting period before ACTP was started, and during this period there was no change in either AB or alcohol consumption, but there was a decline in both measures following the introduction of the AACTP intervention 1 month later (32). Similarly, a second randomized controlled study of a sub-clinical sample of hazardous drinkers (22–50 units per week for men and 15–35 units per week for women) and persons with harmful alcohol use found that the ACTP (compared to a non-active control group) was effective in decreasing alcohol consumption at post-treatment and at the 3-month follow-up, but the reductions had attenuated at the 6-month follow-up (36). A third randomized controlled study investigated whether the AATCP could be successfully delivered *via* a fully automated web-based delivery pathway to a community sample of hazardous drinkers. At post-intervention, a reduction in both alcohol craving and alcohol consumption was found in the AACTP group compared to an active sham-control group. However, the effects on alcohol consumption were not maintained at the 3-month follow-up (37). Finally, a fourth study tested a gamified AACTP delivered though a smartphone application in another community sample of hazardous drinkers (18–40 years old). Results indicated that reductions of up to 40% in alcohol consumption had occurred several months after the training (86).

The fact that the AACTP has to date been tested only in community samples of excessive drinkers highlights the need for this program to be tested in clinical AUD samples to determine its effectiveness as a clinical treatment. There are various facets of the training that might need to be altered when using it in a clinical setting. For instance, it might be necessary to increase the number of the AACTP training sessions, because clinical

samples have a stronger AB than community samples, and the AACTP might have specific dosage effects. Furthermore, whereas prior studies conducted with community samples have treated individuals only with the AACTP, this may not be sufficient for treating AUD patients in a clinical setting. For instance, it might be that the AACTP works best when it is used as an add-on to an existing treatment. That is, changing the attentional pattern of selective attention for alcohol cues may be essential but not sufficient for bringing about enduring changes in the addictive behavior. Combining the AACTP with another treatment, such as CBT, might be more effective in the long term than would treatment when delivered separately. Combining psychological treatments that address AUD-related cognitive dysfunctions in the *reflective* and *impulsive* systems might better prepare patients for their inevitable confrontation with alcohol cues in their natural environment and increase the probability of preventing relapses in the longer term. In short, rigorous, and well-powered clinical studies are needed before firm conclusions can be reached about whether the AACTP is an effective clinical treatment.

In recent years, advances on the internet and mobile technologies have made it possible for neuropsychological treatments, such as the AACTP, to be used outside the laboratory, and several pioneering studies have been conducted to test the effects of this approach. For instance, as mentioned earlier, Wiers et al. (37) administered the AACTP over the Internet in its conventional form and found a reduction in users' alcohol consumption (37). Cox et al. (36) administered a gamified AACTP smartphone application and also found both short-term and longer-term reductions in alcohol consumption (86). The AACTP in its original form has some gamification elements (e.g., a progression in level of difficulty, goal-setting, feedback, and time pressure), and Wiers et al.'s (37) study along with other pioneering studies highlight the potential for cognitive-bias modification to be delivered over the Internet.

Clinical neuropsychological treatments, including the AACTP, have shown great promise in treating cognitive dysfunctions not targeted by conventional psychological treatments, and the use of gamification elements may also enhance compliance and the effectiveness of these interventions, as Cox et al. (36) initially confirmed with their gamified version of the AACTP. However, as these authors also note, it is important to be mindful of the target audience when delivering a gamified neuropsychological treatment.

The use of the Internet and mobile devices to deliver a novel treatment to adults might help us improve standard evidence-based treatments for AUD and related disorders (2–4). However, although eHealth-based interventions might have major advantages in terms of increasing availability and reducing the socio-economic burden on society, when targeting clinical AUD populations, these interventions should be delivered only as an add-on for increasing the effectiveness of a treatment that has already been proven to be effective. Because AB for alcohol cues is proportional to the amount of alcohol habitually consumed, and these biases are not addressed within current evidence-based treatment programs, this study is expected to provide new evidence regarding the effectiveness of the gamified AACTP in a clinical population. Furthermore, the intervention should also provide valuable insights into implicit cognitive processes and relationships among alcohol ABs, action-tendency bias (i.e., approach-avoidance bias), and inhibition bias. These implicit processes have all been studied extensively in patients with AUD (16, 25, 87), but there is still a need for more integrative evidence on the associations between the various types of alcohol-related cognitive biases and their role in the maintenance of addictive behaviors (88).

If this study demonstrates that AACTP is effective in patients with AUD, other means of assessing ABs and delivering cognitive training programs could be implemented by utilizing technologies such as virtual reality (VR) and augmented reality [AR; (89)]. These technologies have already been developed for targeting approach biases through the approach avoidance training program (90). Paradigms using VR and AR might overcome some of the shortcomings of the AACTP by increasing its ecological validity. The multimodal nature of these paradigms might cause them to be perceived as closer to real-life situations than other eHealth options (91). Nonetheless, the implementation of VR and AR technologies is an emerging field of research, and the exact implications of their efficacy and effectiveness in treatments targeting AB in AUDs are yet to be examined (91).

Overall, the promising results from the use of AACTP in community samples suggest that the AACTP treatment in this study will be effective, thus paving the way for such a treatment to be implemented in clinical settings. We expect that this study will increase the effectiveness of an existing evidence-based AUD treatment (i.e., CBT) and that it will show that a low-cost and easily available gamified treatment is also effective. Thus, this study is likely to have an impact at the scientific, clinical, and societal level.

ETHICS STATEMENT

The protocol has been approved by the Regional Scientific Ethical Committees for Southern Denmark (Project ID: S-20200200). All participants will be provided with oral and written information about the study and sign written informed consent before enrollment in the study.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study.

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The Moderating Effects of Personal Resources on Caregiver Burden in Carers of Alzheimer's Patients

Anna Sołtys[1], *Mariola Bidzan*[2] *and Ernest Tyburski*[3]*

[1] Institute of Psychology, University of Szczecin, Szczecin, Poland, [2] Institute of Psychology, University of Gdansk, Gdansk, Poland, [3] Department of Health Psychology, Pomeranian Medical University in Szczecin, Szczecin, Poland

Caring for persons with Alzheimer's disease can be an extremely difficult experience. To date, there has been a lack of research into the role of intermediary variables in the relationship between caregiver personality and psychosocial functioning. The growing numbers of dementia patients worldwide mean that more people are involved in their care, making research into this area a pressing concern. Both a caregiver's personality and personal resources play a key role in their capacity to cope with stressful situations. In order to determine how personal resources moderate the relationship between personality and burden of care, a total of 100 caregivers of Alzheimer's patients (78 women and 22 men) were asked to complete a set of questionnaires to assess personality, personal resources (sense of coherence, generalized self-efficacy, and perceived social support), as well as their levels of stress, depression, and commitment to care. Structural equation modeling and latent growth analysis suggest that personal resources explain the mechanisms underlying burden of care and moderate its relationship with personality. Our findings indicate that personal resources are a critical predictor of burden of care. Therefore, caregivers must be provided with appropriate support, taking into account their resources and personality profiles.

Keywords: burden of care, Alzheimer's disease, personality, personal resources, sense of coherence, generalized self-efficacy, perceived social support

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***Correspondence:**
Ernest Tyburski
ernest.tyburski@gmail.com

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INTRODUCTION

Alzheimer's disease (AD) is a progressive, degenerative disease of the nervous system with many negative consequences. It involves cognitive and functional impairment, gradual loss of memory, and behavioral and neuropsychiatric disturbances, which together lead to a significant decline in the ability to perform routine daily activities (1, 2). It is associated with significant suffering in both patients and their caregivers. Early onset of neuropsychiatric symptoms often results in early institutionalization (3), deterioration in quality of life (4), elevated caregiver stress (5), and significantly greater cost of care (6).

Excessive engagement in caregiving leads to poorer physical health (7), anxiety and depressive disorders (8, 9), sleep disorders and increased use of psychotropic drugs (10), poorer quality of life (11, 12), poorer immune response (13), and greater morbidity and mortality (14) in caregivers.

Provision of long-term care may result in significant caregiver burden, reflected in problems with mental, physical, social, economic, and emotional functioning (15). Objective burden refers to the strain manifested in the form of negative outcomes affecting health, social life, work, and the

family system of carers. Subjective burden is linked to individual reactions and experiences, such as tension, anxiety, depression, or feelings of helplessness and loneliness (16, 17). The associated changes to one's life alongside the need to give up some, if not all, of one's previous activities, needs, and expectations in order to care for the patient may lead to a significant feeling of burden in caregivers (18). Interestingly, a greater sense of responsibility for the patient is associated with a reduced quality of care, leading to neglect, abuse, reluctance, and premature institutionalization (19, 20).

Personality and Caregiver Burden

Personality seems to play a central role in caregiver burden. Caregivers with less mature personality types, especially high neuroticism, have been shown to be at higher risk of experiencing severe caregiver burden (21–23). Therefore, it is necessary to study the relationship between personality and burden of care, as well as the mechanisms that potentially mediate it. To date, studies on caregivers of dementia patients have shown that it is necessary to take personality into account in care research, as it plays a significant role in caregiving. High levels of neuroticism have been reported to be associated with greater stress and depressive disorders (24–26), while high levels of extroversion and agreeableness have been linked with lower sense of burden (27–29). Openness to experiences and cognitive flexibility are linked with greater senses of cognitive, emotional, and physical well-being (29, 30) as well as lower mortality (31, 32). On the other hand, high levels of conscientiousness correlate with better cognitive functioning (33) and more pro-health behaviors (34). Therefore, the aim of this study was to examine the relationship between personality and caregiver burden, taking into account the moderating effects of personal resources.

Sense of Coherence as a Moderating Variable

Due to the key role of caregivers in the provision of care, it seems of paramount importance to examine factors that may protect against caregiver burden. Previous studies have indicated that sense of coherence (SOC) plays a significant role in alleviating caregiver burden and preventing the development of depressive symptoms (35–40). Other findings suggest that a high SOC is associated with reduced caregiver burden and sense of isolation as well as better mental health (41, 42). The ability to find meaning, to understand one's experience, to positively re-evaluate one's situation, and the belief that one has can cope with the challenges of care are all critical factors that protect against depression (36, 43, 44) and reduce caregiver stress (37). In his concept of salutogenesis, Antonovsky points out that personality traits determine behavior in people with low SOC, while it seems to work the other way around in those with high SOC (45). Sense of coherence is therefore an important buffer against the negative influence of personality.

Social Support as a Moderating Variable

The exact relationships between personal resources and caregiver burden is poorly understood. Among personal resources, social support seems to play a particularly significant role in shaping the sense of burden and the development of depressive symptoms (46–48). However, little is known about the mediating role of social support in the relationship between personality and sense of burden. Kim et al. (49) indicate that previous studies provide no evidence that social support has a mediating role in the relationship between personality and mental health. Wang et al. (50) suggest that social support may act as a moderator in the relationship between factors related to the functioning of the patient and the feeling of burden in the caregiver. Social support alleviates the impact of cognitive impairment and depressive symptoms on caregiver's burden. Ong et al. (51) showed that both mental resilience and perceived social support contribute to a caregiver's sense of burden, and the relationship between mental resilience and the sense of being overburdened by the work of caring is may be affected by the level of perceived social support. In a study by Dias et al. (52), social support turned out to moderate mental resilience, with various types of support alleviating the physical and psychological effects of burden of care.

Self-Efficacy as a Moderating Variable

According to the theory of social learning, self-efficacy, expressed *via* an individual's conviction about their capacity to act, promotes better coping (53). Previous studies emphasize the significant role of self-efficacy in reducing levels of stress, depression (54), and the sense of burden (55–57). One study on caregivers of people with dementia demonstrated the moderating effect of caregiver self-efficacy on the relationship between the behavioral and psychological symptoms of dementia and subjective burden of care, as well as between social support and burden of care (58). Self-efficacy reduced the impact of behavioral and psychological symptoms of dementia on the subjective strain experienced by the carers. The relationship between social support and burden was influenced by the caregiver's level of self-efficacy. Therefore, enhancing the sense of self-efficacy should be an important element of interventions aimed at reducing caregiver burden.

Aims of the Study

This study aimed to investigate (1) whether there is a relationship between the Big Five personality dimensions and psychological and social burden in caregivers of Alzheimer's patients, (2) whether personal resources explain the mechanism underlying the development of caregiver burden, and (3) whether the indirect relationship between personality and caregiver burden is moderated by personal resources (sense of coherence, perceived social support, and generalized sense of self-efficacy). Based on the current literature, we hypothesize that: there is a relationship between the Big Five personality dimensions and psychological and social burden in caregivers of Alzheimer's patients (hypothesis 1); personal resources explain the mechanism of caregiver burden (hypothesis 2); and personal resources moderate the strength of the relationship between personality and caregiver burden (hypothesis 3). All hypotheses and relations between variables are presented in **Figure 1**. Given the relative paucity of research concerning the unique effect of personal resources on the relationship

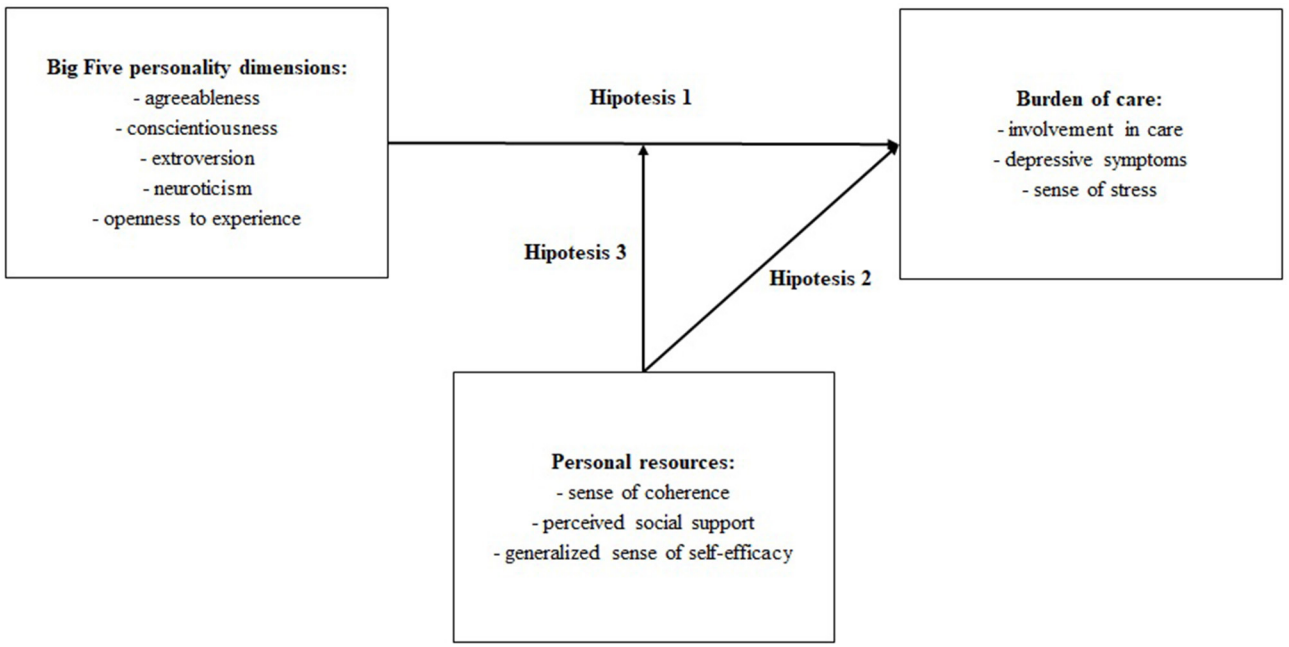

FIGURE 1 | Theoretical model of the relationship between variables (based on literature and studies presented in the introduction).

between personality and caregiver burden, we believe that a better understanding of personal resources is crucial for the development of therapeutic strategies.

METHODS

Procedure and Study Design

This cross-sectional observational study was conducted in a sample of family caregivers recruited from local support centers and welfare institutions, as well as formal caregivers (employees of the aforementioned centers). We conducted home visits (in the case of informal caregivers) and institutional visits (for formal caregivers) that included established demographic interviews and questionnaire sets provided in the same order. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Institute of Psychology at University of Szczecin (KB 2/2017). All participants gave written informed consent. Participation in the study was voluntary, confidential, and the personal well-being of the respondents was of utmost importance. Significant inclusion criteria were: having been a carer for a minimum of 2 years and providing at least 8 h of care per week to a patient with Alzheimer's disease. Exclusion criteria were provision of care to a patient with a different type of dementia, death of the patient, and the caregiver being under 18 years old.

Participant Characteristics

The sample consisted of a total of 100 primary caregivers of Alzheimer's patients (the informal carers group consisted of 50 family members of patients with AD and the formal caregivers group consisted of 50 employees of help centers providing care for AD patients), including 78 women and 22 men, who provided care for $M = 28.82$ ($SD = 6.39$) hours a week, and whose mean age was $M = 55.84$ ($SD = 13.36$) and total duration of care was $M = 5.18$ years ($SD = 4.25$). Most respondents (58%) devoted >32 h a week to caring for AD patients, 28% spent 17-32 h, and 14% spent 8-16 h caring. A total of 37 of the AD patients being cared for were in the first stage of the disease, 44 were in the second stage, and 19 were in the third stage of the disease. We defined the stages of AD based on (59). The primary carers were children (46%), spouses/partners (34%), or other relatives (12%), friends (6%), and siblings (2%) of the patients.

Psychological Assessment

To meet our research aims, we selected the relatively more significant personal resources and factors related to caregiver burden: sense of coherence, perceived social support, and generalized sense of self-efficacy. To assess the personality traits of the caregivers, we used the NEO Personality Inventory (NEO-PI-R) (60). This is a 240-item questionnaire, with each statement rated on a 5-point scale. The scores are presented on six scales: agreeableness, conscientiousness, extroversion, neuroticism, and openness to experience. The Polish version of the NEO-PI-R has high reliability (Cronbach's alpha equals from 0.81 to 0.86 for each scale). Sense of coherence was examined using Antonovsky's Sense of Coherence Scale (SOC-29) (61). This 29-item questionnaire (each statement rated on a seven-point scale) measures general sense of coherence and its three domains: comprehensibility, manageability, and meaningfulness. The Polish version of the SOC-29 has high reliability (Cronbach's alpha ratio in the entire sample between 0.78 and 0.95). The social support of carers was examined using

the Perceived Social Support Questionnaire (F-SozU K-22; 22 items, with each statement rated on a five-point scale) (62), which quantifies the general level of perceived social support as well as its three dimensions: emotional support, practical support, and social integration. The Polish version of the F-SozU K-22 has high reliability (Cronbach's alpha ratio in entire sample 0.91). Generalized self-efficacy was measured using the Generalized Self-Efficacy Scale (GSES) (63). This is a 10-items questionnaire (each statement rated on a four-point scale) and the Polish version has high reliability (Cronbach's alpha ratio in entire sample 0.85). The level of caregiver burden was estimated based on involvement in care, sense of stress, and depression. For this purpose, we used the Involvement Evaluation Questionnaire (IEQ) (64) to determine the general level of burden and its four domains (tension, supervision, worrying, urging). This is a 29-item questionnaire, with each statement rated on a five-point scale. The Polish version of the Depression Assessment Questionnaire (DAQ; 75-items questionnaire; each statement rated on a four-point scale) (65) was used to assess depression and the four aspects thereof: cognitive deficits and energy loss; thoughts about death, pessimism, and alienation; guilt and anxiety; psychosomatic symptoms and loss of interests; and an additional fifth scale for assessing self-regulation to measure resources that protect against depression. Most of the DAQ scales have high or very high reliability (Cronbach's alpha ratios range from 0.70 to 0.97). The Sense of Stress Questionnaire (SSQ; 29-item questionnaire, with each statement rated on a seven-point scale) (66) was used to determine general levels of stress as well as emotional tension, external stress, and social integration. The Polish version of the SSQ has high reliability (Cronbach's alpha equal to 0.78).

Statistical Analysis

Pearson r correlation coefficient was used to establish the relationships between the investigated variables (testing the first hypothesis). Correlation analysis was performed with the GNU PSPP-0.10.1-gbe241b program. Partial least squares structural equation modeling (PLS-SEM) in the WarpPLS 6.0 0 program (67) was used to examine the relationships between personal resources and caregiver burden. Finally, Full Latent Growth Analysis (68) was used to investigate the moderating effects of personal resources. To test the second hypothesis, partial least squares structural equation modeling was performed with WarpPLS 6.0 (67). The analysis revealed that the model was free of average and full collinearity (AVIF = 1.26, AFVIF = 1.59) and had very good predictive power (GoF = 0.53). Moreover, to test the third hypothesis, we performed Full Latent Growth Analysis (69). Sometimes the inclusion of moderating variables and corresponding indicators in PLS-SEM may lead to problems, such as increased levels of collinearity and the emergence of Simpson's Paradox (67); these problems may be avoided if Full Latent Growth Analysis is applied. This method is used to estimate the effects of a latent variable or indicators on all paths in the model (all at once) without the need to include any new paths or variables. Full Latent Growth Analysis should be viewed as a comprehensive statistical analysis of moderating effects, where the moderating variable is latent in the sense that it does not "disturb" the model in any way. The form of this analysis is conceptually similar to Multi Group Analysis (70). The model that was verified in subsequent stages took into account single consecutive moderating variables. PLS-SEM was used because there is a tiny sample size and the amount of latent and visible variables is large in comparison to the number of observations. A PLS-SEM model is a path model in which some variables may be effects of others, while still being causes for variables later in the hypothesized causal sequence. It is a good alternative to covariance-based structural models, so it is a method that can be viewed as a comprehensive analysis of moderating effects in which the moderating variable is latent (68).

RESULTS

Personality and Psychological and Social Burden

Statistics for all investigated variables are presented in **Table 1** (mean scores of all variables), **Table 2** (correlations between variables). There is a positive relationship between neuroticism and all dimensions of burden. High levels of neuroticism in caregivers are associated with greater involvement in care, more severe depressive symptoms, and greater stress. In turn, carers who report high levels of extroversion, openness to experience, agreeableness, and conscientiousness reveal fewer depressive symptoms and less perceived stress. Our results thus confirm that there is a relationship between the Big Five personality dimensions and sense of mental and social burden in the caregivers of AD patients (hypothesis 1). In particular, carers manifesting high levels of neuroticism are at greater risk of feeling overburdened with care.

The Effect of Personal Resources on the Variance of Perceived Burden of Care

Hypothesis 2 suggested that personal resources explain the mechanism underlying perceived burden of care. The tested model is presented in **Figure 1**. The goodness of fit statistics are presented in **Table 3**.

The statistics for all variables are presented in **Table 4**. The analysis of path coefficients for the model showed that a rise in sense of coherence was linked with reduced depression, sense of stress, and involvement in care. As **Table 4** shows, elevated perceived social support is associated with reduced sense of stress, while increased generalized self-efficacy is associated with greater involvement in care. Our analysis shows that the largest portion of the explained variance was observed when measuring the general sense of stress, as presented in **Table 5**. The results allowed for a partial confirmation that personal resources explain the mechanism underlying caregiver burden (hypothesis 2). And so, as personal resources increase, the sense of burden of care tends to drop.

Testing for Moderating Effects

Hypothesis 3 suggested that personal resources moderate the relationship between personality and perceived burden of care. The results suggest that personal resources moderate the strength

TABLE 1 | Mean scores of all variables in the studied group ($n = 100$).

	Caregivers		
	M	*SD*	Min-Max
Personality (NEO-PI-R)			
Neuroticism	84.50	19.59	40-133
Extroversion	98.81	22.37	46-161
Openness to experience	102.24	19.31	54-153
Agreeableness	121.77	15.63	38-160
Conscientiousness	123.49	17.13	72-163
Sense of coherence (SOC-29)			
General sense of coherence	139.29	20.41	96-188
Comprehensibility	49.05	7.84	27-71
Manageability	47.95	7.34	28-64
Meaningfulness	38.66	6.22	26-52
Perceived social support (F-SozU K-22)			
General level of perceived social support	87.59	14.48	30-110
Emotional support	27.00	4.34	11-35
Practical support	32.90	5.30	18-40
Social integration	28.19	4.82	16-35
Generalized self-efficacy (GSES)			
Generalized self-efficacy	28.74	4.92	16-40
Involvement in care (IEQ)			
General level of burden	1.78	0.63	0-3
Urging	2.37	0.98	0-4
Supervision	1.12	0.82	0-4
Tension	1.26	0.77	0-3
Worrying	1.99	0.93	0-4
Depressive symptoms (DAQ)			
General levels of depression	99.64	23.23	61-163
Cognitive deficits and energy loss	32.17	8.19	19-53
Thoughts about death, pessimism, and alienation	20.88	5.22	15-36
Guilt and anxiety	28.15	6.55	16-47
Psychosomatic symptoms and loss of interests	18.44	5.06	10-31
Self-regulation	40.34	6.08	25-55
Sense of stress (SSQ)			
General levels of stress	53.72	14.48	25-80
Emotional tension	19.84	5.79	8-35
External stress	16.96	5.57	7-29
Social integration	16.92	4.95	7-31

DAQ, Depression Assessment Questionnaire; F-SozU K-22, Perceived Social Support Questionnaire; GSES, Generalized Self-Efficacy Scale; IEQ, Involvement Evaluation Questionnaire; NEO-PI-R, NEO Personality Inventory; SOC-29, Antonovsky's Sense of Coherence Scale; SSQ, Sense of Stress Questionnaire.

TABLE 2 | Correlations between personality dimensions and caregiver burden.

	Involvement in care (IEQ)	Depressive symptoms (DAQ)	Sense of stress (SSQ)
Neuroticism	0.26*	0.45**	0.69**
Extroversion	−0.19	−0.39**	−0.57**
Openness to experience	−0.03	−0.23*	−0.31**
Agreeableness	−0.04	−0.23*	−0.21*
Conscientiousness	0.06	−0.33***	−0.41**

DAQ, Depression Assessment Questionnaire; IEQ, Involvement Evaluation Questionnaire; SSQ, Sense of Stress Questionnaire.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.*

TABLE 3 | Goodness of fit statistics.

Ratio	Value
AVIF	1.26
AFVIF	1.59
Tenenhaus GoF	0.53
SPR	1.00
SSR	0.78

AFVIF, Average full collinearity VIF; AVIF, Average variance inflation factor; GoF, Goodness of fit expressed in generalized predictive power of the model; SPR, Simpson's Paradox Ratio; SSR, Statistical Suppression Rate.

TABLE 4 | Path coefficients in the tested model.

	Sense of coherence (SOC-29) PK—β	Perceived social support (F-SozU K-22) SWS—β	Self-efficacy (GSES) PWS—β
Depressive symptoms	−0.44***	−0.11	−0.13
Sense of stress	−0.47***	−0.21*	−0.06
Involvement in care	−0.40***	0.06	0.28**

β, Standardized beta coefficient; F-SozU K-22, Perceived Social Support Questionnaire; GSES, Generalized Self-Efficacy Scale; SOC-29, Antonovsky's Sense of Coherence Scale.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.*

TABLE 5 | Explained variance of the tested dimensions of caregiver burden.

Measurement	R^2	ΔR^2	Q^2
Depressive symptoms	0.30	0.28	0.30
Sense of stress	0.38	0.36	0.38
Involvement in care	0.15	0.13	0.16

R^2, Coefficient of explained variance; ΔR^2, Corrected ΔR^2; Q^2, Nonparametric equivalent of R^2.

of the relationship between personality and perceived burden of care, which is in line with Hypothesis 3.

The Moderating Effect of General Sense of Coherence

Our analysis showed that an increase in levels of general SOC entailed a greater effect of neuroticism on guilt and anxious tension alongside a lesser effect of neuroticism on psychosomatic symptoms and loss of interests, interpersonal tension, supervision, and urging. Further analysis showed that in response to an increase in general SOC, the impact of extroversion on guilt and anxious tension tended to drop, while its effect on the level of psychosomatic symptoms and loss of interest, interpersonal tension, supervision, and urging increased. Furthermore, an increase in general SOC increased the

TABLE 6 | The moderating effect of sense of coherence on the relationship between personality and burden of care.

PK—β	Neuroticism	Extroversion	Openness to experience	Agreeableness	Conscientiousness
Depressive symptoms (DAQ) as a moderator					
Cognitive deficits and energy loss	0.15	−0.07	−0.04	0.13	0.23**
Thoughts about death, pessimism, and alienation	0.14	−0.03	−0.03	0.05	0.21**
Guilt and anxiety	0.26**	−0.20*	−0.05	0.05	0.08
Psychosomatic symptoms and loss of interests	−0.25**	0.19*	0.43***	0.05	0.11
Self-regulation	−0.16	0.10	−0.05	0.03	−0.02
Involvement in care (IEQ) as a moderator					
Tension	−0.35***	0.32***	0.48***	0.04	0.05
Worrying	−0.05	0.00	0.19*	0.04	0.04
Supervision	−0.21*	0.32***	0.27**	−0.14	0.07
Urging	−0.31***	0.33***	0.38***	−0.15	0.14
Sense of stress (SSQ) as a moderator					
Emotional tension	−0.01	−0.02	0.19*	0.11	0.16
External stress	−0.13	0.14	0.27**	0.08	0.04
Social integration	−0.03	0.00	0.21*	0.11	−0.07

β, Standardized beta coefficient; DAQ, Depression Assessment Questionnaire; IEQ, Involvement Evaluation Questionnaire; SSQ, Sense of Stress Questionnaire.
$^{*}p < 0.05$. $^{**}p < 0.01$. $^{***}p < 0.001$.

impact of openness to experience on psychosomatic symptoms, loss of interests, interpersonal tension, worrying, supervision, urging, emotional tension, external stress, and intrapsychic stress. General SOC did not moderate any relationship between agreeability and individual stress measures. In turn, an increase in general SOC led to an increase in the effect of conscientiousness on cognitive deficits and energy loss as well as thinking about death, pessimism, and alienation. All results are presented in **Table 6**.

The Moderating Effect of Perceived Social Support

Our analysis showed that with increased perceived social support, the influence of neuroticism on thinking about death, pessimism, and alienation, guilt, and anxious tension tended to rise, while its impact on psychosomatic symptoms and loss of interests, interpersonal tension, worrying, supervision and urging was likely to drop. Further analysis showed that as general perceived social support increased, so did the impact of extroversion on psychosomatic symptoms and loss of interests, interpersonal tension, supervision, and urging, while its effect on guilt and anxious tension decreased. A rise in general perceived social support also entailed an increase in the impact of openness to experience on psychosomatic symptoms and loss of interests, interpersonal tension, worrying, supervision, urging, and external and intrapsychic stress. We did not observe a moderating effect of general perceived social support on the relationship between agreeableness and caregiver burden measures. Further analysis showed that as general perceived social support increased, so did the effect of conscientiousness on thinking about death, pessimism, and alienation, worrying, and urging, while its influence on emotional stress tended to drop. All results are shown in **Table 7**.

The Moderating Effect of Generalized Self-Efficacy

Our analysis showed that the effect of neuroticism on cognitive deficits, energy loss, thinking about death, pessimism, and alienation, as well as the effect of extroversion on supervision were likely to increase with increased self-efficacy. No moderating effect of generalized self-efficacy was found on the relationship between openness to experience and caregiver burden measures. We did, however, observe that as self-efficacy scores increased, the impact of agreeableness on thinking about death, pessimism, and alienation, guilt and anxious tension, and supervision was likely to drop. Further analysis also demonstrated that a rise in generalized self-efficacy led to a decrease in the effect of conscientiousness on interpersonal tension and supervision and an increase in its impact on cognitive deficits and energy loss. The results are presented in **Table 8**.

DISCUSSION

In this study, we analyzed the relationship between personality and caregiver burden in the carers of people with Alzheimer's disease, taking into account the variables moderating said relationship.

Relationship Between Personality and Psychological and Social Burden

The results partially confirmed the first hypothesis. Our results showed that highly neurotic caregivers report a greater burden of care. In turn, carers who are more extroverted, open to experience, agreeable, and conscientious experience less stress and fewer depressive symptoms. Largely in line with our findings, previous studies also indicate that personality is significantly associated with stress levels. A particularly high level of neuroticism among caregivers is associated with the use of

TABLE 7 | The moderating effect of perceived social support on the relationship between personality and burden of care.

SWS—β	Neuroticism	Extroversion	Openness to experience	Agreeableness	Conscientiousness
Depressive symptoms (DAQ) as a moderator					
Cognitive deficits and energy loss	0.12	−0.04	−0.05	0.10	0.06
Thoughts about death, pessimism, and alienation	0.18*	−0.11	−0.01	0.14	0.16*
Guilt and anxiety	0.25**	−0.21*	−0.08	−0.02	0.06
Psychosomatic symptoms and loss of interests	−0.22*	0.27**	0.37***	0.02	0.03
Self-regulation	−0.10	0.12	0.03	−0.09	−0.06
Involvement in care (IEQ) as a moderator					
Tension	−0.49***	0.47***	0.49***	−0.05	0.03
Worrying	−0.25**	0.11	0.21*	−0.07	0.17*
Supervision	−0.30***	0.25**	0.22*	−0.08	0.13
Urging	−0.45***	0.26**	0.30***	−0.04	0.18*
Sense of stress (SSQ) as a moderator					
Emotional tension	0.13	−0.09	0.02	0.02	−0.21*
External stress	−0.10	0.15	0.22*	0.03	0.07
Social integration	0.01	0.03	0.18*	−0.11	0.06

β, Standardized beta coefficient; DAQ, Depression Assessment Questionnaire; IEQ, Involvement Evaluation Questionnaire; SSQ, Sense of Stress Questionnaire.
**p < 0.05. **p < 0.01. ***p < 0.001.*

TABLE 8 | The moderating effect of generalized self-efficacy on the relationship between personality and burden of care.

PWS—β	Neuroticism	Extroversion	Openness to experience	Agreeableness	Conscientiousness
Depressive symptoms (DAQ) as a moderator					
Cognitive deficits and energy loss	0.29**	−0.08	−0.07	−0.03	0.16*
Thoughts about death, pessimism, and alienation	0.09	0.15	−0.01	−0.26**	0.03
Guilt and anxiety	0.17*	0.00	0.01	−0.21*	0.05
Psychosomatic symptoms and loss of interests	0.00	−0.01	0.10	−0.06	0.03
Self-regulation	−0.04	0.01	−0.09	0.05	0.01
Involvement in care (IEQ) as a moderator					
Tension	−0.05	−0.03	0.05	−0.13	−0.20*
Worrying	−0.01	0.04	−0.05	−0.05	0.01
Supervision	−0.12	0.24**	−0.01	−0.28**	−0.17*
Urging	−0.01	0.10	0.05	−0.11	−0.10
Sense of stress (SSQ) as a moderator					
Emotional tension	0.11	−0.04	0.10	0.06	0.13
External stress	0.02	0.12	0.10	−0.06	0.11
Social integration	0.01	−0.07	0.15	−0.08	0.03

β, Standardized beta coefficient; DAQ, Depression Assessment Questionnaire; IEQ, Involvement Evaluation Questionnaire; SSQ, Sense of Stress Questionnaire.
**p < 0.05. **p < 0.01.*

maladaptive strategies to cope with the demands of care (21, 22) and a greater need to control the care recipient (23). There are also links between neuroticism and depression (71, 72), increased sense of stress (73), greater sensitivity to care-related stressors (74), and fewer pro-health behaviors (71) in the population of carers.

In turn, high levels of extroversion in carers are associated with fewer negative emotions, less severe depressive symptoms (49, 75), and better physical and mental health (73). Highly extroverted caregivers are more involved in interpersonal relationships, more optimistic and cordial toward others, and generally more active, which means that they are likely to find more benefits in caring for others (74) and be less sensitive to care-related stressors (76).

Caregiver agreeableness is associated with greater readiness to help, kindness, and trust, thus fostering relationships with care recipients (77), allowing them more freedom in functioning (23), reducing caregiver stress (78), and helping them maintain better mental health (28, 29).

Similarly, high levels of conscientiousness, associated with greater purposefulness and determination, meticulousness, reliability, and sense of duty, are conducive to maintaining better relationships with recipients of care (77), more positive perceptions of the care situation (74, 77), fewer depressive

symptoms, more pro-health behaviors (34), better cognitive functioning (33), and lower mortality (28, 31, 32).

Caregiver openness to experience is linked to greater curiosity and cognitive flexibility. Evidence suggests that it is also associated with caregiving-related growth (77), higher levels of emotional, cognitive, and physical well-being (29, 30), and lower mortality (31, 32).

Our results are consistent with research to date, suggesting that caregivers with less mature personality types are more vulnerable to experiencing greater burden of care (23). Numerous authors indicate that neuroticism is associated with greater stress and depressive symptoms (24–26, 72). In turn, other personality traits are associated with better mental and physical health in caregivers (78). It therefore seems reasonable to include personality in conceptual models and research pertaining to care.

Relationship Between Personal Resources and Perceived Burden of Care

A partial confirmation of the second hypothesis was possible, our findings suggest that caregivers with greater sense of coherence exhibit less burden due to provision of care. It is therefore consistent with previous reports indicating that high levels of SOC lead to reduced experience of stress (37, 44), lower burden of care (41, 42) and less severe depressive symptoms (36, 43, 44, 79). As a meta-resource, SOC seems to have a significant effect on stress. Enhancing caregivers' capacity to comprehend their situation, their ability to find meaning in their experience, and the belief that they can manage all the potential adversities ahead can help them develop adequate coping strategies and reduce the level of burden resulting from provision of care (80).

We also found perceived social support to be associated with reduced stress in caregivers, which is consistent with other studies (81, 82). Previous reports also indicate that a high level of perceived social support may lead to reduced level of burden (83), reduced depressive symptoms (84), and alleviation of negative effects of care (17, 85, 86).

Carers with high levels of generalized self-efficacy were reported to manifest greater commitment to caregiving. The available evidence suggests that a high generalized sense of self-efficacy may result in reduced stress and fewer depressive symptoms experienced by caregivers (54) and lower burden of care (55–57, 87). Such results may highlight another aspect of self-efficacy: feeling that one is able to deal with stressors and having confidence in one's competence. Based on the belief that they have the capacity to cope with the demands of care, caregivers can become more involved in caring activities and take more control over the functioning of their patients.

Moderating Effects of the Relationship Between Personality and Burden of Care

The third hypothesis was confirmed in a complex way. The nature of the relationship between personality and burden of care can be explained by in-depth analyses with sense of coherence as a moderator. In our research, we found that SOC moderated the relationship between caregiver personality and burden of care. We found that increased SOC was linked with stronger relationships between neuroticism and guilt and anxious tension as well as weaker relationships between neuroticism and psychosomatic symptoms and certain aspects of commitment to care—interpersonal tension, supervision, and urge. Given that, as a trait, neuroticism is associated with experiencing negative emotions, anxiety, and fear, highly neurotic caregivers who have the capacity to positively re-evaluate their situation and find meaning in their experience, to understand the challenges ahead, and are sure of their ability to cope with the tasks involved in caring may still be prone to the presence of increased, unfounded anxiety, emotional problems, and self-blame. On the other hand, they are less vulnerable to developing psychosomatic symptoms (i.e., problems with sleep or concentration), experience less tension in their relationships with care recipients, are less likely to control their functioning, and more likely to foster their independence. According to the theory of salutogenesis (45), the availability of resources is not the only condition for successful coping. A possible explanation of our results may be that neuroticism manifested as a general tendency to feel negative emotions may hinder adaptation and coping. Other reports suggest that neuroticism may be associated with lower SOC (88, 89). It can therefore be assumed that high levels of SOC among highly neurotic caregivers constitute only a partial protection against depressive symptoms. On the other hand, they may serve as an important protective factor against over-involvement in care.

The results of our research also demonstrated that an increase in SOC led to weaker relationships between extroversion and guilt and anxious tension and stronger relationships between extroversion and decreased psychosomatic symptoms, tension in relationships with care recipients, supervision, and urging. We also observed that with increased SOC, openness to experience was more associated with a decrease in psychosomatic symptoms, supervision, and all investigated types of stress. In addition, it was more closely linked with increased tension in relations with care recipients and worrying. Furthermore, we found that an increase in SOC was linked to a greater association between conscientiousness and decreased cognitive deficits and thinking about death. Our results are consistent with previous reports, highlighting the key role of SOC in reducing the sense of burden (41, 42), depressive symptoms (36, 43, 44, 79), and the severity of stress (37, 44). The analysis of personality traits leads to very diverse conclusions, especially in relation to involvement in care. High levels of openness to experience are associated with an increase in tension in relations with the care recipient and an increase in concerns about the patient and their future. This may be due to more frequent positive and negative feelings experienced by more open caregivers and their greater cognitive curiosity, which may be additionally reinforced by a high sense of comprehensibility, meaningfulness, and their self-perceived capacity to cope. The role of openness to experience seems to be somewhat overlooked in research. It is worth emphasizing, however, that the sense of coherence plays an important intermediary role in shaping the sense of caregiver burden. Previous studies indicate that sense of coherence plays a significant role in the perception

of mental health (90) and the development of psychosomatic disorders (91).

The nature of the relationship between caregiver personality and burden of care is also explained by the moderating effect of perceived social support. We found increased perceived social support to be linked to neuroticism having a stronger relationship with decreased thinking about death and increased guilt and anxious tension. At the same time, it had a weaker relationship with increased psychosomatic symptoms, tension in relations with the patient, worrying, supervision, and urging. On the other hand, increased perceived social support resulted in extroversion having a stronger relationship with decreased psychosomatic symptoms and tension in relations with the patient, as well as increased supervision, and its having a weaker relationship with decreased guilt. Perceived social support also moderated the relationship between openness to experience and conscientiousness and the investigated dimensions of caregiver burden. Openness to experience was more associated with a decrease in psychosomatic symptoms and supervision, as well as an increase in tension in relationships with the patient, worrying, urging, and external and intrapsychic stress. Conscientiousness, on the other hand, was more closely related to decreased thinking about death and increased worrying and urging. At the same time, it was less associated with decreased emotional tension. Previous studies indicate a significant role of social support in reducing care-related stress (81, 82, 92, 93), burden of care (15, 46–48), and depression (84). Researchers particularly emphasize the key role of family support in alleviating the negative effects of stress (17, 85, 86, 94). Ong et al. (51) describe the mediating effect of social support on the relationship between mental resilience and burden. In turn, Kim et al. (49) point out that there is insufficient evidence that support plays a mediating role between personality and mental health. Our findings suggest that the potential moderating role of social support remains somewhat unclear. Increasing tension in the relationship between the caregiver and the care recipient may lead to greater involvement in care. On the other hand, making efforts to maintain a high level of support (greater social activity, fostering interpersonal relationships) may increase the tension due to the patient's greater expectations concerning the amount of time and attention they should receive.

The nature of the relationship between caregiver personality and burden of care is also explained by the analyses of the moderating effect of generalized sense of self-efficacy. Our research showed that with increased generalized sense of self-efficacy, neuroticism had a stronger relationship with increased cognitive deficits and decreased thinking about death. We also found extroversion to have a stronger relationship with increased supervision, while agreeableness had a weaker relationship with decreased thinking about death, guilt, and supervision. Along with the increase in self-efficacy, conscientiousness was less related to the increase in tension in relations with the patient and supervision, and more related to decreased cognitive deficits. Studies to date indicate a significant role of self-efficacy in reducing sense of burden (55–57, 87) as well as levels of stress and vulnerability to depression (54). Interestingly, our findings suggest the opposite relationship. Self-efficacy, associated with a high level of confidence in one's own competence and self-perceived capacity to cope, may lead to greater involvement in care. A high sense of self-efficacy may be linked to the need to take more control over the patient's functioning. According to Bandura's socio-cognitive theory (53), taking action may be accompanied by the belief that said action is worth the effort.

Thus, personal resources play an important role in moderating the relationship between personality and burden of care. However, their moderating effects in the studied sample are rather diverse. Our research indicates that personality has both a direct and indirect effect on caregiver burden, in the latter case involving personal resources. Hence, to improve caregivers' functioning and reduce their perceived burden of care, it is essential to take into account their personality traits and the repertoire of personal resources they have at their disposal.

Limitations, Strengths, and Future Directions

This study had several strengths and limitations. First of all, a major limitation is its relatively small sample size. Further research could include larger groups. Nevertheless, this research provokes reflection on the factors that could play a significant role in improving the psychosocial functioning of caregivers. Studies to date tend to focus mainly on the negative consequences of providing care, therefore it seems all the more necessary for further research to shed light on the role of resources in reducing the sense of burden. In the future, this aspect of caregivers' functioning should be addressed using a larger group of respondents. Another important limitation is the relatively small number of male carers. Previous studies show that it is women rather than men who tend to provide care and are mainly responsible for ill persons (95–97). It therefore seems crucial to investigate the situation of men who undertake caregiving roles. In addition, in this study we have focused on caregivers of people with Alzheimer's disease. Further research could consider patients with other types of dementia, such as frontotemporal dementia, vascular dementia, and Lewy body dementia.

Despite these limitations, the study also had several strengths. First of all, to the best of our knowledge, this study is one of the few that have considered the role of personality components in the development of caregiver burden. One of its major strengths is therefore its approach toward personal resources as important determinants of the relationship between caregiver personality and burden, thus helping to identify factors that can transform or prevent negative consequences of care.

Our findings shed further light on the factors that may be construed as critical in shaping perceived burden of care. The results of this study could prove useful for both psychological practice and psychoeducation. Furthermore, this study suggests that the caregiver's personality and personal resources should be considered when developing assistance programs. Proper assessment of a caregiver's personality and personal resources

could help identify the most significant contributors to subjective feeling of burden.

CONCLUSIONS

This study provides evidence that carers with less mature personality types are more likely to be burdened with care, thus confirming the key role of personality components in caregiver burden. In addition, personal resources are an important predictor of burden of care. The nature of the relationship between personality and perceived burden depends on levels of personal resources. Therefore, it seems crucial to properly support caregivers and strengthen their resources. This may have implications for future research. Proper assessment of resources and personality should be an important goal for all psychotherapeutic activities. Identification of the factors that make one vulnerable to increased burden can help in the selection of the most suitable strategies for coping with the demands of care. Therefore, to protect the caregiver against depression and reduce their stress and burden, it seems of utmost importance to undertake all the necessary measures to rebuild or recover any resources that might have been lost or depleted. Such actions can also protect against premature institutionalization of patients. Individual caregiver personality profiles and assessment of personal resources could improve the provision of effective aid to carers.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Institute of Psychology at University of Szczecin (KB 2/2017). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS was the coordinator of the project, was involved in the study design, took part in recruitment of the participants, conducted research, managed the literature searches and analyses, performed the statistical analysis, and wrote the first draft of the manuscript. MB was involved in the study design, was a supervisor, and corrected the manuscript. ET was involved in the study design, took part in recruitment of the participants, managed the literature searches and analyses, performed the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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CASE REPORT
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Case Report: Repeated Series of Ketamine Infusions in Patients With Treatment-Resistant Depression: Presentation of Five Cases

Maria Gałuszko-Węgielnik, Adam Włodarczyk, Wiesław Jerzy Cubała, Alina Wilkowska, Natalia Górska and Jakub Słupski*

Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland

Purpose: Approximately 30% of patients with major depressive disorder (MDD) are treatment resistant. There is an unquestionable need for new treatment strategies. Subanesthetic doses of intravenous (IV) ketamine have a rapid antidepressant effect in treatment-resistant depression (TRD). This paper describes the efficacy of repeated series of intravenous ketamine infusions as an add-on treatment in five TRD inpatients.

Methods: Eligible patients aged 43–63 were given eight ketamine infusions as an add-on treatment for patients with MDD. The subjects have readministered the intervention due to worsening depressive symptoms.

Results: Of the five inpatients given ketamine as a series of eight infusions, one underwent three, and four had two treatment series. Four patients achieved remission after first series and three after the second series of ketamine infusions. The adverse reactions were mild and transient with no sequelae.

Limitations: Presented case series applies to short-term intervention with IV ketamine as an add-on therapy. The results cannot be generalized to the long-term maintenance treatment nor other ketamine formulations as well as different administration schedules and dosing.

Conclusions: This case series showed efficacy and safety of the repeated series of IV ketamine treatment in TRD in MDD and bipolar disorder type I. The subsequent interventions were safe and observed adverse events were mild and transient. Interestingly, the IV ketamine treatment at successive administrations seems to alter the major depression severity of the next affective episode. There is a critical need for further research regarding IV ketamine treatment effectiveness and long-term safety in future studies.

Keywords: treatment-resistant depression, ketamine, treatment response, multiple administrations, transformative treatment

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Hanna Karakula-Juchnowicz, Medical University of Lublin, Poland

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Fengchun Wu, Guangzhou Medical University, China

****Correspondence:***
Adam Włodarczyk
aswlodarczyk@gumed.edu.pl

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INTRODUCTION

The antidepressant effect of ketamine persists days or weeks beyond treatment, and the assumption may be that the rapid effect will appear, nevertheless, in subsequent ketamine treatment (1).

There is evidence for ketamine use in treatment-resistant depression (TRD) in major depressive disorder (MDD) and bipolar disorder (BD). Current pharmacological treatments for depression prove unsatisfactory efficacy with a proportion of subjects demonstrating TRD. The observation applies both to MDD and BD type I (BD I). Many studies confirmed the antidepressant effect of ketamine used in a single sub-anesthetic intravenous (IV) dose in patients with major depression and TRD patients (2, 3). Subsequent studies confirmed this effect in repeated doses (4, 5), twice-weekly (3, 6, 7), and thrice-weekly (8–10) administration schedules. However, the worsening of depression may occur after infusions are completed, and there is a need for the development of new strategies to maintain the beneficial effects of ketamine treatment. To our knowledge, there are no published data to date on multiple, short-term ketamine administration treatment cycles. This report presents the antidepressant effect of two and three repeated series of IV ketamine in TRD patients with MDD and BD I.

Moreover, ketamine is known to trigger dissociative symptoms with its wide spectrum of sensations, which are one of the major issues of adverse events associated with ketamine intake. These phenomena are to be measured by the Clinician-Administered Dissociative States Scale (CADSS) and Brief Psychiatric Rating Scale (BPRS) are used. That may represent the overall intensity of the dissociative symptomatology (2, 11–13, 30). This case report aims to review safety in course of the treatment of resistant depression in patients with somatic comorbidities.

METHODS

The sample selection methods for this study have been described in detail elsewhere (14). Five inpatients with TRD were administered 0.5 mg/kg ketamine hydrochloride throughout 40 min as an add-on treatment to standard of care. The treatment included two or three series of ketamine infusions (each series included eight infusions performed twice weekly) with safety monitoring.

The psychometric assessment included Montgomery Åsberg Depression Rating Scale structured interview (MADRS-Sigma), Columbia Suicide Severity Rating Scale, and Young Mania Rating Scale completed before infusions and at days 8, 14, 21, and 35. The dissociation and psychomimetic effects scales, the BPRS and the CADSS scales, were completed before every ketamine infusion and 15, 30, 45 min, and 1 h after the infusion, and 1.5 h after the infusion if the two measurements before were >0 points. Qualification procedures and ketamine administration were in line with the APA consensus (15). Psychometric endpoints included rates of response (≥50% reduction from baseline MADRS total score) and rates of remission (MADRS ≤12 at day 35).

The cases discussed comprise the naturalistic ketamine registry approved by the bioethical regulatory of the institution (NKBBN/172/2017; 172-674/2019). Patients provided written informed consent for treatment, describing potential risks and limitations as well as reasonable expectations of ketamine treatment for depression.

CASE SERIES

Patient 1 was a 56-year-old Caucasian male with 9 years of MDD history and six adequately treated MDD episodes. His medical history included hypertension (HTN). The current MDD episode started 7 months before admission. The patient underwent two courses of antidepressants with no effect, and was, therefore, offered ketamine infusions. He achieved remission after eight ketamine infusions. During the first ketamine infusion, we observed a transient blood pressure increase to 180/97 mmHg, but the values returned to normal 123/78 mmHg immediately after the end of ketamine infusion. Ketamine-induced dissociative symptoms were mild and resolved within 0.5 h after each application (CADSS at 15′ = 6 points; BPRS = 1 point). No other adverse events (AEs) appeared during ketamine treatments. The next MDD episode started 5 months after the first one and the patient underwent the second series of eight ketamine infusions with remission lasting the next 6 months. He was admitted again due to a subsequent MDD episode for the third series of infusions, which caused remission sustained for 10-month-long follow-up. During the second and third series, no AEs were observed.

Patient 2 was a 51-year-old Caucasian male diagnosed with MDD at the age of 41 with a history of nine adequately treated MDD episodes. The patient had also been diagnosed with HTN and cerebrovascular incident. The current depression started 13 months before the admission and did not respond to two courses of antidepressants, atypical antipsychotics, and two courses of electroconvulsive therapy (ECT); therefore, he was offered ketamine treatment. After the first series of eight ketamine infusions, he achieved remission lasting 7 months, then MDD appeared. He did not respond to second series of ketamine treatment, but little improvement was observed within the next 12 months. During the first ketamine infusion, his blood pressure increased to 178/95 mmHg and spontaneously dropped to 125/84 mmHg within 30 min. He also had mild dissociative symptoms and dizziness (CADSS at 15′ = 8 points, BPRS = 2 points, at 30′ = 9/1, respectively, and 45′ = 3/0, respectively), which resolved completely within 1 h from the administration. No other AEs were observed. We also did not observe any AEs during the second series of ketamine treatment.

Patient 3 was a 43-year-old Caucasian man diagnosed with BD I 15 years before admission with a history of eight adequately treated manic and 13 adequately treated MDD episodes. He had also been diagnosed with leukemia and dyslipidemia. The current depressive episode, lasting 15 months, failed to respond to one course of antidepressant, augmentation agents, and two ECT courses, and he was offered eight ketamine infusions. After the first series, he achieved remission lasting 9 months. He was

admitted again due to further worsening and agreed for the second series of ketamine infusions, which ended with remission sustained for the next 12 months. No manic or hypomanic symptoms during or after ketamine treatment were observed. No AEs during ketamine infusions appeared. CADSS and BPRS scores remained stable, 0 points.

Patient 4 was a 63-year-old Caucasian woman diagnosed with BD I 10 years before admission and had experienced one adequately treated manic and six adequately treated MDD episodes. The current MDD episode started 7 months before and was resistant to one course of antidepressant and one ECT treatment. She received eight ketamine infusions with no response, but a 40% reduction in total MADRS scores; 3 weeks later, due to worsening of depressive symptoms, she received a second series of eight ketamine infusions. However, the reduction in MADRS total scores did not meet response criteria. Dissociative symptoms were also mild and rapidly remitting up to 0.5 h (CADSS at $15' = 3$ points; BPRS $= 0$ points). No AEs appeared during and between infusions.

Patient 5 was a 60-year-old Caucasian man diagnosed with MDD 15 years before admission with a history of five adequately treated MDD episodes. He had also been diagnosed with obsessive-compulsive disorder, HTN, and psoriatic arthritis. The current depressive episode started 9 months before admission and failed to respond to one course of antidepressant, augmentation agents, and one ECT treatment; therefore, a series of eight ketamine infusions was offered. The patient achieved short-term remission—after 3 weeks, he experienced decline and reported suicidal thoughts. He agreed to the second series of ketamine infusions, which ended with remission lasting for the next 13 months. We observed a rapid reduction of suicidal thoughts after the first ketamine infusion; he also reported mild dissociative symptoms abating within 45 min (CADSS at post-infusions $= 5$ points; BPRS $= 1$ point; after $30' = 2/0$, respectively). No AEs during the second series appeared.

DISCUSSION

Here, we report beneficial effects of oral ketamine application in the treatment of patients experiencing TRD and comorbid somatic diseases with regards to general safety, in particular of most common AEs (dissociative and cardiovascular). Although we presented case series and the result must be interpreted with caution, the study shows the restoration of antidepressant response with ketamine after a relapse of depressive symptoms and allowed the direct comparison of response rates for single series and repeated infusions and the general safety profile with regard to dissociative symptomatology. Of the five inpatients given ketamine as a series of eight infusions, one underwent three, and four had two treatment series. Four of five patients achieved remission after the first series and three of five patients met common criteria for remission after the second series of ketamine infusion (**Table 1**). We noticed that the percentage of change in total MADRS score was lower after the second series than the first, except patient 1. Interestingly, subsequent depressions in patients described were less severe on treatment entry and course (**Figure 1**). During ketamine treatment, we did not observe any serious AEs, and AEs (dissociative and psychomimetic) that appeared were mild and transient and did not need any rescue medication. Despite multiple comorbidities along with several concomitant medications, the treatment was well-tolerated. The observed effect of ketamine efficacy in subsequent series shall be emphasized as being in line with the esketamine nasal spray studies showing the need for rather continuous than intermittent maintenance administration and with add-on to monoaminergic antidepressants (16).

To our knowledge, this is the only study reporting efficacy and safety of repeated series of ketamine infusions. Much of the literature describing the benefits of IV ketamine infusions have been based on single infusions. Single doses have been shown to cause a rapid response and mild side effects, but the antidepressant effect was transient (2, 17). This short-acting effect suggested a need for repeated infusions. Further research confirmed that repeated infusions of ketamine extend the durability of antidepressant efficacy and are more effective than a single dose (4, 10, 18). In the study by Shiroma et al. (10), 14 TRD patients achieved higher response after six ketamine infusions than a single infusion (92 vs. 25%) and the response maintained for 4 weeks, which was also longer compared with a single infusion. Zhan et al. (18) recently reported the response of depression in 59.3% and remission in 40.7% after six ketamine infusions during 12 days in the Chinese population of 86 unipolar and bipolar patients with depression and suicidal ideation. The authors also found the rapid response to suicidal ideation. Phillips et al. (19) conducted a randomized, double-blind crossover comparison of single infusions and continued with 41 TRD participants. The study had three phases: with a single infusion, succeeded by six infusions thrice weekly over 2 weeks, and the maintenance phase with four once-weekly infusions. Bryant et al. (20) reported a series of six geriatric patients treated with acute (5–27) ketamine infusions followed by the long-term maintenance phase (8–22). Five of six patients showed a robust response including further improvement after the acute phase, but they lost the response over time. None of the subjects returned to the baseline level of depression measured by the MADRS, which is in line with our results.

Data on arketamine (another enantiomer of ketamine) are starting to emerge as the open-label pilot trial, including seven subjects with TRD, receiving single intravenous infusion of arketamine (0.5 mg/kg), showed reduction in MADRS scores with almost no dissociative symptoms present. Authors state that arketamine might produce rapid-onset and lasting antidepressant effects in humans with satisfactory safety profile (21). According to Wei et al. (22), it is precarious that NMDAR plays a prevalent role in the antidepressant effects of arketamine. However, at present, the major molecular mechanism by which arketamine exerts its antidepressant actions is unknown.

A systematic review of the safety of ketamine in the treatment of depression, which included 60 studies with 899 patients who had received at least one dose of ketamine, revealed that acute side effects associated with a single dose are common,

TABLE 1 | Depressive symptoms in the course of ketamine treatment.

		Pre-treatment MADRS scores:	Day 8	Day 14	Day 21	Post-treatment (1 week after final infusion, day 35)	Improvement, *n* (%)
Patient 1	Series 1	37	27	19	10	9	28 (75)
	Series 2	31	19	14	9	6	25 (80)
	Series 3	21	17	11	10	9	12 (57)
Patient 2	Series 1	41	37	32	21	12	29 (70)
	Series 2	33	35	26	19	19	14 (42)
Patient 3	Series 1	40	30	9	6	7	33 (82)
	Series 2	36	8	4	4	4	32 (88)
Patient 4	Series 1	27	19	25	21	16	11 (40)
	Series 2	25	13	10	12	16	9 (36)
Patient 5	Series 1	35	29	19	12	11	24 (68)
	Series 2	16	20	18	9	12	4 (25)

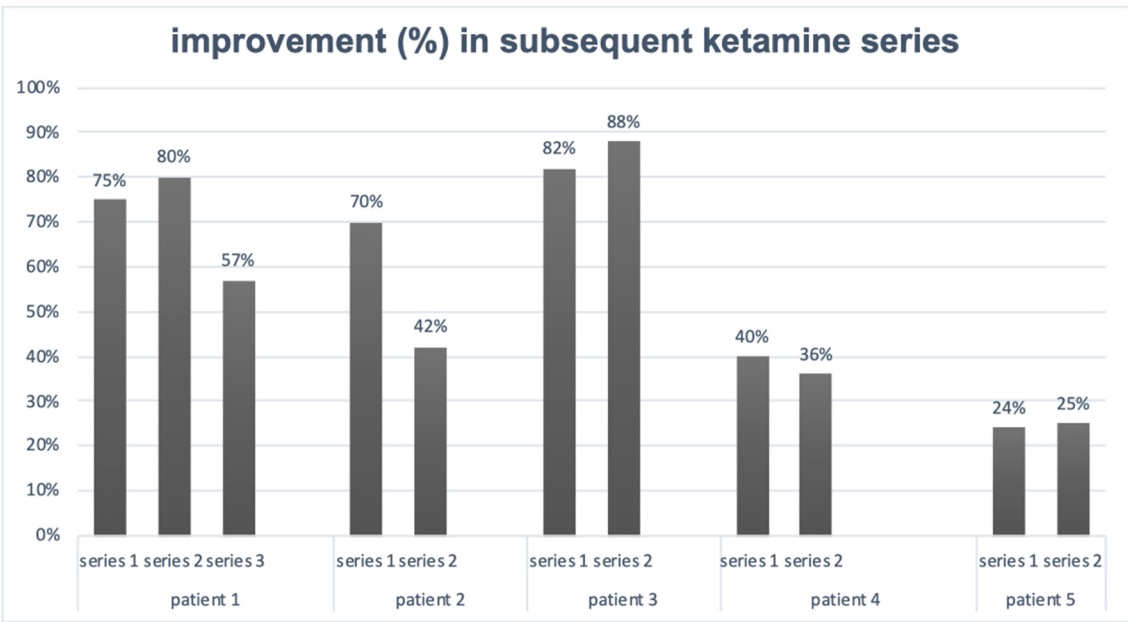

FIGURE 1 | Improvement in subsequent ketamine series.

although generally transient and resolve spontaneously (23). In a study by Wilkinson et al. (7), repeated use (12 or more infusions) was also well-tolerated. In the aforementioned case series by Bryant et al. (20), the authors also did not observe significant side effects although included patients were elderly and had multiple somatic comorbidities; however, the recurrence of addictive behavior appeared in two out of six studied patients. According to the APA, consensus caution is warranted regarding its cardiovascular, cognitive, dissociative, and psychotic effects as well as abuse potential (15). High doses and abuse of ketamine have been associated with potentially serious and possibly persistent toxic effects, including urological, hepatic, but also craving or dependence. To date, these side effects have not been adequately assessed in studies investigating ketamine use in depression. The safety of the long-term, repeated ketamine dosing, as is increasingly used in clinical practice, is therefore uncertain (23).

The use of repeated series of ketamine possibly results in the transformation of the course of the disease (24). Considering that ketamine acts on transcription (25), increases connectivity, neuroplasticity, and cell survival (24), acts on epigenetic mechanisms, and modulates the inflammatory system (26), it may be hypothesized that it exhibits transformative treatment effect modifying the course and the severity of MDD and BP I disorder. This transformation could not only decrease the severity of episodes, reduce suicidality, and extend remissions but also lessen the burden of the stigma associated with mood disorders and become a source of hope to patients and their

families (29). The effect may be particularly well-observed across repeated ketamine administration.

The safety and tolerability of dissociative and/or psychotic symptoms induced by antidepressant ketamine and its possible association with a better response to depression reduction were examined. However, currently, the literature does not support the conclusion that dissociation is essential for antidepressant response to ketamine (27). Ketamine is preferred in the treatment of mood disorders for its safety and efficacy, which appear to overlap in several populations, including its use for occasional pain, non-hemodynamic dressings, or sedation (31). This safety report complements the current literature on the safety of ketamine in mood disorders, especially in the TRD-BP population for which limited data are currently available.

Of importance is to acknowledge TRD treatment in line with esketamine nasal spray per FDA-approved label (28), as esketamine nasal spray was proved to be effective in short-term ketamine treatment and, above all, in relapse prevention in TRD-MDD. Although speculative, the case reports presented support long-term relapse prevention in ketamine administration (14). Further studies in a larger population are needed, as well as safety report registries in ketamine/esketamine TRD subjects who discontinued the treatment to observe the relapses and the treatment response pattern to ketamine/esketamine in subsequent depressive episodes.

The presented case series applies to short-term intervention with IV ketamine as an add-on therapy. The results cannot be generalized to the long-term maintenance treatment nor other ketamine formulations (subcutaneous, oral, intranasal, inhalations) as well as different administration schedules and dosing.

CONCLUSION

This case series showed the efficacy of the repeated series of IV ketamine treatment in TRD in MDD and BD I. The subsequent interventions were safe and observed AEs were mild and transient. Interestingly, the IV ketamine treatment at successive administrations seems to alter the major depression severity of the next affective episode and impacts the quality of remission with regard to the residual symptoms and suicidality. There is a critical need for further research regarding IV ketamine treatment effectiveness and long-term safety in future studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk, Poland: NKBBN/172-674/2019. https://clinicaltrials.gov/ct2/show/NCT04226963. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG-W and AWł: conceptualization, methodology, and writing—original draft preparation. AWi and WC: validation. AWł and WC: formal analysis. AWi: investigation. AWł: resources, data curation, and writing—review and editing. MG-W and WC: supervision. MG-W, JS, and NG: project administration. WC: funding acquisition. All authors contributed to the article and approved the submitted version.

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Confirmatory Factor Analysis of Three Versions of the Depression Anxiety Stress Scale (DASS-42, DASS-21, and DASS-12) in Polish Adults

Marta Makara-Studzińska[1], Ernest Tyburski[2], Maciej Załuski[1], Katarzyna Adamczyk[1], Jacek Mesterhazy[1] and Agnieszka Mesterhazy[1]*

[1] Department of Health Psychology, Institute of Nursing and Midwifery, Jagiellonian University Medical College, Kraków, Poland, [2] Department of Health Psychology, Pomeranian Medical University in Szczecin, Szczecin, Poland

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***Correspondence:**
Ernest Tyburski
ernest.tyburski@gmail.com

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Background: The Depression Anxiety Stress Scales (DASS) are designed to identify quickly and differentiate between the symptoms of depression and anxiety in the non-clinical population. Different versions (original and short) were validated in many cultures. Nevertheless, there are no data of factorial validity of the different versions of this scale in Polish culture. Thus, the aim of this study was to evaluate the factor structure using confirmatory factor analysis (CFA) and internal consistency of DASS-42 (original version) and two short versions (DASS-21 items and DASS-12 items) in the Polish population.

Methods: The DASS-42 was administered to a non-clinical sample, broadly representative of the general Polish adult population ($n = 1{,}021$) in terms of demographic variables. The DASS-21 and DASS-12 version used in this study comprise seven and four items from each of the following corresponding three subscales of the Polish version of DASS-42.

Results: There were two models that fitted best for DASS-42: (a) modified three correlated factors (depression, anxiety, and stress) with cross-loadings and (b) second order (general factor of psychological distress) and three factors with cross-loadings. There were also two models that fitted best for DASS-21 and DASS-12: (a) modified three correlated factors (depression, anxiety, and stress) and (b) second order (general factor of psychological distress) and three factors.

Conclusions: All three versions of DASS appear to have an acceptable factorial structure. However, the shorter versions (DASS-21 and DASS-12) may be more feasible to use in general medical practice and also be less burdensome to participants.

Keywords: depression, anxiety, stress, factor structure, confirmatory factor analysis, psychometric properties, non-clinical sample, DASS

INTRODUCTION

Data from the World Health Organization (WHO) show that depression and anxiety (pathological level of anxiety) disorders occur worldwide (1). It is well-known for its negative impact on the quality of human life and the social and economic costs (2–4). The results of research under the Global Burden of Disease program conducted from 1990 to 2010 indicated the growing position of depressive disorders among the sources of life burdens for people around the world (5). At the same time, the lack of high quality of epidemiological research is emphasized, which limits the accuracy and usefulness of the obtained results (6). The quality of the research depends, among others, on the research tools used, characterized by satisfactory psychometric properties. Their limited number is the reason for low detection of emotional disorders in the population during routine tests conducted by healthcare professionals (4). One of the most difficult tasks in building a satisfactory tool is the specificity of the symptoms that make up the disorders in question (7). There are difficulties in clinically differentiating between the symptoms of depression and anxiety overlapping. This is despite the formulated concepts explaining the mechanisms of symptom formation (8). The three-factor model of depression and anxiety proposed by Clark and Watson was supposed to remove the above-mentioned inconveniences (9). On its basis, a clinical tool was developed—the Depression Anxiety Stress Scale Long Form questionnaire (DASS-42) (8)—repeatedly empirically verified in terms of psychometric properties (10).

The DASS-42 scale (8) is a self-report tool designed to maximize the differences between symptoms of depression and anxiety and to reveal their common features called stress. This questionnaire has been translated to many languages and has been shown to have a transcultural validity (http://www2.psy.unsw.edu.au/dass/). Currently, it is a widely used tool for screening in non-clinical (11–16) and clinical groups with various diagnoses (10, 17–21). One of the significant limitations of the DASS-42 questionnaire is its length, resulting from the number of items, which slows down the examination time (3, 14). For this reason, among others, shortened versions were created: 21-item (3–20), 18-item (22), 12-item (3), and 9-item (11). The 21-item version is the most used in various clinical and non-clinical groups around the world. It is known that it has quite good psychometric parameters (3, 14, 23). However, the factor structure of the full version of DASS-42 is still not well-defined, which best meets the need to maximize the differences between symptoms of depression and anxiety. In the literature, there are reports from 89 analyzes checking 4, 3, 2, or 1-factor models taking into account and omitting the correlated errors, carried out on data obtained using a different number of items in the full version of the questionnaire (24–26). The search for the DASS factor model with the best psychometric properties is another reason for creating shortened versions of the scale.

The original DASS-42 questionnaire (long version) and their short versions have been translated into many languages and have been empirically evaluated in diverse cultures. Nevertheless, the factorial validity of the different versions of this scale has never been evaluated in the Polish culture. There is only one paper by Zawislak et al. (27) about construct validity and reliability but on the medical student population, not the general population. Given the limitations of the above findings, the aim of this study was to evaluate the factor structure using confirmatory factor analysis (CFA) and internal consistency of three versions of DASS: DASS-42 (23), DASS-21 (14, 26), and DASS-12 (3, 14) in the Polish population. Based on Crawford and Henry (28), we tested the three-factor model of DASS-42 (following the test's original scoring) using CFA. Moreover, we evaluated a three-factor model modified scoring in which cross-loading of specific items was permitted. Based on similar cross-loading items found in exploratory factor analyses (10, 23), Crawford and Henry permitted the anxiety item 9 to also load on the stress factor, the stress item 33 to load on the stress factor, and the anxiety item 30 to load on all three factors. Therefore, the same cross-loadings were permitted in the present sample. Crawford and Henry also tested these various models when the error associated with a particular item was permitted to correlate with the error in another item. This was important because model testing should not only address the relationships between the variables but also between the error terms since the residual of one item may provide information about that associated with another item.

METHODS

Participants

The non-clinical sample was collected from citizens coming from various towns and villages of southern Poland. The inclusion criteria were age over 18 years, the ability to independently read the text of the questionnaires, and the ability to understand its content and provide answers. No upper age limit has been established. The exclusion criterion was the subjects' current or past psychiatric diagnosis during the completion of the questionnaire. The participants were recruited in person with the help of nursing and medicine students. The participants were people known to the volunteers (family members, friends). Volunteers administered the 42-item full versions of the DASS questionnaire and collected completed questionnaires between January and May 2021. The average time that elapsed from administering the questionnaire to the moment it was completed was 2 weeks. The participants were administered the 42-item full version of the DASS questionnaire. The data of the present study were collected with the help of nursing and medicine students, who volunteered to administer the battery of tests. The volunteers were trained on the distribution, administration, and collection of the questionnaires. After signing an informed consent form, participants were administered a sociodemographic data sheet and the DASS-42 questionnaires. Each respondent was instructed to fill in the questionnaire from research assistants. Participation in this study was anonymous and voluntary. This study was approved by the Ethics Committee of Jagiellonian University (1072.6120.65.2021).

Materials and Procedure

The DASS-42 measures symptoms of depression, anxiety, and stress (8). It comprises three subscales that each has 14 items: depression (DASS-42 Depression), anxiety (DASS-42 Anxiety),

and stress (DASS-42 Stress). Each item is scored on a 4-point Likert scale ranging from 0 ("did not apply to me at all") to 3 ("applied to me very much"). The scores for the total DASS-42 and for each subscale are summed. In this study, we used the shorter versions of DASS: DASS-21 comprises seven items (DASS-21 Depression; items 3, 10, 17, 26, 31, 38, and 42; DASS-21 Anxiety; items 2, 4, 20, 25, 28, 40, and 41; DASS-21 Stress; items 6, 8, 12, 18, 22, 35, and 39), and DASS-12 (DASS-12 Depression; items 10, 17, 31, and 42; DASS-12 Anxiety; items 20, 28, 40, and 41; DASS-21 Stress; items 6, 22, 35, and 39) comprises four items from each of the following corresponding three subscales of DASS-42, which was suggested by Lee et al. (3), Osman et al. (14), and Henry and Crawford (26). The English version of the DASS-42 was translated into Polish with the permission of the original author (Dr. Lovibond and Dr. Lovibond) in accordance with the translation and back-translation (29). Two bilinguals independently translated the English version to Polish based on semantic equivalence rather than word-to-word equivalence.

Statistical Analysis

Statistical analysis of the results was done using Statistical Package for Social Sciences (SPSS) version 26 and the Analysis of Moment Structure (AMOS) software version 26. Before conducting the analysis, the data for the 42 items of the DASS were screened for missing values and normality. Missing data were excluded from the analysis. The normality of the distributions was assessed at both the univariate and multivariate levels. Basic information on the variables, i.e., means, standard deviations, standard errors, skewness, and kurtosis, was provided. Internal consistency of the items was measured using Cronbach's alpha coefficient.

Factorial construct validity was done using the three-factor model, and the second-order three-factor model as used in the original DASS study was assessed. We did not analyze the two-factor model because it is rarely supported (3, 30, 31). The validity was assessed using CFA with maximum-likelihood estimation. The sample size of 1,021 in this study satisfied the estimated size requirement (32). For the CFA, multiple fit indices were used. The selected indices were the chi-square statistic (x^2), the root mean square error of approximation (RMSEA) (33), the standard root mean square residuals (SRMR), the goodness-of-fit index (GFI) (34), and the comparative fit index (CFI) (35). For the RMSEA, values of <0.06, 0.08–0.10, and >0.10 were considered to indicate good, adequate, and poor tests, respectively, and for SRMR, GFI, and CFI, values of <0.05, >0.90, and >0.90 were considered to indicate an acceptable fit, respectively (36, 37). It was suggested that a significant difference in the x^2 (Δx^2) value between a model and its modified model indicates a substantial improvement in model fit (38).

RESULTS

Participant's Characteristics

Data were obtained from 1,294 respondents. After removing incomplete and incorrect records (using a listwise deletion technique), the data collected from 1,021 participants (625 female and 396 male, aged 18–83 years old, $M = 30.67$, $SD = 13.25$) were analyzed. The percentage of data missing for each item was in the range between 10.7 and 11.1%. The mean of DASS-42 scores for total scale were 33.08 ($SD = 22.68$); for Depression subscale, 9.22 ($SD = 8.46$); for Anxiety subscale, 8.78 ($SD = 7.48$); and for Stress subscale, 15.08 ($SD = 9.07$). The mean of DASS-21 scores for total scale were 16.61 ($SD = 11.87$); for Depression subscale 5.21 ($SD = 4.46$); for Anxiety subscale, 4.16 ($SD = 4.14$); and for Stress subscale, 7.24 ($SD = 4.64$). The mean of DASS-12 scores for total scale were 9.41 ($SD = 7.06$); for Depression subscale, 3.10 ($SD = 2.72$); for Anxiety subscale, 2.43 ($SD = 2.67$); and for Stress subscale, 3.89 ($SD = 2.70$).

Base Statistics

As can be seen in **Table 1**, the distribution of each item showed positive skewness (from 0.11 to 2.63) and mixed (positive and negative) kurtosis (from −1.11 to 6.69). Based on (39), we assumed that skewness between −2 to +2 and kurtosis between −7 to +7 indicated normal distribution of variables.

As can be seen in **Table 2**, the interitem correlation coefficients of the DASS-42 ranged from 0.13 to 0.71, that of DASS-21 ranged from 0.15 to 0.67, and that of DASS-12 ranged from 0.28 to 0.62. All correlations were statistically significant ($0.001 < p > 0.05$). These values indicate that there were no redundant or unrelated items.

Cronbach's coefficient was 0.96 for the total DASS-42 and 0.93, 0.89, and 0.92 for the DASS-42 Depression subscale, DASS-42 Anxiety subscale, and DASS-42 stress subscale, respectively. Cronbach's coefficient was 0.93 for the total DASS-21 and 0.86, 0.84, and 0.85 for the DASS-21 Depression subscale, DASS-21 Anxiety subscale, and DASS-21 stress subscale, respectively. Cronbach's coefficient was 0.89 for the total DASS-12 and 0.77, 0.81, and 0.76 for the DASS-12 Depression subscale, DASS-12 Anxiety subscale, and DASS-12 stress subscale, respectively. Both DASS versions, therefore, satisfied internal consistency.

Factorial Construct Validity

As can be seen in **Table 3**, three correlated factors of DASS-42 (Model 1) did not represent a good fit of the data (SRMR = 0.056; GFI = 0.797; CFI = 0.845; the only RMSEA = 0.068 have fit adequate criteria). The modified three correlated factors of DASS-42 (Model 1a) represented a significant improvement over Model 1 ($\Delta x^2 = 1{,}572.61$; $p < 0.001$) and yielded a good fit across all indices (RMSEA = 0.053; SRMR = 0.048; CFI = 0.908) except for GFI (0.865). The modified three correlated factors with cross-loadings of DASS-42 (Model 1b) represented a significant improvement over Model 1a ($\Delta x^2 = 72.94$; $p < 0.001$) and yielded a good fit across all indices (RMSEA = 0.052; SRMR = 0.047; CFI = 0.911) except for GFI (0.870), and Model 1c (second-order three factors with cross loadings). For Model 1b and for Model 1c, all the items loaded meaningfully on their designated factors (with a critical ratio value of >1.96), and their standardized factor loading values ranged from 0.345 to 0.797 (except item 9 = 0.122). Details are shown in **Supplementary Materials** (**Supplementary Tables S1A,B**; **Supplementary Figures S1–S4**).

Three correlated factors of DASS-21 (Model 2) represented a good fit of the data (RMSEA = 0.070; SRMR = 0.046;

TABLE 1 | Mean scores for three versions of the Depression Anxiety Stress Scale (DASS-42, DASS-21, and DASS-12) and distribution parameters ($n = 1,021$).

No	Item	*M*	*SD*	Skewness	Kurtosis
1	I found myself getting upset by quite trivial things.	1.27	0.90	0.34	−0.63
2	I was aware of dryness of my mouth.	0.62	0.83	1.16	0.39
3	I couldn't seem to experience any positive feeling at all.	0.62	0.79	1.14	0.65
4	I experienced breathing difficulty (e.g., excessively rapid breathing, breathlessness in the absence of physical exertion).	0.44	0.76	1.76	2.46
5	I just couldn't seem to get going.	0.30	0.69	2.53	5.88
6	I tended to over-react to situations.	1.24	0.90	0.30	−0.69
7	I had a feeling of shakiness (e.g., legs going to give way).	0.79	0.92	0.91	−0.15
8	I found it difficult to relax.	1.19	0.92	0.40	−0.67
9	I found myself in situations that made me so anxious I was most relieved when they ended.	1.45	1.02	0.11	−1.11
10	I felt that I had nothing to look forward to.	0.70	0.91	1.13	0.26
11	I found myself getting upset rather easily.	1.35	0.95	0.21	−0.86
12	I felt that I was using a lot of nervous energy.	1.13	0.94	0.46	−0.69
13	I felt sad and depressed.	0.99	0.92	0.61	−0.50
14	I found myself getting impatient when I was delayed in any way (e.g., elevators, traffic lights, being kept waiting).	1.24	0.96	0.33	−0.82
15	I had a feeling of faintness.	0.29	0.64	2.43	5.87
16	I felt that I had lost interest in just about everything.	0.65	0.87	1.15	0.36
17	I felt that I wasn't worth much as a person.	0.68	0.87	1.11	0.31
18	I felt I was rather touchy.	1.04	0.94	0.51	−0.70
19	I perspired noticeably (e.g., hands sweaty) in the absence of high temperatures or physical exertion.	0.54	0.83	1.45	1.26
20	I felt scared without any good reason.	0.56	0.79	1.28	0.88
21	I felt that life wasn't worthwhile.	0.39	0.74	1.89	2.80
22	I found it hard to wind down.	0.96	0.89	0.59	−0.49
23	I had difficulty in swallowing.	0.24	0.58	2.63	6.69
24	I couldn't seem to get any enjoyment out of the things I did.	0.64	0.79	1.03	0.33
25	I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat).	0.67	0.88	1.18	0.49
26	I felt down-hearted and blue.	1.04	0.91	0.54	−0.54
27	I found that I was very irritable.	1.07	0.89	0.45	−0.59
28	I felt I was close to panic.	0.62	0.84	1.17	0.40
29	I found it hard to calm down after something upset me.	0.96	0.93	0.67	−0.48
30	I feared that I would be "thrown" by some trivial but unfamiliar task.	0.77	0.88	0.90	−0.07
31	I was unable to become enthusiastic about anything.	0.54	0.76	1.27	0.82
32	I found it difficult to tolerate interruptions to what I was doing.	0.86	0.88	0.75	−0.28
33	I was in a state of nervous tension.	1.09	0.95	0.50	−0.68
34	I felt I was pretty worthless.	0.51	0.81	1.52	1.48
35	I was intolerant of anything that kept me from getting on with what I was doing.	0.77	0.85	0.94	0.20
36	I felt terrified.	0.53	0.79	1.34	0.88
37	I could see nothing in the future to be hopeful about.	0.52	0.80	1.47	1.35
38	I felt that life was meaningless.	0.46	0.79	1.67	1.89
39	I found myself getting agitated.	0.92	0.89	0.73	−0.24
40	I was worried about situations in which I might panic and make a fool of myself.	0.71	0.90	1.13	0.37
41	I experienced trembling (e.g., in the hands).	0.54	0.83	1.46	1.24
42	I found it difficult to work up the initiative to do things.	1.18	0.99	0.44	−0.84

M, mean; SD, standard deviation.

GFI = 0.901; CFI = 0.908). The modified three correlated factors of DASS-21 (Model 2a) represented a significant improvement over Model 2 ($\Delta x^2 = 389.11$; $p < 0.001$) and yielded a good fit across all indices (RMSEA = 0.055; SRMR = 0.035; GFI = 0.936; CFI = 0.946), and Model 2b (second-order three factors). For Model 2a and for Model 2b, all the items loaded meaningfully on their designated factors (with a critical ratio value of >1.96), and their standardized factor loading values ranged from 0.408 to 0.776. Details are shown in **Supplementary Materials** (**Supplementary Tables S2A,B**; **Supplementary Figures S5–S7**).

Three correlated factors of DASS-12 (Model 3) represented a good fit of the data (RMSEA = 0.060; SRMR =

TABLE 2 | Internal consistency of the three versions of the Depression Anxiety Stress Scale (DASS-42, DASS-21, and DASS-12).

	DASS-42		DASS-21		DASS-12	
	Interitem correlation	Cronbach's α	Interitem correlation	Cronbach's α	Interitem correlation	Cronbach's α
Depression subscale	0.16–0.72	0.93	0.25–0.60	0.86	0.32–0.62	0.77
Anxiety subscale	0.17–0.61	0.89	0.24–0.58	0.84	0.46–0.58	0.81
Stress subscale	0.32–0.71	0.92	0.37–0.67	0.85	0.40–0.47	0.76
Total scale	0.13–0.71	0.96	0.15–0.67	0.93	0.28–0.62	0.89

TABLE 3 | Model fit indices for the three versions of the Depression Anxiety Stress Scale (DASS-42, DASS-21, and DASS-12).

	x^2	df	RMSEA (90% CI)	SRMR	GFI	CFI	x^2 difference (Δx^2)
DASS-42							Model 1–Model 1a = 1572.61***
Model 1: three correlated factors	4611.64***	816	0.068 (0.066–0.069)	0.056	0.797	0.845	Model 1a–Model 1b = 72.94***
Model 1a: modified three correlated factors	3039.03***	792	0.053 (0.051–0.055)	0.048	0.865	0.908	
Model 1b: modified three correlated factors with cross loadings	2966.09***	788	0.052 (0.050–0.054)	0.047	0.870	0.911	
Model 1c: second-order three factors with cross loadings	2966.09***	788	0.052 (0.050–0.054)	0.047	0.870	0.911	
DASS-21							Model 2–Model 2a = 389.11***
Model 2: three correlated factors	1103.63***	186	0.070 (0.066–0.074)	0.046	0.901	0.908	
Model 2a: modified three correlated factors	714.52***	176	0.055 (0.051–0.061)	0.035	0.936	0.946	
Model 2b: second-order three factors	714.52***	176	0.055 (0.051–0.059)	0.035	0.936	0.946	
DASS-12							Model 3–Model 3a = 83.15***
Model 3: three correlated factors	236.19***	51	0.060 (0.052–0.067)	0.037	0.964	0.961	
Model 3a: modified three correlated factors	153.04***	49	0.046 (0.038–0.054)	0.026	0.976	0.978	
Model 3b: second-order three factors	153.04***	49	0.046 (0.038–0.054)	0.026	0.976	0.978	

*** $p < 0.001$.

0.037; GFI = 0.964; CFI = 0.961). The modified three correlated factors of DASS-12 (Model 3a) represented a significant improvement over Model 3 ($\Delta x^2 = 83.15$; $p < 0.001$) and yielded a good fit across all indices (RMSEA = 0.046; SRMR = 0.026; GFI = 0.976; CFI = 0.978), and Model 3b (second-order three factors). For Model 3a and for Model 3b, all the items loaded meaningfully on their designated factors (with a critical ratio value of >1.96), and their standardized factor loading values ranged from 0.529 to 0.767. Details are shown in **Supplementary Materials** (**Supplementary Tables S3A,B**; **Supplementary Figures S8**–**S10**).

DISCUSSION

The study is the first analysis of the DASS factor structure using the CFA method in the general population of adult Poles. It is also the first study to verify the factor structure of three versions of the tool, namely, full (Long Form) and two shortened, i.e., DASS-42, DASS-21 and DASS-12.

Differences in the fit of the models corresponding to the three versions of the questionnaire were obtained. Model-1 with three correlated factors DASS-42 did not get a good fit. For this reason, a modified model with three correlated factors was checked, taking into account intercorrelations (relationships) between measurement errors of individual items. This one turned out to be much better than the previous one and showed a good fit on all metrics except GFI. In the next stage of the analysis, the model of modified three correlated factors with cross-loadings was checked. Item 9, an anxiety factor charger, was allowed to load the stress factor as well; item 33, a stress factor charger, was allowed to load the anxiety factor as well. Item 30 was also allowed to load all three factors. This model proved to be better than the previous model and showed better fit in all indicators except GFI. Finally, the second-order three factors model with cross-loadings was tested. The second-order factor was called "general negative emotion" (8) or "general psychological distress" (26). This model obtained similar indicators as the previous one.

For DASS-21, model-2 with three correlated factors showed a good fit. The procedure used in the long form of questionnaire (DASS-42) analysis was repeated, checking the modified three correlated factors model and the second-order three factors with cross-loading model. Both models mentioned revealed the same best match rates.

In the case of the model-3 (DASS-12), which proved to be a good fit in the version with three correlated factors, the

applied procedure resulted in an improvement of the indicators. In addition, in this model, the version with three modified correlated factors and the second-order factor obtained similar, best fit rates.

The standardized loading factor for each of the three models ranged from 0.345 to 0.797, only in the case of DASS-42 one item (9)—"I found myself in situations that made me so anxious. I was most relieved when they ended"—loaded definitely low. In the studies by Clara et al. (10) and Antony et al. (23), there was also a problem with the above-mentioned item, which was loaded with both the stress and anxiety factors. Brown et al. (40) suggested that this item should belong to both factors at the same time, creating the so-called modified three-factor model. However, a study by Clara et al. (10), conducted in the clinical population, showed that the use of a model in which item 9 cross-loaded two factors simultaneously only slightly improved the psychometric properties of the basic Lovibond and Lovibond model (8). According to the authors, it is better to stop at the classic three-factor model.

The results obtained in the study were consistent with the results presented by other researchers. As for the DASS-42, the own study of the Persian version of the tool (13), also conducted in the non-clinical group, indicated the model with three correlated factors as having the best fit. However, unlike our research, the above-mentioned results resulted in the removal of four items from the full version of the scale. The exploratory analysis carried out by Antony et al. (23) also confirmed the structure of the tool made up of three correlated factors. In the case of DASS-21, both in the Clara et al. (10) study and in ours, we observed better fitting parameters compared to the full version. Sharma et al. (41), while examining the structure of the Indian version of DASS-21, observed high parameters for the model with three correlated factors using confirmatory analysis. They were slightly higher than those obtained in our research. In the study by Henry and Crawford (26), an optimal fit was observed for the bifactor (quadri-partite structure) model consisting of the general anxiety factor and three specific factors—orthogonal (depression, anxiety, stress). The structure of this model was similar to our structure of the second-order three factors model (-2b model). The research of Lee et al. on the Korean versions of DASS-21 and DASS-12 (3) using confirmatory analysis confirmed a good fit of both the three-factor model and the three-factor model with the second-order factor. The authors checked five models for each version of the scale, starting from the one-factor model, which revealed a poor fit, through the basic three-factor model, which also had poor parameters. The three-factor model modified from two covariance error terms with much better parameters and ending with the second-order tree-factor model with modification of two covariance error terms. This model contained a second level of a factor named after Lovibond and Lovibond (8) "general negative emotion," similar to the study by Henry and Crawford (26). It was as good as the three-factor but explained more of the variance in the results and was considered better than the alternative models. Studies by Osman et al. (14) indicated the best fit of two models: second-order factor and bifactor with the general factor G. In the case of DASS-12, modified three-factors model with two covariance error terms turned out to be the best match. The results obtained by us were definitely better than those reported by Osman et al. (14), who reduced the DASS 21 by selecting 12 items for the set.

As in the case of the research carried out with the use of other cultural versions of the questionnaire, it was observed that three-factors crossing models and models with a second-order factor were better suited than the models taking into account only the intercorrelation of items. The DASS-42, DASS-21, and DASS-12 questionnaires have equivalent psychometric parameters and can be successfully used in clinical screening and research studies. In the Polish version, they differentiate well the three mental states, as intended by the authors of the original versions. The preliminary analysis showed that all three versions of the questionnaire (DASS-42, DASS-21, and DASS-12) are characterized by good internal consistency (good to excellent) for both whole scales and subscales, ranging between 0.76 and 0.96. The items making up each of the subscales and the overall score were not redundant and unrelated. Similar results were obtained in studies of other language versions (3). The lower Cronbach's α values obtained in our study of the DASS-12 version may result from the lower number of items and were similar to the values in the Korean studies (3).

In conclusion, DASS-42, DASS-21, and DASS-12 well-differentiate the features of depression, anxiety, and stress. As noted by Antony et al. (23), DASS-21 differentiates clinical groups in a manner comparable to DASS-42. Guided by the results of the DASS-12 research, for practical reasons, it is suggested to use the shortest version of the scale, which has psychometric properties comparable to the full version and at the same time significantly reduces the duration of the study and is less burdensome to use for the respondents. During the current coronavirus disease 2019 (COVID-19) pandemic, DASS tool allows GPs or occupational health practitioners to quickly identify patients for the presence of symptoms of depression, anxiety, and stress. It can also be used before consulting general practitioners and occupational medicine physicians. The results obtained in the screening tests, once in the hands of doctors, can be used in the diagnostic process. As Nieuwenhuijsen et al. (4) noted, routine dissemination of DASS to employees can help occupational health professionals in the early diagnostic process. DASS can also help clinicians identify patients at high risk of comorbid depressive disorders (42). DASS can also be used to study the dimensions of human mental functioning and to measure a controlled variable in comparative studies of different clinical groups, e.g., in the field of cognitive functioning.

Contrary to the approach used in another study of the Polish version of the scale (27), we tried to find a model that would be more consistent with the theory underlying the questionnaire than with the analysis of its items. Moreover, Zawislak et al. (27) conducted exploratory factor analysis (EFA) of DASS-21 on Polish medical students, not the general population. Statistical analysis identified four factors

of DASS-21. Because factor 4 consisted of only three items, the authors decided to conduct EFA in a modified version renamed DASS-18. Results of this study showed limited data on the factor structure of DASS to compare with our study. We wanted to broaden the knowledge of the original form of the questionnaire, matching the versions with different numbers of items [original and two shorter versions, verified in previous studies of different populations (3, 10–14, 16–20, 26)] rather than to check its structure typical of Polish conditions.

The strength of the study was to check three versions of the DASS, full and two abbreviated. In our study, all three versions obtained good psychometric properties. Looking for a solution with the best possible adaptation, we tested various first- and second-order models, without changing the number of items in each of the DASS versions. One of the limitations of our study is to limit itself to the assessment of the tool's factor structure (no assessment of external validity and stability over time). However, we tried to go beyond this limitation by checking the internal consistency and intercorrelations that achieved satisfactory values. Another limitation of our study is the lack of comparison to clinical samples. Thus, we planned to conduct research to explore diagnostic validity based on the comparisons of the results of healthy people and people with various forms of depressive and anxiety disorders. Moreover, we have further validation studies ahead of us: the assessment of congruent validity and the retest reliability test in the longitudinal study. The third limitation was that the choice of the sample was non-random; however, participants came from various towns and provinces of the country.

It should be remembered that DASS is a questionnaire used only for screening; it does not allow to distinguish different forms of depression, e.g., severe depression, depressive disorders in the course of somatic diseases, adaptation disorders, and various forms of anxiety disorders. Nevertheless, our results suggest that three Polish versions of DASS (DASS-42, DASS-21, and DASS-12) are a valuable tool that allows for diagnostic and scientific research in the field of health psychology, clinical psychology, and psychiatry. Moreover, short versions may be more feasible to use in a busy practice and also be less burdensome to respondents.

CONCLUSIONS

The Depression Anxiety Stress Scales (DASS) are designed to quickly identify and differentiate between the symptoms of depression and anxiety in the non-clinical population, and different versions (full and short) were validated in many cultures. Nevertheless, there are no data of factorial validity of the different versions of this scale in the Polish culture. Thus, the aim of this study was to evaluate the factor structure using confirmatory factor analysis (CFA) of DASS-42 (full version) and two short versions (DASS-21 items and DASS-12 items) in the Polish population. Our results suggest that all three versions of DASS appear to have an acceptable factorial structure. However, the shorter versions (DASS-21 and DASS-12) may be more feasible to use in general medical practice and also be less burdensome to participants.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Jagiellonian University (1072.6120.65.2021). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM-S was the principal coordinator of the research project, was involved in the study design, took part in patient recruitment, managed literature searches and analyses, performed statistical analysis, and wrote the first draft of the manuscript. ET was involved in the study design, managed literature searches and analyses, performed statistical analysis, and wrote the first draft of the manuscript. MZ was involved in the study design, took part in patient recruitment, managed literature searches and analyses, performed statistical analysis, and wrote the first draft of the manuscript. KA, JM, and AM were involved in the study design and corrected the manuscript. All authors contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Social Robots for Supporting Post-traumatic Stress Disorder Diagnosis and Treatment

Guy Laban[1†], *Ziv Ben-Zion*[2,3,4,5†] *and Emily S. Cross*[1,6*]

[1] *Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, United Kingdom,* [2] *Tel-Aviv Sourasky Medical Center, Sagol Brain Institute Tel-Aviv, Wohl Institute for Advanced Imaging, Tel-Aviv, Israel,* [3] *Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv, Israel,* [4] *Departments of Comparative Medicine and Psychiatry, Yale School of Medicine, Yale University, New Haven, CT, United States,* [5] *The Clinical Neurosciences Division, VA Connecticut Healthcare System, United States Department of Veterans Affairs, National Center for Posttraumatic Stress Disorder, West Haven, CT, United States,* [6] *Department of Cognitive Science, Macquarie University, Sydney, NSW, Australia*

Post-Traumatic Stress Disorder (PTSD) is a severe psychiatric disorder with profound public health impact due to its high prevalence, chronic nature, accompanying functional impairment, and frequently occurring comorbidities. Early PTSD symptoms, often observed shortly after trauma exposure, abate with time in the majority of those who initially express them, yet leave a significant minority with chronic PTSD. While the past several decades of PTSD research have produced substantial knowledge regarding the mechanisms and consequences of this debilitating disorder, the diagnosis of and available treatments for PTSD still face significant challenges. Here, we discuss how novel therapeutic interventions involving social robots can potentially offer meaningful opportunities for overcoming some of the present challenges. As the application of social robotics-based interventions in the treatment of mental disorders is only in its infancy, it is vital that careful, well-controlled research is conducted to evaluate their efficacy, safety, and ethics. Nevertheless, we are hopeful that robotics-based solutions could advance the quality, availability, specificity and scalability of care for PTSD.

Keywords: post-traumatic stress disorder, social robots, trauma, mental health, human-robot interaction, affective computing, affective science, emotion

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***Correspondence:**
Emily S. Cross
emily.cross@mq.edu.au

[†] These authors have contributed equally to this work and share first authorship

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1. INTRODUCTION

Stress occurs when our dynamic biological and/or psychological equilibrium is threatened or perceived to be threatened (1, 2). The feeling of stress is prevalent and ubiquitous in our everyday lives, significantly impacting the maintenance of both physical and mental health (3), with increasing social and economic costs (4). Critically, even a single stressful event, if perceived as life-threatening (i.e., traumatic), can lead to longstanding psychopathology as exemplified by Post-Traumatic Stress Disorder (PTSD) (5). PTSD is a prevalent and severe psychiatric disorder with profound public health impact due to its chronic nature, accompanying functional impairment, and highly common comorbidities (6, 7). Existing therapeutics for PTSD show limited efficacy, presumably because they do not meet minimal quality criteria or because they attempt to treat rather than prevent the disorder (8). Furthermore, many PTSD treatments were developed without directly targeting the specific underlying mechanisms (2, 9). As both PTSD diagnosis and treatment still face significant challenges, here we aim to highlight how a novel technological solution, namely, social robots, might be able to offer assistance in the diagnosis and treatment of PTSD.

Digitization in psychiatry is gaining momentum, providing those who suffer from low mental health with an increasing array of self-help solutions, many of which are available on users' mobile devices (see 10–12). PTSD diagnosis and treatment can take many different forms, ranging from traditional questionnaires (see 13, 14) to ecological momentary assessment (EMA) (e.g., 15, 16) and intervention (EMI) (e.g., 16–18), mobile applications, virtual agents (e.g., 19–22), and exposure treatments using virtual reality (VR) devices (e.g., 23, 24). However, in the following, we argue that social robots offer another promising approach for supporting PTSD diagnosis and treatment, due to their availability, autonomy, and embodiment. Hence, this perspective paper specifically focuses on the potential application of social robots for PTSD diagnosis and treatment.

The definition of a social robot in this work is an autonomous machine that interacts and communicates with humans or other agents by following social behaviors and rules relevant to their role (25). Furthermore, for the purposes of this paper, we further include in our social robots definition that these machines are autonomous, and function in physical and social spaces alongside humans (26) (see **Figure 1** for examples). In this paper, we wish to particularly emphasize the relevance and value of social robots' physical embodiment, as we believe this offers additional benefits beyond other digital and AI-fuelled innovations that are screen or voice-based. Social robots are attracting increasing attention for their potential use in autonomous health interventions (26). Such robots are already being applied in psychosocial interventions (27, 28), in mental health settings (29), and deployed as supportive agents to aid in rehabilitation (30, 31). Due to many social robots features, including human-like design (32–35), autonomous abilities, and high mobility (26), we suggest that some of these machines could also be well-suited to helping overcome some of the challenges of PTSD diagnosis and treatment. In this paper, we propose a novel approach for the integration of social robots in PTSD clinical management, in order to improve diagnosis and early interventions aiming to prevent and/or treat post-traumatic psychopathology. In the following, we introduce some major challenges faced in PTSD diagnosis and treatment, present an overview of recent developments in social robotics research, and reflect on the potential of these robotics developments to overcome PTSD diagnosis and treatment challenges.

2. CHALLENGES FOR PTSD DIAGNOSIS AND TREATMENT

Challenges for PTSD diagnosis and treatment include the short critical time-frame for intervention after trauma exposure (36, 37); the high dependency on available qualified medical teams and trauma specialists in emergency departments (38–40); and the limited efficacy and high dropout rates of current first line pharmacological and psychological treatments (41). Moreover, when patients overcome the physical consequences resulting from the traumatic event, they often end or limit their relationship with the medical team, resulting in diminished compliance with or cessation of mental health recommendations (42).

PTSD is the only mental disorder to have a salient onset, thus providing an excellent target for secondary prevention and the mapping of pathogenic processes (43). Symptom trajectories provide an observable dimension of PTSD development or remission. Prospective studies of PTSD resulting from single traumatic incidents consistently show a progressive reduction in the symptoms' prevalence and severity during the year following trauma exposure (44–46). These early observed symptoms, seen shortly after trauma, subside in most of those initially expressing them and persist in about 30 percent of those diagnosed with PTSD 1 month after trauma (47, 48). Given the importance of interventions in the early aftermath of traumatic events, we suggest that early introduction of technology-assisted and self-help interventions should be further explored to prevent and treat post-traumatic psychopathology. Technology-assisted clinical interventions are becoming increasingly common in the health care field and in combating mental health as these interventions are often aimed at improving access to and cost-effectiveness of care (49–51).

3. SUPPORTING EARLY DIAGNOSIS IN EMERGENCY DEPARTMENTS

In emergency departments (ED) of general hospitals, diagnosing acute PTSD symptoms in trauma survivors can be a long complicated process, highly dependent on qualified human resources (e.g. trauma teams)(38–40). Moreover, the ED medical staff often focus mainly on physical injuries, prioritized by the

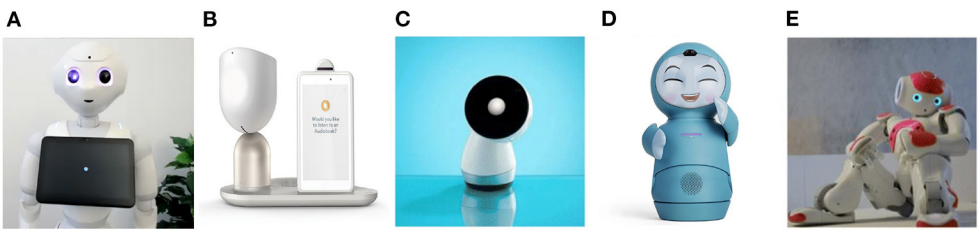

FIGURE 1 | Examples of several social robotics platforms that are heavily used in research and/or have enjoyed commercial success, and are discussed in this perspective paper. **(A)** Pepper, a humanoid by SoftBank Robotics. **(B)** ElliQ, a household robot by Intuition Robotics. **(C)** Jibo, a personal home assistant robot by NTT Disruption. **(D)** Moxi, an animated household robot by Embodied. **(E)** Nao, a humanoid robot and Pepper's little sibling by SoftBank Robotics.

degree of severity, disregarding mental health symptoms such as acute stress symptoms after trauma exposure. This results in patients not being diagnosed for Acute Stress Disorder (ASD) symptoms early after trauma, and receiving no intervention or treatment. If these acute stress symptoms persist for over a month after trauma exposure, the individuals are given the diagnosis of PTSD (14). Hence, it is highly important to assess early clinical symptoms shortly after trauma, and to follow-up on these throughout this early critical time-frame (36, 37). Furthermore, PTSD diagnosis rarely relies on formal and objective biological indicators, and instead indicated merely by subjective symptoms reported in clinician-administered interviews (14, 52). The clinician-administered PTSD Scale for DSM-5 (CAPS-5) is the current gold standard of PTSD assessment (14). It was designed to be administered by clinicians or clinical researchers who have a working knowledge of PTSD, but can also be administered by appropriately trained para-professionals. When necessary, to make a provisional PTSD diagnosis, the PTSD Checklist for DSM-5 (PCL-5), a 20-item self-report measure that assesses the 20 symptoms of PTSD defined by the DSM-5, can also be used (14).

While PTSD diagnosis is highly dependent on a clinician interpretation and expertise (38), it could nonetheless benefit from automation in the administration phase. For example, surveys of trauma survivors using self-reported measures (e.g., PCL-5 (13)) could be administer by a social robot, supporting human trauma teams in EDs after large-scale traumatic events, moving between trauma survivors and collecting relevant health data for diagnosing PTSD in an early stage. The current diagnosis procedure imposes a high data registration workload on medical staff, including nurses and clinicians who often demonstrate high rates of burnout due to the intense nature of EDs (53). This has serious implications, especially since trauma medical teams are often called on beyond normal working hours (54), and in case of large-scale traumatic events (e.g., large scale industrial accidents, natural disasters, terror attacks) with many trauma survivors (39). Medical teams in EDs could use the support of automatic systems to diagnose trauma survivors' mental condition in a fast and efficient way. This would provide them with time and energy to focus on other emergency medical procedures and will reduce their already-heavy workload. Trauma teams are a fundamental component for improving trauma-related care (40), hence, reducing the workload where possible can support trauma teams' performance in emergency situations. These common challenges faced in EDs and on site at traumatic events worldover also limit PTSD diagnosis, with only 7% of trauma centers reporting to be screening for PTSD (55).

Measures like the PCL-20 are constructed as self-reporting instruments that can be filled individually by trauma survivors. However, automation of some aspects of early trauma screening should also ensure that trauma survivors start the diagnosis procedure for PTSD during their hospitalization and in an early stage shortly after being exposed to a traumatic event, which should in turn reduce the patient burden of completing self-administered questionnaires in this critical time frame. As the PCL-5 is a straight-forward self-report tool that is easy to administer (13), a social robot should be able to communicate the items to most trauma survivors, and calculate a score on the spot. Moreover, due to the social robot's communication abilities, human-like design, and physical presence (see 26, 56), we propose that these self-reported items could be communicated in a more natural way. Rather than administering a questionnaire, a social robot could converse with a patient and elicit the necessary information naturally following the instrument's items (e.g., 34, 57). Using the robot's interactivity features, the social robot can update the system and prioritize fast and personalized reactions from relevant medical professionals (e.g., a psychiatrist, social worker, psychologist) for further elaborate diagnosis and early intervention.

Previous studies and ecologically valid study reports positive evidence for the use of social robots in autonomous health data acquisition among hospitalized patients. Moreover, these studies reported for social robots administrating health data acquisition in a variety of settings such as hospitals, homes, schools, and nursing homes (58–60). A randomized controlled cross-over trial with a social robot (Pepper, SoftBank Robotics, see **Figure 1**) and a nurse administering three questionnaires (52 questions in total) showed minimal differences in health data acquisition effectiveness between the two conditions (the Pepper robot vs. the nurse). Moreover, the study results demonstrated that the social robot was accepted by the patients (older adults) (58). The study suggests that social robots may effectively collect health data autonomously in public settings, and assist medical teams in diagnosing patients. As mentioned earlier, using a social robot for surveying trauma survivors via a self-reported tool can reduce the load on the trauma medical teams and ensure that relevant data for the diagnosis will be collected and reported in the relevant medical system on time for early intervention.

It is important to highlight that while there is vast evidence in the social robotics and human—robot interaction research literature for the effect of social robots on human's behavior in health settings (e.g., 28, 29, 61), and on self-disclosure in particular (34, 62–66), eliciting information from trauma survivors (especially regarding the trauma and the associated affect) is substantially different and will impose different and new challenges. This will require further investigation via future empirical research, as it is vital to understand disclosure to a social robot (and how different it is from disclosure to a human or disembodied technologies) when people are in a hyper-vulnerable state.

4. OVERCOMING LOGISTICAL BARRIERS

Following the administration of acute medical treatment, immediately following a trauma, several further logistical barriers exist that can prevent trauma survivors from receiving proper mental health diagnosis and intervention. These can be personal (e.g., living in rural areas with limited local mental health providers, limited mobility, language barriers, legal status, poor relationships and communication with providers, fragmentation of care) or professional (e.g., lack of support from the employer, lack of time, high responsibility, isolated employment) (67). These logistical barriers can be crucial considering the shortage

of mental health professionals, especially in rural and difficult-to-access regions (4, 68, 69). An example is the barriers experienced by active-duty and ex-serving military personnel who suffer from PTSD. Studies involving active-duty infantry US soldiers demonstrate that 28% of soldiers met self-reported criteria for PTSD or major depressive disorder in the post-deployment period (70). Nevertheless, less than 40% of soldiers with mental health problems utilize mental health services, and only 50% seek intervention following a clinical referral (70). Active-duty soldiers report for logistical barriers when seeking mental health. These include difficulties in arranging appointments, lack of mental health professionals and/or limited availability in remote military bases, and lack of opportunities to see mental health professionals in their limited time outside military basis (71, 72). Importantly, active-duty soldiers are not the only people who suffer from limited access to mental health services. People who live in rural areas, or in regions with limited mobility, also frequently report having limited access to mental health services (4, 67, 73).

While a social robot can not and would not replace a human clinician in these settings, it could possibly be situated in these unique hard-to-reach environments, aiming to expand some aspects of mental health service delivery. These aspects include, but not limited to, local clinics in rural areas, far military bases, community centers, and homes of people with limited mobility. A social robot could collect health-related data in one's home or another familiar environment, monitor and report symptoms, and potentially offer early intervention in familiar settings. Deploying social robots in such a way could provide cost-effective mental health support, offering solutions to those with limited opportunities to access mental health services in their everyday settings. Accordingly, clinical symptoms of trauma survivors could be monitored early after trauma exposure (6, 74), and clinical teams could prioritize those who are at high-risk for PTSD development. This in turn would allow employment of early interventions aiming to prevent the development of the chronic disorder, which is more efficient than trying to treat chronic PTSD (8). Furthermore, small accessible social robotic devices designed for the home—such as ElliQ (Intuition Robotics), Moxi (Embodied), and Jibo (NTT Disruption) (see **Figure 1**)—could be placed in people's homes to monitor symptoms of trauma survivors with limited mobility. These social robots are easy to operate, easy to transport, and can elicit meaningful responses from humans in relevant settings (26, 75, 76).

A social robot in these settings can also be remotely operated by a clinician from afar, serving as a telepresence medium to provide access to professional mental health care providers in isolated settings (see 77, 78). For example, SoftBank Robotics recently introduced a new telepresence feature for their Pepper robot (79, 80). In contrast to other telepresence robots that are merely an extension of the telepresenced human, here the human telepresenced through the social robot shares a body with another social entity - such as Pepper, the humanoid social robot. This feature could introduce valuable opportunities for using social robots for PTSD, where they can perform both autonomously and/or be controlled by proxy. Therefore, aided by their physical embodiment, social robots offer the potential to provide human-mediated care by proxy as well as by using their autonomous programming to administer clinical management tasks independently when needed.

5. OVERCOMING SOCIAL BARRIERS

Extending from logistical barriers, social robots can also help to overcome social barriers for those seeking mental health treatment for PTSD. Some trauma survivors consider their hospitalization to be traumatic, hence they tend to avoid visiting or consulting with clinicians (81). Others avoid seeking mental health treatment at all due to personal internal social barriers such as stigma, isolation, stress, prejudice and feelings of shame (67, 82) associated with traumatic experiences (70, 82–86). Indeed, evidence of active-duty members and veterans demonstrating an unwillingness to discuss their mental health or emotions with medical teams due to prejudice and stigma has been well-documented (70, 82). Individuals with combat-related PTSD often feel strong negative emotions (e.g., anger, guilt, shame) in relation to the trauma and their subsequent mental condition. For examples, feeling of shame were associated with worse clinical outcomes in veterans with PTSD, specifically increase in suicidal ideation (85). Furthermore, sexual assault victims exhibited difficulties to discuss their traumatic events in both formal and informal settings (87). Finally, other individuals are not willing to receive mental health assistance mainly due to lack of support from family, friends, and their community (67).

We suggest that a social robot can potentially bypass some of the above-mentioned social barriers, and encourage individuals to report and treat their post-traumatic symptoms. We see compelling evidence for people being willing to disclose sensitive information, including stressors and mental health symptoms, to avatars and virtual agents. For example, a study by Utami et al. (19) explored the reactions of older adults when having "end-of-life" conversations with a virtual agent. The study's results show that all study participants were comfortable discussing with the agent about death anxiety, last will and testament, providing compelling evidence for the potential utility of artificial agents in these complex socioemotional domains. Another study by Lucas et al. (20) employed a virtual agent that affords anonymity while building rapport to interview active-duty service members about their mental health symptoms after they returned from a year-long deployment in Afghanistan. The study reports that participants disclosed more symptoms to a virtual agent interviewer than on the official Post-Deployment Health Assessment (PDHA), and than on an anonymized PDHA. Moreover, the results of a larger sample experiment with active-duty and former service members reported a similar effect (20).

Furthermore, another recent study (34) examined the extent to which social robot and disembodied conversational agent (voice assistant) can elicit rich disclosures, and accordingly might be used to support people's psychological health through conversation. The study reported that a social robot (NAO, SoftBank Robotics, see **Figure 1**) was successful in eliciting rich

disclosures from human users, evidenced in the information that was shared, people's vocal output, and their perceptions of the interaction (34). This is in line with additional works that report different behavioral and emotional effects when communicating with social robots, and increased willingness of participants to disclose information and emotions in the presence of embodied artificial agents (e.g., 63, 65, 88–91). While participants were aware of many of the obvious differences between speaking to a humanoid social robot (NAO, SoftBank Robotics) compared to a disembodied conversational agent (Google Nest Mini voice assistant), their verbal disclosures to both were similar in length and duration (34). Another study (92) demonstrated positive responses of human users to a humanoid robot taking the role of couples counselor, aiming to promote positive communication. It is of note that the robot also played a meaningful role in mediating positive responses (in terms of behavior and affect) within the couples' dyadic interaction in this same study. While social robots obviously can not offer the same opportunities for social interaction and engagement as humans (33), their cognitive architectures and embodied cognition can nonetheless elicit socially meaningful behaviors from humans (93). As such, they can afford valuable opportunities for engagement with humans when introduced in specific contexts, and in careful ethically responsible ways (94).

6. DISCUSSION AND CONCLUSIONS

Through this paper, we aimed to introduce several challenges related to PTSD diagnosis and treatment, and highlight suitable opportunities to address them by introducing social robots in PTSD diagnosis and treatment. As it is crucial to diagnose acute PTSD early after trauma, social robots can support clinical assessments of trauma survivors during the hospitalization phase. They may also aid trauma teams in EDs by reducing some of their stress and burden during busy times (39, 40). As social robots can support high fidelity data collection and on-line, on-going analysis of human behavior, emotions, and physiological reactions, they might have the potential to support early diagnosis of PTSD among trauma survivors. Finally, social robots can assist with overcoming several logistical and social barriers that trauma survivors face when required to monitor symptoms and when seeking mental health interventions (67, 73, 81, 82).

We clearly acknowledge that various screen-based (or virtual), non-embodied technologies can also assist with some of the challenges, for example, via the use of EMA and EMI methodologies (e.g., 15, 17), or through use of a virtual agent on one's mobile device (e.g., 19, 20). While these kinds of tools and instruments might be useful and widely available, social robots provide an additional benefit through their embodiment, in that they have the potential to communicate and interact with people in a more socially meaningful way by initiating interactions more naturally than mobile devices, and providing rapid and responsive ecological momentary interventions in users' natural physical settings. While mobile apps require the user to take a certain initiative to log information, take action, or respond to a notification, social robots can elicit interactions more naturally due to their design, animated behavior, and social roles (see 26, 95, 96). This would be extremely helpful when monitoring symptoms for trauma survivors since they often prefer to refrain from discussing the trauma (67, 82). In fact, most EMA and EMI mobile solutions for self-monitoring are highly dependent on users' initiative and responsibility (see 97–99), which can be very challenging after experiencing a traumatic event. Moreover, EMA's and EMI's repetitive nature could be further triggering when addressing aspects related to traumatic events (see 98). Accordingly, social robots might just fall at the ideal intersection between being an autonomous and physically present technology that can capture emotion and information while also being able to demonstrate social and cognitive cues that might help to elicit rich and valuable disclosures from these patients. We do not argue that social robots are a perfect solution, but rather that they could potentially help overcome some of the barriers that other solutions might still struggle with.

It should also be mentioned that while social robots are indeed more expensive and less readily available than smartphone devices, they remain reasonably employable in social spaces (see 100), and can take on a cost-effective and user-friendly embodiment of a household robot (see 26, 75). To sum up, while smartphone applications have clear benefits in terms of availability, cost and scalability, in our perspective social robots' physical embodiment and cognitive architectures could support richer interactions with human users, which in turn could potentially help to overcome some of the logistical and emotional barriers of PTSD diagnosis and treatment.

To the best of our knowledge, no social robotics studies to date have been conducted with trauma survivors or individuals diagnosed with PTSD. Nonetheless, a study by Nomura and colleagues (101) provides evidence for the benefits of employing social robots for minimizing social tensions and anxieties. Through this work, the authors showed that participants with higher social anxiety tended to feel less anxious and demonstrated lower tensions when knowing that they would interact with a robot, as opposed to a human, in a service interaction. In addition, the authors suggested that an interaction with a robot elicited lower tensions compared to an interaction with another person, regardless of one's level of social anxiety. Extrapolating to PTSD settings, it is reasonable to assume that social robots might support trauma survivors with overcoming their social barriers to disclose and monitor their symptoms over time. Whether these robotic agents are situated at home, the local clinic, community center or hospital, they hold the potential to reach patients and invoke authentic reactions that could be critical for early diagnosis and treatment of PTSD.

Due to the lack of empirical work on this issue, in this perspective paper, our primary aim was to address the potential for introducing social robots for PTSD diagnosis and treatment, based on evidence gathered from a variety of different applications and perspectives from both clinical and non-clinical contexts. As such, we would like to stress that the ideas presented in this perspective paper are at a very early stage, based on studies with a variety of populations, and will need to be carefully and ethically tested before applying them to interventions with people in a hyper vulnerable state (such as those who experienced

traumatic events or have already been diagnosed with PTSD). Studies looking into this should start by testing participants after experiencing trauma but without demonstrating PTSD symptoms or with subthreshold symptoms. When seeing good and valid results, studies could then carefully and responsibly move on to being replicated with clinical populations carefully. These sorts of trials should be accompanied/supervised or monitored by a mental health professional to ensure that participants do not experience negative effects.

Most of the preventive therapies for PTSD to date have been developed without directly documented neurocognitive targets (9). The currently most effective treatment for PTSD (cognitive behavioral training (CBT)) (102) was conceived entirely on psychological grounds. Similarly, trials of the most effective drugs for PTSD, selective serotonin reuptake inhibitors (SSRIs) (103), were based on these drugs' observed antidepressant effect; the recognition that the serotoninergic system is involved in the biology of PTSD only came afterward. Despite the abundance of biological insights into PTSD that have been achieved, the development of treatments for PTSD has not been different from the history of much of medicine: effective agents are discovered by serendipity, and their biological mechanisms of action are only clarified later. As social robots could potentially hold out the prospect of providing a nuanced and novel solution to some of the challenges that PTSD diagnosis and treatment are facing, future research should be appropriately conducted to test this premise.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

GL and ZB-Z conceptualized the paper and wrote the first draft. EC supervised and revised. All authors edited and approved the final version.

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CASE REPORT
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Case Report: Anomalous Experience in a Dissociative Identity and Borderline Personality Disorder

Hugo André de Lima Martins[1], *Valdenilson Ribeiro Ribas*[2]*, *Ketlin Helenise dos Santos Ribas*[2], *Luciano da Fonseca Lins*[3] and *Alessandra Ghinato Mainieri*[4]

[1] Unidade do Cérebro, Surubim, Brazil, [2] Instituto do Cérebro de Pernambuco, Jaboatão dos Guararapes, Brazil, [3] Universidade de Pernambuco (UPE), Garanhuns, Brazil, [4] Federal University of Rio Grande do Sul, Porto Alegre, Brazil

Introduction: Dissociative identity disorder, formerly called multiple personality disorder, is a rupture of identity characterized by the presence of two or more distinct personality states, described in some cultures as an experience of possession.

Objective: The case of a 30-year-old woman with dissociative identity disorder and borderline personality disorder associated with a previous history of anomalous experience was reported.

Case Report: A 30-year-old woman who fulfilled the DSM-5 criteria for dissociative identity disorder and borderline personality disorder reported the presence of unusual sensory experiences (clairvoyance, premonitory dreams, clairaudience) since she was 5 years old. The patient told that for 12 months she presented episodes in which a "second self" took charge of her actions: she would then speak with a male voice, become aggressive, and require several people to contain her desire for destruction. After 3 months of religious follow-up, and accepting her unusual experiences and trance possessions as normal and natural, she had significant improvement.

Conclusion: When approaching DID and BPD patients, it is necessary to observe the anomalous phenomena (in the light of) closer to their cultural and religious contexts, to promote better results in the treatment of their disorders, which has not been explored in the treatment guide.

Keywords: borderline, personality, dissociation, mediumship, anomalous experience, case report

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***Correspondence:**
Valdenilson Ribeiro Ribas
ribas.professor@gmail.com

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INTRODUCTION

Pierre Janet was the first to describe, in 1889, dissociation as disaggregation of the unity of experience at the mental level (1). Dissociative identity disorder (DID) is characterized by two or more distinct identities or dissociated personalities.

Dissociation is characterized by a disturbance in integrated dimensions of the mind such as consciousness, attention, memory, and perception of the environment. This dispersion of the sense of self-oneness causes deterioration of chronological, biographical, and perceptive unity (1–4).

Dissociative disorders seem to arise because of the transaction between genetic factors, which determine an individual's biological vulnerability and environmental condition (5). Among the latter, the socio-cognitive model highlights the importance of social-cultural self-oneness as the

cause of deterioration of chronological, biographical, and perceptive unity (1, 2, 4), while the trauma model, which has received more support and was studied more, underlies the role of traumatic life experiences (6, 7). Very recently, aligned with the transdiagnostic model, it was proposed that dissociation can be understood as failures of normally adaptive systems and functions (8).

Some theorists believe that the alleged personalities would be an attempt to defend the weakened ego from childhood trauma or abuse that occurs in more than 80% of cases of DID (1, 4). In such cases, dissociation acts as a self-hypnotic defense mechanism that provides conditions for the individual to cope with trauma (1, 9–11). Other researchers, more skeptical, think that DID is not a real condition, but a disorder produced by doctors or cultural influence in highly hypnotizable and "suggestible" patients (12). These are the two main lines of thought about the etiology of DID, although the latter seems to have less empirical support.

Symptoms of dissociation are present in a variety of mental disorders such as DID and post-traumatic stress disorder (PTSD) (13). Borderline personality disorder (BPD) is a very serious psychiatric condition characterized by severe affective instability and impulsivity, associated with problems in self-image and interpersonal relationships (1). Transient, stress-related severe dissociative symptoms" serve as a criterion for borderline personality disorder (14). Most patients with BPD present episodes of identity confusion, derealization, depersonalization, and dissociative amnesia (4).

'Anomalous Experiences' (AE) is a term proposed to designate unusual experiences which are considered 'outside the ordinary explanations' (hallucinations, synesthesia, and experiences interpreted as telepathic, paranormal, among others), without assuming psychopathological implications. These phenomena are reported in all cultures and in all times of humanity, which were the object of study of official science in the late nineteenth and early twentieth centuries, but which only in recent years have returned as interesting areas in the academic field. Some examples of AE are clairvoyance, premonitions, xenoglossia, and mediumistic incorporations (15–17). In general, authors make a distinction between those who present AE, which represents a form of non-pathological dissociation, from those who fulfill criteria for DID which causes discomfort and suffering (18).

We report a case of DID associated with BPD that draws attention to the presence of AE, such as clairvoyance, premonitory dreams, and clairaudience, from 5 years of age, preceding the onset of possession-type dissociative identity crises in more than two decades. The patient gave informed consent for this case report and the study was approved by the ethical committee with number 3,605,351. There was no funding for this research.

CLINICAL CASE

A 30-year-old woman presented with a history of repeated episodes of identity disturbance characterized by a marked change in behavior, aggression, psychomotor agitation, and voice change (from female to male voice). The episodes started in March 2018 and lasted from 10 min to 6 h, at an average frequency of 3 times a week.

The patient generally had a partial or total recollection of events. She was ashamed of the people who witnessed the episodes because she felt ridiculed. She could not avoid possession, which happened in places like churches, at the school where she worked as a teacher, at home, and at the doctor's office. Since the beginning of the condition, she had been showing moderate social isolation, because the community where she lives believed that she was possessed by an evil entity. She had several days of absenteeism at work due to crises and failed several medical treatments.

She often attended masses of the Catholic Church, where these occurrences were not well regarded. After one almost uncontrollable crisis, the patient broke the pews of the church during the service. The priest decided to submit her to a ritual of exorcism, which consisted of prayers, holy water, and crucifix presentation. During the session, the patient attacked eight people, including the priest, who had his clothes torn.

The treatment was abandoned, as the patient's family was embarrassed by the amount of stuff broken and people injured during the "possession" state, besides not obtaining satisfactory results, which diminished the interest in continuing this procedure.

She did not intend any kind of secondary gain with that disorder and, most of the time, she would get physically exhausted along with the trance: at the start, she would get overly strong and, up to the end, she would be very weak. Practitioners of her religion (Catholic) were not used to dealing with these manifestations. As time went by, the trance episodes increased in frequency and intensity and she felt more isolated at work and in her social relationships. Concomitantly with those religious sessions, the patient went through several unsuccessful psychiatric treatments over a year. Our service was then referred to the patient by another colleague.

At the initial consultation, she was quite frightened, as she had several embarrassing situations and was profoundly affected by the fact that she had no control over her body. Personal background: She denies a history of abuse or neglect. She said that at the age of 5, she was in the recovery room of a tonsillectomy surgery when she had a vision of a spiritual entity, dressed in light clothes, who told her about the importance of ethical and moral behavior in life.

She reported the vision to her family, but it was not taken seriously, and they mocked her. The most striking case was that of a repetitive dream with an unknown middle-aged man, whom she met after a few months at a horse farm.

She had other similar dreams between the ages of 5 and 11. When she was 10 years old, she was awakened in the middle of the night by an entity who stated to be her grandfather, who had died 2 years before. She wrote a letter dictated by her deceased grandfather to her father regarding personal matters that were completely unknown to her. The signature showed some resemblance to her grandfather's. The next day, her parents read the letter and said they were sure it was the devil's work and tore the entire manuscript. In her early teens, she had the

feeling that a spiritual entity intended to have sex against her will. She was very bothered by the feeling that someone was running his hands all over her body, including her private parts. She did not talk to others about these feelings, because she was afraid someone might think she was "crazy." After starting her sexual life, she had an invisible and unusual sensory experience as rape-like provoked by supposed bad spiritual beings. These sensations were so threatening that they led her to frequent suicidal thoughts. The patient reports that the episodes were completely unwanted and aroused a feeling of despair, with an intense resemblance to reality.

She made several suicide attempts through lethal methods such as hanging, drowning, moving motorcar, and electric shock, always being driven by a male voice that guided her. At several moments, she completely lost her mind and body control during the episodes and assumed that an external entity commanded her. The patient consulted several specialists, who gave various diagnoses such as depression, anxiety disorder, schizophrenia, and panic disorder. She took nortriptyline 75 mg daily for 6 months, fluoxetine 40 mg daily for 4 months, escitalopram 20 mg daily for 3 months, risperidone 6 mg daily for 4 months, quetiapine 600 mg at night for 4 months, some of them in combination in the last year, with no clinical improvement. She did not have any therapeutic benefits from these drugs, although she experienced all the side effects. In this case, there was probably a good adherence to pharmacological treatment, although it is not been proven by measuring the plasma level of the substances.

Among the symptoms, the patient said that she heard voices, saw figures, often dreamed of deceased people, thought randomly about things that came to happen after a while, believed to write automatically and unconsciously, driven by a force external to her thinking. She complained of many very rapid mood swings, fear of abandonment, and an intense feeling of emptiness.

The patient was born by transpelvian delivery and had normal neuropsychomotor development. She had a tonsillectomy at 5 years of age. She never attended psychological counseling. The patient denied a history of childhood abuse or neglect. The patient spent her childhood and adolescence in a situation of low socioeconomic level. Her mother had behavioral problems but never went through any kind of treatment. There is no information on family health and AE history.

In the mental state examination, the patient did not present alterations except for a very anxious mood. The structure of thought was completely normal. The physical and neurological examination revealed no abnormalities. The patient obtained 45 points in the Beck anxiety inventory (BAI) and 45 on the dissociative experiences scale (DES). Lab Tests, Brain MRI, and 3 repetitive EEGs were normal.

The patient fulfilled all criteria for diagnosis of dissociative identity disorder according to DSM-V: characterized by two or more distinct personality states (also called alter egos or self-states or identities). There is also an inability to recall daily events, important personal information, and/or traumatic or stressful events, all of which typically would not normally be lost with normal forgetting. The symptoms caused social and professional harm, were not part of a context accepted by religious practice, and were not due to a physiological effect of substances or other medical conditions.

The patient refused psychotherapy for economic reasons and decided to attend Spiritism, which accepts communication among the living and the dead as part of its doctrinal framework. Spiritism started initially in France as a spiritualistic movement developed in the 19th century, and nowadays it has spread around the world. In Brazil, it is the third-largest religion and its practices strongly emphasize controlled psychotic and dissociative experiences called mediumship. Mediumistic practices are not reimbursed but are considered charitable voluntary work (19, 20).

After 3 months in the new religious order, where her dissociative manifestations were naturally accepted, without the interpretation that it would be the result of the influence of the supreme evil, the patient had marked improvement in anxiety symptoms, reducing the BAI score to 26, becoming able to speak spontaneously about her crises and very rarely presented the picture outside the appropriate religious context. People sometimes refer to fear in participating in Spiritism meetings due to the lack of proper information about the safety of the procedure. The patient denied any concern about it, although she kept discretion about her treatment for people outside its context, due to the fear of suffering prejudice. She also returned to her social and occupational activities.

DISCUSSION

The patient reported dreams that seemed very real to her. Some authors have correlated dissociative symptoms with sleep disorders (21), even highlighting the role of the latter as a cause of dissociation (22–25). For instance, sleep improvement reduces dissociative symptoms (26). When sleep and dream systems are impaired, the memory process during (REM) sleep becomes unregulated and it may as well induce dissociative symptoms (24).

The reported case shows a patient with unusual and premonitory dreams in her childhood, which seem to be related to a current psychopathological condition. A very interesting study evaluated the frequency of dream recall and the experience of unusual dreams, longitudinally, in children of both genders, aged between 10 and 11 years, for 2 years, with an initial assessment and after 12 and 24 months. The tendency to have unusual dreams, such as repetitive dreams, remembering dreams over a long period, or dreams that cannot be understood, was associated with internalizing and externalizing behavioral problems reported by the adolescents' parents (27).

A particular type of dreaming is designated by the term lucid dreaming in which the dreamer is aware of dreaming (28, 29). Furthermore, in this condition, control (the capacity to change the dream events) and dissociation represent the other criteria (30). In this report, the patient had no control over the dream plot and perceived it as real and unpleasant. Lucidity in dreaming has been linked with positive rather than negative emotions (24), but when the person has no control over the dream, which

seems to be more common, lucid dreaming is associated with psychopathological distress and several types of symptoms (31).

There were not remarkable events that might be considered very traumatic in the patient's childhood and adolescence. The possibility of abuse and neglect was extensively researched and no evidence was found. It has been widely documented in specialized literature that in most cases of DID there is a serious and traumatic event during the patient's life, which might justify the onset of dissociative symptoms (12, 32, 33). Otherwise, minor traumas, such as surgery at age 5 with hallucination, associated with an invalidating attitude from the family who mocked her, could lead to the DID.

The patient heard commanding voices ordering her to commit suicide, which resulted in several attempts. Auditory hallucinations present in epileptic seizures are generally elementary, characterized by repetitive and simple sounds (4). She also fulfilled the criteria for borderline personality disorder as an unstable sense of self; chronic feeling of emptiness; inappropriate and intense anger; history of recurrent suicidal behavior; and severe dissociative symptoms, which justify the absence of effectiveness in pharmacological treatment.

Recently, some researchers have studied the accuracy of the information contained in a letter supposedly dictated by a deceased person to the influential Brazilian "medium" Chico Xavier, encountering highly specific hits (34). The patient's letter was torn and could not be evaluated. Otherwise, the automatic writing may be explained by dissociative absorption and imaginative involvement, which is not necessarily pathological and is characterized by a tendency to become immersed in a stimulus while neglecting to attend to one's surroundings (35). As a quite common dissociative process, automatic writing may be characterized by a diminished sense of agency (36) and it can alternatively explain why someone assigns the authorship of the letter to someone else.

Since childhood, the patient had AE, such as clairvoyance and premonitions, which were never studied with attention, probably because this is an unknown field to the lay public and poorly explored by the scientific community. Although AE, in general, occurs in people with no mental disorders, the present case pointed to the possibility of overlapped events like AE and psychopathologic alterations as the patient underwent various suicide attempts during her life and it is in general associated with a mental disorder. There has been recently a new tendency to make AE an object of study in the natural sciences again (16, 37).

The patient was refractory to various drug therapy regimens, which are widely cited in the literature related to the dissociative identity disorder (10). Unfortunately, there was no opportunity to perform psychotherapy to integrate identities, because the patient lacked the financial resources to do so.

A very interesting fact was the clinical improvement of the patient, evidenced by both the mental state examination and the use of a psychometric instrument (BAI) after being welcomed into a religious community (Spiritism) that accepted possession as part of its doctrinal structure. According to the DSM-5, one of the criteria for diagnosing DID is that it does not belong to a widely accepted religious or cultural practice (38).

In low- and middle-income countries, psychotic experiences are present at least occasionally in more than 90% of the people. There is an assumption that these experiences are more culturally accepted in these countries, which justifies the numbers. For these individuals, lower distress is predicted by spiritual appraisals and better social support from family and friends (39). Possibly, this approach influenced the favorable outcome in this case report.

CONCLUSION

This study explored the importance of cultural and religious contexts, and consequently, their interference in the evolution of patients with anomalous experiences and dissociative disorder, and explored the relationship between anomalous experience and dissociative disorder, expanding the explanatory possibilities for this disorder.

The main strength of this report is showing an alternative way to manage the complex DID. The limitation is related to the type of study (case report) and to the possibility that the patient improved by accepting her AE as natural, which could, in theory, happen in supportive psychotherapy.

Although it should be acknowledged that parts of some cases of DID have traumatic etiological factors, the present case reflects the positive association between the event and the trajectory of the dissociation that changed once she found a social or religious group that accepted her possession crises as a natural event, providing a positive framework not just for the present symptoms, but also a possible explanation to the different events that she had all along her life.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Federal University of Pernambuco. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HM contributed substantially to the design of the study: he was responsible for the acquisition of data (articles) for the work and for the critical review of the work and also participated in the writing of the introduction, in the critical review of the case report, and in preparing the abstract. VR was responsible for the choices of scientific articles related to

the study, participated with substantial contributions to the design of the study, and in discussions about interpretations of the chosen articles and also as a corresponding author. KR contributed to the writing of the case report, participated in discussions on the choices and interpretations of the chosen scientific articles and submission to the ethics and research committee. LL participated in the discussions and interpretations of the scientific articles related to the study and in the critical review. AM participated in all discussions related to data and the study phenomenon, agreed to be responsible for all aspects of the work, and ensuring that issues related to the accuracy or integrity of any part of the work are investigated. All authors contributed to the article and approved the submitted version.

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