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Psychopathology of psychiatric patients presenting autoantibodies against neuroglial antigens

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Background: Autoantibody-mediated psychiatric disorder is often difficult to diagnose as the clinical features of psychiatric disorder associated with neural autoantibodies are often similar. Thus, it is of major relevance to investigate whether psychopathology can differentiate between both disease entities as a biomarker and help us in searching for specific autoantibodies associated with psychiatric symptoms.

Methods: We enrolled 154 patients of the Department of Psychiatry and Psychotherapy of the University Medical Center Göttingen with psychopathology data and retrospectively evaluated their patient records using the classification systems AMDP (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie) and HiTOP (Hierarchical Taxonomy of Psychopathology).

Results: We identified 35 psychiatric patients revealing autoantibodies in their serum and/or cerebrospinal fluid (CSF) and 119 with no autoantibodies. Relying on the AMDP system, many more psychiatric patients with serum autoantibodies (51%) had problems with orientation than those without autoantibodies (32%) ($p < 0.05$). Furthermore, fewer psychiatric patients with serum autoantibodies exhibited a blunted affect (11.4 vs. 32.8%, $p < 0.01$) and affective rigidity (20 vs. 45%, $p < 0.01$). In particular, psychiatric patients presenting CSF autoantibodies (indicating an autoimmune symptomatic basis) experience more loss of vitality (5%) than those without autoantibodies (0%) ($p < 0.05$). Another interesting finding is that according to the AMDP classification, a manic syndrome is much more frequent in autoantibody-positive (8.6%) than autoantibody-negative psychiatric patients (0.8%) ($p < 0.05$). Another aspect is the more frequent occurrence of attention and memory deficits in patients with autoantibodies against intracellular targets compared with targets on the membrane surface.

Conclusion: Our findings indicate that neural autoantibodies in psychiatric patients could indicate a phenotype more often characterized by a manic syndrome, orientation disturbances within the cognitive spectrum, and

fewer affect disturbances characterized by less blunted affect and not as seriously impaired feelings of vitality compared to controls. The novelty of our approach is the extensive autoantibody tests for various psychiatric syndromes in combination with a profound psychometric measurement with two different scales.

KEYWORDS

psychopathology, neural autoantibody, autoimmunity, psychiatry, HiTOP classification, AMDP system

Introduction

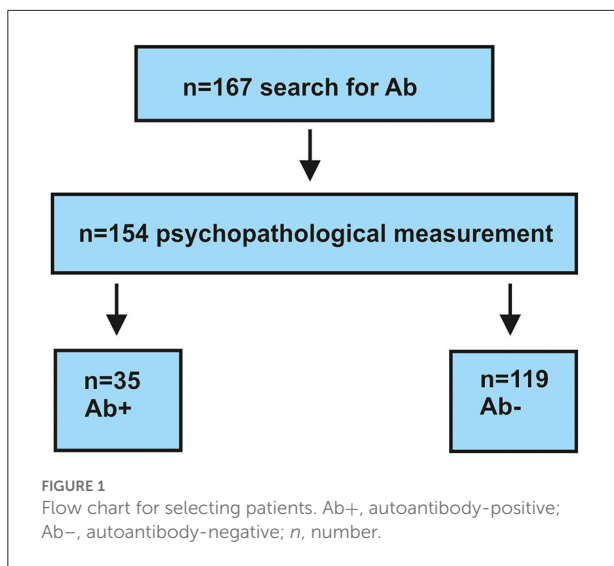
The quantification and diversity of psychopathology in neural autoantibody-associated psychiatric syndromes is an under-investigated topic in immunopsychiatry that deserves more attention since psychopathology may be an early important biomarker for diagnosing neural autoantibodies in psychiatric disorders. Neural autoantibodies associated psychiatric syndromes might be an initial manifestation of autoimmune encephalitis on the one hand. On the other hand, neural autoantibody-associated psychiatric disease might not fulfill autoimmune-encephalitis criteria. Autoimmune encephalitis is a designation that relies on specific criteria ranging from clinical features, like psychiatric symptoms and memory impairment, to diagnostic indices of central nervous system (CNS) inflammation derived from cerebrospinal fluid (CSF) analysis, neuroimaging, and electroencephalography (1). There are sometimes no clear indications of autoimmune encephalitis, although neural autoantibodies are associated with psychiatric syndromes. The distinction is therapeutically highly relevant, as there are clear therapeutic guidelines for autoimmune encephalitis or encephalopathy (1–3) where isolated serum autoantibodies have less clear meaning and a therapeutic intervention is limited to individual therapeutic healing attempts. In such cases, a consortium called “Cerebrospinal Fluid Analysis in Psychiatry” (4) developed additional clinical criteria such as a dynamic psychopathology (5) or catatonia (6) to diagnose an autoimmune basis of psychiatric syndrome presentation. These additional parameters have not been evaluated in large sample cohorts as biomarkers and therefore require validation in randomized large-scale trials. We are not yet aware of any novel early biomarkers that would improve such patients’ diagnosis and therapy. The patient’s phenotypic appearance is often an early hint implying the direction the diagnostic approach should take. Thus, psychopathological factors may eventually prove to be biomarkers that are better at distinguishing between patients who may possess neuronal autoantibodies than those who do not. This assumption is based on recent studies that show that specific psychopathological

features are associated with neural autoantibodies, such as anti-adaptor-related protein complex 3, beta 2 subunit (AP3B2) autoantibodies in conjunction with persecutory delusions, or anti-tryptophan 2,3-dioxygenase (TDO2) antibodies (7) together with hallucinations in patients or N-methyl-D-aspartate receptor (NMDAR) antibodies in patients with a common coexisting depressive and psychotic symptomatology (8). Thus, the primary goal of the study is to assess the psychopathology retrospectively applying two different psychometric measurement scales to compare the psychopathological profile of autoantibody-associated psychiatric syndromes to psychiatric syndromes without autoantibodies. We hypothesize that the psychopathology as measured by the AMDP or HiTOP will differ between autoantibody-positive and autoantibody-negative psychiatric patients. Our second aim is to evaluate the usefulness of the AMDP and HiTOP classifications in terms of their usefulness in detecting specific psychopathologic features that would facilitate differentiating between neural autoantibody-associated psychiatric syndromes from those without autoantibodies. Furthermore, as our third aim, we will correlate the semiquantitative measurement score of antibody intensity with the expression of psychopathology in autoantibody-associated psychiatric syndromes. We hypothesize that the psychopathology as measured by the AMDP or HiTOP will differ between autoantibody-positive and autoantibody-negative psychiatric patients.

Methods

Selection of patient cohort

We retrospectively screened between 2017 and 2020 a cohort of 167 patients (Figure 1) from the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen. All patients presented different psychiatric diagnoses and were screened for specific autoantibodies (see section autoantibody determination) because we suspected that their psychiatric symptoms had an organic origin. Organic origin has been suspected due to various features associated with



the presentation of clinical features with a fulminant course, the acuity of symptoms, the rapid progression of symptoms, the atypical severity of cognitive dysfunction associated with other symptoms or alone, or the presence of autoimmune indicators recently presented in a review (4). Severe cognitive dysfunction including orientation and attention functions, which is not explained otherwise, is a strong indicator than the red flag (5) of an autoimmune base of symptoms and thus another reason for screening neuronal autoantibodies in patients. Our cohort was divided into two subgroups: (1) consisted of 35 serum antibody-positive and (2) contained only 132 serum antibody-negative patients (Figure 1). Our inclusion criterion was a psychiatric disorder for which we had determined autoantibodies for differential diagnostic reasons. We did not exclude patients with comorbidities or additional neurologic conditions. All patients recruited in 2020 had been screened for a CoV-SARS-2 infection. Patients recruited in 2016–2019 did not undergo testing for CoV-SARS-2. Their psychopathology was retrospectively assessed *via* two psychopathological classification systems by studying patient files. Patient data were classified by one rater (IMG) according to the AMPD system (9) and the HiTOP classification system (10, 11). An ultimate total of 154 patients who had undergone complete psychopathological investigation according to AMDP were included in our study. Among the total 154 patients, our groups consisted of 35 serum antibody-positive and 119 serum antibody-negative patients (Figure 1). We used the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines to organize and describe our observational study better. Our investigations were approved by our local ethics committee and are in accordance with the Declaration of Helsinki.

Assessment of psychopathology

Psychopathology was retrospectively assessed from patient files by one rater (IMG). Psychopathological features according to AMDP were assessed as single items from the following domains: disturbances of consciousness, orientation, memory and attention, formal thought disorder, worries and compulsions, delusions, disorders of perception, hallucinations, ego disturbances, disturbances of affect, disorders of drive and psychomotor activity, circadian disturbances, and other disorders. Furthermore, we applied spectra from the HiTOP classification system entailing somatoform, internalizing, thought disorder, disinhibited externalizing, antagonistic externalizing, and detachment spectra. Sexual problems, eating pathologies, fear, distress, mania, substance abuse, and antisocial behavior functioned as HiTOP factors. The two HiTOP superspectra emotional dysfunction (12) and psychosis (13) were also evaluated. The superspectra emotional dysfunction consists of the single spectra somatoform and internalizing, whereas the superspectra psychosis comprises the single spectra detachment and thought disorder. For AMDP domains, we established a total score consisting of the AMDP items from one AMDP domain that were present in the patients. Thus, the total AMDP domain's scoring range is different [disturbances of consciousness (0–4), disturbances of orientation (0–4), disturbances of memory and attention (0–6), formal thought disorder (0–12), worries and compulsions (0–6), delusions (0–6), disorders of perception (0–6), hallucinations (0–6), ego disturbances (0–6), disturbances of affect (0–21), disorders of drive and psychomotor activity (0–9), circadian disturbances, and other disturbances (0–10)]. Moreover, we set up an HiTOP sum score for the superspectra emotional dysfunction and psychosis consisting of the presence of individual spectra present in the patients [psychosis (0–2), emotional dysfunction (0–2)]. Psychopathology was retrospectively assessed from patient files by one rater (IMG).

Autoantibody determination

Our cerebrospinal fluid samples resulted from lumbar puncture. CSF and blood samples were taken at the same time and were processed according to the standard protocol in the neurochemistry laboratory in the University Medical Center Göttingen's Neurology Department. Freshly extracted cerebrospinal fluid is used, as *in vitro* cytolysis is so rapid. All biomaterial samples were processed within 1–2h after they were received to ensure accurate cell count samples. The CSF samples were centrifuged to separate cells from CSF at these settings (700 revolutions correspond to 105 × g, 10 min, room temperature). The degeneration marker (ptau181, t-tau) and Reiber scheme were determined on the

TABLE 1 Composition of psychiatric diagnosis in cohort of patients.

Category of psychiatric disorder ICD10	Complete cohort	Complete cohort	Ab+		Ab-	
			<i>n</i>	%	<i>n</i>	%
Organic, including symptomatic, mental disorders, F00–F09	77/154	50	24/35	69	53/119	45
Mental and behavioral disorders due to psychoactive substance use, F10–F19	4/154	3	–	–	4/119	3
Schizophrenia, schizotypal and delusional disorders, F20–F29	19/154	12	1/35	3	18/119	15
Mood disorders, F30–F39	40/154	26	5/35	14	35/119	29
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders, F40–F49	6/154	4	2/35	4	4/119	3
Adult personality and behavior disorders, F60–F69	2/154	1	–	–	2/119	2

Ab–, antibody negative; Ab+, antibody positive; ICD10, International Classification of Diseases, Tenth Revision; *N*, number.

same day. However, the serum was centrifugated different settings (5,000 revolutions corresponding to $4,528 \times g$ for 5 min at 20°). All serum samples were stored until they were sent as aliquots (500 μ l serum) to the Euroimmun laboratory for the detection of autoantibodies. About 300 μ l CSF aliquots were also sent to the Euroimmun laboratory. All patients' neural autoantibodies were assessed by the Clinical Immunological Laboratory Prof. Stöcker. We sought diverse neural autoantibodies in peripheral blood (PB) and CSF entailing autoantibodies against membrane cell surface targets [α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors 1/2 (AMPA1/2), Aquaporin 4, contactin-associated protein 2 (CASPR2), dipeptidyl-peptidase-like 6 protein (DPPX), gamma aminobutyric acid B1/2 receptor (GABAB1/2R), glutamic acid decarboxylase (GAD65), leucine-rich glioma inactivated protein 1 (LGI1), and N-methyl-D-aspartate receptor (NMDAR)] and autoantibodies against intracellular often paraneoplastic antigen targets [autoantibodies against intracellular autoantibodies: amphiphysin, CV2, glutamic acid decarboxylase (GAD65), HuD, Ma1/ Ma2, neurochondrin (NC), Ri, TR, Yo, and Zic4]. Euroline immunoblot and cell-based assays were utilized to determine autoantibodies. Neural autoantibodies were assessed in a semiquantitative scale possessing three intensity levels: 1 (mild intensity), 2 (moderate intensity), and 3 (strong intensity). The groups were divided into patients with neural autoantibodies and those without them in serum and or cerebrospinal fluid (CSF). The CSF was analyzed in the Neurochemistry Laboratory, University Medical Center Göttingen.

Statistical approach

Data were analyzed with SPSS (IBM, SPSS, version 28, Ehningen, Germany). Graphs were made with Sigma Plot

(Version 11, Palo Alto, United States). Mean and standard error of the mean were calculated for gender and age. In addition, for the investigation of age differences between men and women, the Mann–Whitney *U*-test was used. The psychopathological items and domains from AMDP as well as factors, superspectra, and spectra from HiTOP classification were compared between autoantibody-positive and autoantibody-negative groups *via* Fisher's exact test with no correction for multiple testing because of the data exploratory nature and our small sample. We conducted no power analysis beforehand, as our retrospective cohort analysis has exploratory character. We used Spearman's rho correlation including correcting for multiple testing *via* Bonferroni to investigate the relationship between the semiquantitative autoantibody-intensity score and psychopathological items sum score of the AMDP system and HiTOP classification. To estimate effect sizes and our results' robustness, we also conducted Bayesian testing and calculated the effect sizes *via* Cramer's *V*. A *p*-level of <0.05 was considered as significant.

Results

Demographics and clinical characteristics of patients

We enrolled 154 patients in this study with the following diagnostic spectrum shown in Table 1. In 35 of 154 (22.7%) psychiatric patients, we detected a neural antibody in the peripheral blood (Ab+ PB), and 13 of 154 (8.5%) had antibodies detected in CSF (Ab+ CSF). We divided the patients in a group of 35 psychiatric patients with peripheral blood autoantibodies (PsychAb + PB) and 119 psychiatric patients with no PB autoantibodies (PsychAb – PB). A patient classification found that 27 out of 35 (78%) of serum autoantibody-positive patients

TABLE 2 Classification of neural autoantibody-positive patients.

Patient number	Ab serum	Ab CSF	Possible AE	Definitive AE	Autoimmune psychosis
1	Ma2	Ma2	Present	Not-present	Present
2	CV2/CRMP5	CV2/CRMP5	Present	Present	Present
3	Yo	Not present	Not present	Not present	Not present
4	Myelin	Not present	Present	Not present	Not present
5	NMDAR	Not present	Present	Not present	Not present
6	NMDAR		Present	Present	Present
7	NC and Titin	NC and Titin	Not present	Not present	Not present
8	Not present	Yo	Present	Present	Not present
9	Neuropil (unspecific)	Not present	Present	Not present	Not present
10	GlycineR	Not present	Present	Not present	Not present
11	GAD65, Recoverin	Not present	Present	Not present	Not present
12	GAD65, TR/DNER, Yo	–	Present	Not present	Not present
13	Recoverin	Not present	Not present	Not present	Not present
14	KCNA2	KCNA2	Present	Not present	Not present
15	Myelin	Not present	Present	Not present	Not present
16	Titin, Yo	Not present	Present	Present	Not present
17	Recoverin	–	Present	Not present	Not present
18	NMDAR	NMDAR	Present	Present	Not present
19	Zic4	–	Not present	Not present	Not present
20	NMDAR	–	Not present	Not present	Not present
21	Yo	Not present	Present	Not present	Not present
22	GlycineR	Not present	Not present	Not present	Not present
23	Amphiphysin	Not present	Not present	Not present	Not present
24	KCNA2	Not present	Not present	Not present	Not present
25	CV2	Not present	Present	Not present	Not present
26	NMDAR	Not present	Present	Present	Present
27	NMDAR	NMDAR	Present	Present	Present
28	CASPR2	CASPR2	Present	Present	Present
29	Zic4, SOX, Ma1	Zic4, SOX, Ma1	Present	Not present	Present
30	NMDAR	NMDAR	Present	Not present	Not present
31	Myelin	Not present	Present	Not present	Not present
32	Titin	Titin	Present	Not present	Not present
33	Neuropil (unspecific)	Neuropil (unspecific)	Present	Not present	Not present
34	Recoverin	–	Present	Not present	Not present
35	CASPR2	Not present	Not present	Not present	Not present
36	IgLON5	IgLON5	Present	Present	Not present

AE, autoimmune encephalitis; CASPR2, contactin-associated protein-2; CV2/CRMP5, cronveinten 2/Collapsin response mediator protein 5; GAD65, glutamic acid decarboxylase of kDa65; KCNA2, Potassium Voltage-Gated Channel Subfamily A Member 2; NMDAR, N-methyl-D-aspartate receptor; NC, Neurochondrin; SOX1, Recoverin, sry-like high motility group box 1; Zic4, zinc finger protein of the cerebellum 4; Ab PB, autoantibody peripheral blood; Ab CSF, autoantibody cerebrospinal fluid; –, no CSF analysis done.

had possible autoimmune encephalitis and six out of 35 (17%) had definitive autoimmune encephalitis according to the criteria of Graus et al. (1), while seven out of 35 (20%) showed autoimmune psychosis according to the criteria of Pollak et al. (14) (Table 2). A lumbar puncture could not be performed in four patients with serum autoantibody detection and in three patients without serum autoantibody detection. Our patient

groups consisted of various psychiatric diagnoses whose main diagnoses did not differ in their frequency between groups (Table 1). PsychAb + PB patients were diagnosed with disorders belonging to organic, including symptomatic, mental disorders (60%, $n = 24$), schizophrenia, schizotypal and delusional disorders (3%, $n = 1$), mood disorders (5%, $n = 14$), anxiety, dissociative, stress-related, somatoform, and other nonpsychotic

TABLE 3 Demographics and clinical data of patient groups.

<i>n</i>	PsychAb + PB		PsychAb - PB		<i>p</i> -value	PsychAb + CSF		PsychAb - CSF		<i>p</i> -value
	35		119			13		141		
Gender	M	F	M	F		M	F	M	F	
<i>n</i> (%)	19/35 (54%)	16/35 (46%)	55/119 (46%)	64/119 (54%)		8/13 (62%)	5/13 (38%)	66/141 (47%)	75/141 (53%)	
Age mean value (range)	61.3 (55.9–66.7)		56.9 (53.7–60.1)		0.241	59.5 (48.8–70.3)		57.72 (54.9–60.6)		0.701
Psychiatric syndrome										
Paranoid hallucinatory, <i>n</i> (%)	9/35 (25.70%)		37/119 (31.10%)		0.349	7/13 (53.80%)		39/141 (27.70%)		0.053
Depressive, <i>n</i> (%)	21/35 (60.0)		74/119 (62.2%)		0.482	6/13 (46.2%)		89/141 (63.1%)		0.182
Manic, <i>n</i> (%)	3/35 (8.6%)		1/119 (0.8%)		<0.05	2/13 (15.4%)		2/141 (1.4%)		<0.05
Apathic, <i>n</i> (%)	4/35 (11.4%)		15/119 (12.6%)		0.558	2/13 (15.4%)		17/141 (2.1%)		0.497
Vegetative, <i>n</i> (%)	1/35 (2.90%)		8/119 (6.70%)		0.351	1/13 (7.70%)		8/141 (5.7%)		0.558
Hostility	4/35 (1.40%)		7/119 (5.90%)		0.22	2/13 (15.40%)		9/141 (6.4%)		0.234
Neurological, <i>n</i> (%)	4/35 (11.4%)		17/119 (14.3%)		0.454	1/13 (7.7%)		20/141 (14.2%)		0.445
Psychorganic, <i>n</i> (%)	30/35 (85.7%)		88/119 (73.9%)		0.109	11/13 (84.6%)		107/141 (75.9%)		0.375

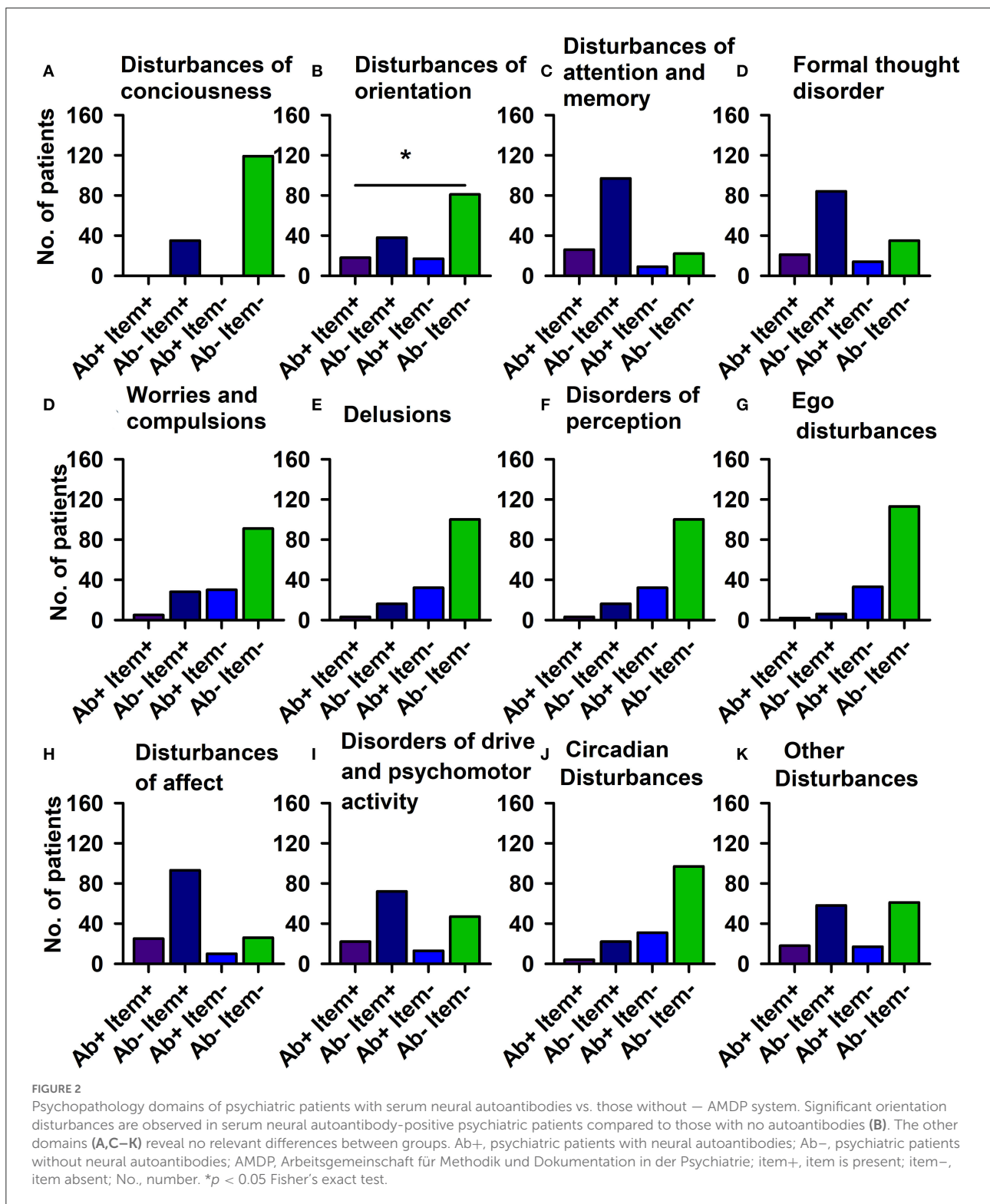
N, number of patients; PsychAb + CSF, psychiatric patients with cerebrospinal fluid neural autoantibodies; PsychAb + PB, psychiatric patients with serum neural autoantibodies; PsychAb - CSF, psychiatric patients without cerebrospinal fluid neural autoantibodies; PsychAb - PB, psychiatric patients without serum neural autoantibodies; M, male; F, female.

mental disorders (4%, $n = 2$). On the contrary, PsychAb - PB patients were diagnosed with organic, including symptomatic, mental disorders (45%, $n = 53$), schizophrenia, schizotypal and delusional disorders (18%, $n = 15$), mood disorders (35%, $n = 29$), anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (4%, $n = 2$), and adult personality and behavior disorders (2%, $n = 2$) (Table 1). The psychiatric diagnoses were made after the differential diagnostic approach was carried out, including the determination of neuronal autoantibodies. We formed a group of 13 of 154 (8.5%) patients who presented CSF neural autoantibodies (PsychAb + CSF) (Table 2) and a corresponding group of 141 patients with no CSF autoantibodies (PsychAb - CSF). See for autoantibodies of the PsychAb + PB group, serum and CSF group as well as CSF-only group autoantibodies (Table 2). In total, our cohort consisted of 80 women and 74 men. The men had a mean age of 54 years (54.3 ± 2.1 years), and the women were 61 years old (61.2 ± 1.7 years). However, the age of men and women did not differ throughout our entire cohort, the PsychAb + PB and PsychAb - PB patients. Age and gender did not differ between groups (PsychAb + PB vs. PsychAb - PB, and PsychAb + CSF vs. PsychAb - CSF) (Table 3). Several psychiatric syndromes did not differ among the (PsychAb + PB vs. PsychAb - PB, and PsychAb + CSF vs. PsychAb - CSF) groups (Table 3). However, many more psychiatric patients with a manic syndrome according to the AMDP classification presented neural autoantibodies (PsychAb+ or PsychAb + CSF) (8.6%) compared to neural autoantibody-negative psychiatric patients (PsychAb - PB or PsychAb - CSF) (0.8%) ($p < 0.05$) (Table 3).

Psychiatric patients with neural serum autoantibodies

AMDP classification

Using domains of the AMDP system, our analysis revealed more orientation disorders (51.4%) in our PsychAb + PB than the PsychAb - PB group (31.9%) (Figure 2; Table 4A, $p < 0.05$, Cramer's V: 0.170, Cronbach's alpha: 0.807, Bayesian test: 2.7, log odds ratio: 0.81). However, other AMDP criteria like disturbances of consciousness, attention and memory disorder, formal thought disorder, worries and compulsions, delusions, hallucinations, ego disturbances, affective disorders, drive and psychomotor disorders, circadian, and other disorders did not differ between PsychAb + PB and PsychAb - PB patients (Figure 2; Table 4A). When looking closer at the AMDP system's affective characteristics, PsychAb + PB (11.4%) showed less blunted affect than PsychAb - PB patients (32.8%) ($p < 0.01$, Cramer's V: 0.199, Bayesian test: 7.3, log odds ratio: -1.23, Figure 3; Table 4B). Furthermore, the affective rigidity was more pronounced in PsychAb- (45.4%) than PsychAb+ patients (20%, $p < 0.01$, Cramer's V: 0.22, Bayesian test: 13.44, log odds ratio: -1.14; Figure 3; Table 4B). However, no other affective symptoms were revealed such as the feeling of perplexity, loss of feeling, feeling loss of vitality, depressive mood, hopelessness, anxiety, euphoria, dysphoria, irritability, inner restlessness, complaining, feelings of insufficiency, increased self-esteem, feelings of guilt, feelings of impoverishment, ambivalence, parathymia, affect lability, affective incontinence, and lack of effects (Figure 3; Table 4B).



HiTOP classification

We found no differences between PsychAb + PB and PsychAb – PB groups in various spectra (somatoform,

internalizing, thought disorder, disinhibited externalizing, and antagonistic externalizing) from the HiTOP classification (Table 5A; Supplementary Figure 1). Furthermore, HiTOP

classification's frequency subfactors did not distinguish PsychAb + PB from PsychAb - PB patients (Table 5B; Supplementary Figure 2).

Psychiatric patients with cerebrospinal fluid neural autoantibodies

AMDP classification

The PsychAb + CSF patients could not be distinguished from PsychAb - CSF patients in their AMDP psychopathology domains such as orientation disorder, disturbances of consciousness, attention and memory disorder, formal thinking disorder, apprehensions and compulsions, delusions, hallucinations, ego disturbances, affective disorders, drive and psychomotor disorders, and circadian and other disorders (Table 4C). But if affective symptoms are inspected more carefully, the feeling of lost vitality was much stronger in PsychAb + CSF (5%) than PsychAb - CSF patients (0%) ($p < 0.05$, Cramer's V: 0.204, Figure 4; Table 4D).

HiTOP classification

The differences in specific psychopathologic symptoms revealed by analyzing the HiTOP classification were not apparent if HiTOP spectra between PsychAb + CSF vs. PsychAb - CSF patients (somatoform, internalizing, thought disorder, disinhibited externalizing, antagonistic externalizing, and detachment) were analyzed (Table 5C; Supplementary Figure 3). In addition, the frequency of HiTOP classification factors did not distinguish PsychAb + PB from PsychAb - PB patients (Table 5D; Supplementary Figure 5). We ran an additional analysis to seek superspectra differences between patient groups. The superspectra emotional dysfunction and psychosis did not differ between PsychAb + PB and PsychAb - PB patients, or between PsychAb+ and PsychAb - CSF patients (Tables 5E,F).

Correlation between serum and CSF neural autoantibody intensity and psychopathological features

We did not find relevant correlations between neural autoantibody intensity in serum ($n = 27$), neural autoantibody intensity in CSF ($n = 5$), combined neural autoantibody intensity in serum and CSF ($n = 9$), and the respective AMDP domain sum score, HiTOP spectrum score, HiTOP subfactor score, and HiTOP superspectrum scores.

Autoantibody subgroup analysis

To look for differences between autoantibody subtypes, we compared psychiatric patients with autoantibodies against membrane surface targets ($n = 15$) with autoantibodies against intracellular antigens ($n = 17$). We deleted these patients with the detection of not one, but various neural autoantibodies ($n = 3$). Surprisingly, we found more attention and memory impairment in patients with intracellular autoantibodies than in patients with antibodies to membrane surface antigens (Table 6A, Fisher's exact test: $p < 0.005$, Bayesian BF Poisson = 55.30). In affective psychopathology assessed by AMDP, it was surprisingly noticeable that patients with membrane surface autoantibodies did not have blunted affect in contrast to patients with autoantibodies against intracellular antigens (Table 6B, Fisher's exact test: $p < 0.005$, Bayesian BF Poisson = 3.26). However, no differences between the autoantibody subgroups with regard to the HiTOP spectra and subfactors could be demonstrated (Tables 6C,D). Furthermore, we performed an analysis of only NMDAR antibodies compared to PsychAb - PB patients as NMDAR depicted the largest size of one autoantibody subtype. We found less attention and memory impairment in patients with NMDAR autoantibodies ($n = 3$) than in PsychAb - PB patients ($n = 96$) (Supplementary Table 1A, Fisher's exact test: $p < 0.05$, Bayesian BF Poisson = 2.09). In addition, patients with NMDAR showed fewer formal thinking disorders ($n = 2$) compared to PsychAb-PB patients ($n = 83$) (Supplementary Table 1A, Fisher's exact test: $S < 0.05$, Bayesian BF Poisson = 2.09). After an in-depth analysis of affective psychopathology, it has been shown that patients with NMDAR autoantibodies had a greater percentage of the feeling of loss of vitality (Supplementary Table 1B, Fisher's exact test: $p < 0.05$, Bayesian BF Poisson = 0.85) and ambivalence (Supplementary Table 1B, Fisher's exact test: $p < 0.05$, Bayesian BF Poisson = 0.58) compared to PsychAb - PB patients. No relevant differences emerged between NMDAR antibody-positive patients and PsychAb - PB patients concerning HiTOP subfactors and spectra (Supplementary Tables 1C,D).

Discussion

Our study revealed that orientation disorder is a specific psychopathological feature that is more prominent in neural autoantibody-associated psychiatric syndromes compared to those without antibodies. On the contrary, a blunted affect and affective rigidity appears less often in psychiatric patients with than in those without neural autoantibodies. Our results in the field of cognitive and affective psychopathology applying a statistical procedure (Fisher's exact test) were confirmed in another, different statistical procedure, namely Bayesian statistic, obtaining Bayesian values between 3 and 13 regarding

TABLE 4 (A–D) Psychopathology of psychiatric patients presenting serum or cerebrospinal fluid neural autoantibodies versus those without them – AMDP domains and affective symptoms.

A	PsychAb –PB		PsychAb+AB		Fischer's exact test	Effect size	Cronbach's	Bayesian test	Log odds ratio
	Not present	Present	Not present	Present	<i>p-value</i>	Cramers V	Alpha	BF 10 poisson	
Disturbance of consciousness	100%	–	100%	–		–	–	–	–
Disturbances of orientation	68.1%	31.9%	48.6%	51.4%	<0.05	0.170	0.807	2.780	0.806 (0.059/1.554)
Disturbances of memory and attention	18.5%	81.5%	25.7%	74.4%	0.239	0.076	0.583	0.428	–0.437 (–1.311/0.437)
Formal thought disorders	29.4%	70.6%	40%	60%	0.164	0.095	0.307	0.626	–0.477 (–1.247/0.293)
Worries and compulsions	76.5%	23.5%	85.7%	14.4%	0.174	0.094	0.210	0.504	–0.551 (–1.564/0.463)
Delusions	84%	16%	91.4%	8.6%	0.209	0.089	0.804	0.385	–0.595 (–1.797/0.607)
Disorders of perception	84%	16%	91.4%	8.6%	0.209	0.089	0.417	0.385	–0.586 (–1.781/0.610)
Ego disturbances	95%	5%	94.3%	5.7%	0.579	0.013	0.431	0.159	0.281 (–1.214/–1.776)
Disturbances of affect	21.8%	78.2%	28.6%	71.4%	0.27	0.067	0.636	0.407	–0.365 (–1.201/0.471)
Disorders of drive and psychomotor activity	39.5%	60.5%	37.1%	62.9%	0.482	0.020	0.054	0.331	0.091 (–0.768/0.859)
Circadian disturbances	81.5%	18.5%	88.6%	11.4%	0.24	0.079	–	0.370	–0.483 (–1.568/0.601)
Other disturbances	51.3%	48.7%	48.6%	51.4%	0.465	0.023	0.309	0.343	0.111 (–0.635/0.856)

(Continued)

TABLE 4 (Continued)

B	PsychAb –PB		PsychAb+AB		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
	Not present	Present	Not present	Present	<i>p-value</i>	Cramers V	BF 10 poisson	
AMDP items affectivity disturbances								
Perplexity	94.1%	5.9%	97.1%	2.9%	0.421	0.057	0.167	−0.419 (−2.195 /1.357)
Feeling of loss of feeling	94.1%	5.9%	100%	–	0.158	0.118	0.319	−1.432 (−4.077/1.212)
Blunted affect	67.2%	32.8%	88.6%	11.4%	<0.01	0.199	7.299	−1.232 (−2.265/−0.198)
Feeling loss of vitality	39.3%	6.7%	94.3%	5.7%	0.594	0.017	0.167	−0.419 (−2.195/1.357)
Depressed mood	47.1%	52.9%	62.9%	37.1%	0.073	0.132	1.247	−0.626 (−1.393/0.140)
Hopelessness	83.2%	16.8%	94.3%	5.7%	0.078	0.133	0.847	−1.026 (−2.408/0.356)
Anxiety	60.5%	39.5%	65.7%	34.3%	0.363	0.045	0.369	−0.210 (−0.985/0.566)
Euphoria	96.6%	3.4%	100%	–	0.352	0.089	0.143	−0.898 (−3.604−1.807)
Dysphoria	93.3%	6.7%	88.6%	11.4%	0.277	0.074	0.293	0.636 (−0.566/1.837)
Irritability	96.6%	3.4%	91.4%	8.6%	0.194	0.105	0.334	1.018 (−0.425/2.460)
Inner restlessness	85.7%	14.3%	82.9%	17.1%	0.428	0.034	0.268	0.261 (−0.728/1.249)
Complaintiveness	97.5%	2.5%	97.1%	2.9%	0.648	0.009	0.118	0.400 (−1.508/2.307)
Feelings of inadequacy	91.6%	8.4%	88.6%	11.4%	0.397	0.044	0.238	0.399 (−0.754/1.553)
Exaggerated self-esteem	100%	–	97.1%	2.9%	0.227	0.149	0.221	2.222 (−0.754/5.198)
Feelings of guilt	92.4%	7.6%	94.3%	5.7%	0.524	0.030	0.176	−0.137 (−1.593/1.318)
Feelings of impoverishment	98.3%	1.7%	97.1%	2.9%	0.541	0.036	0.122	0.714 (−1.336/2.763)
Ambivalence	99.2%	0.8%	97.1%	2.9%	0.404	0.075	0.142	1.234 (−1.011/3.479)
Parathymia	99.2%	0.8%	100%	–	0.773	0.044	0.065	0.220 (−2.760- 3.199)
Affective lability	89.9%	10.1%	91.4%	8.6%	0.543	0.021	0.199	−0.076 (−1.325/1.173)
Affective incontinence	100%	–	100%	–	–	–	–	–
Affective rigidity	54.6%	45.4%	80%	20%	<0.01	0.217	13.446	−1.144 (−2.024/−0.264)

(Continued)

TABLE 4 (Continued)

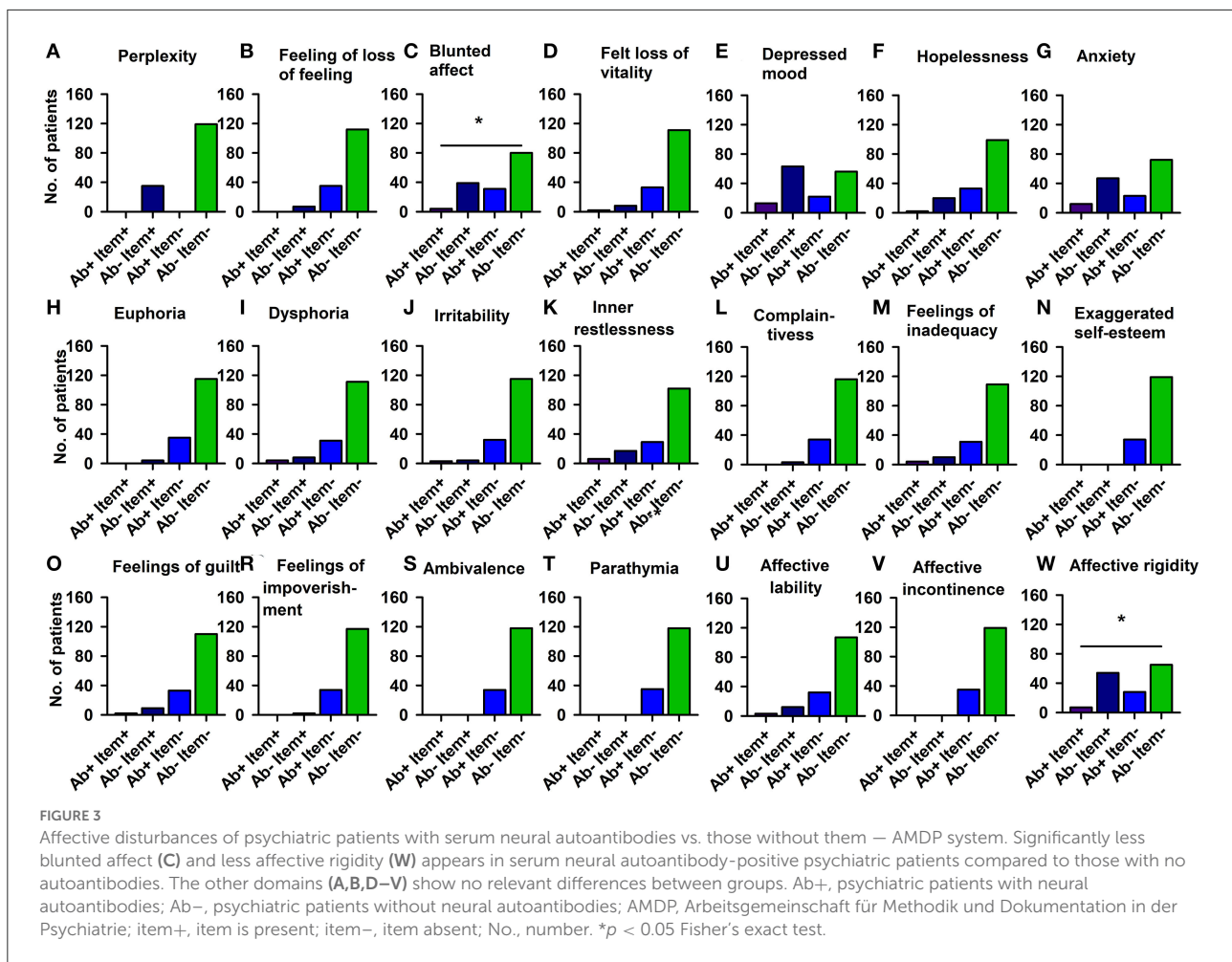
C	PsychAb –CSF		PsychAb +CSF		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
	Not present	Present	Not present	Present	<i>p-value</i>	Cramers V	BF 10 poisson	
Disturbance of consciousness	100%	–	100%	–	–	–		
Disturbances of orientation	65.2%	34.8%	46.2%	53.8%	0.143	0.110	0.539	0.779 (–0.332/1.890)
Disturbances of memory and attention	19.9%	80.1%	23.1%	76.9%	0.508	0.022	0.195	–0.287 (–1.561/0.988)
Formal thought disorders	32.6%	67.4%	23.1%	76.9%	0.357	0.057	0.247	0.381 (–0.888/1.649)
Worries and compulsions	79.4%	20.6%	69.2%	30.8%	0.293	0.069	0.284	0.587 (–0.615/1.788)
Delusions	86.5%	13.5%	76.9%	23.1%	0.277	0.076	0.274	0.738 (0.572/2.047)
Disorders of perception	85.1%	14.9%	92.3%	7.7%	0.417	0.057	0.171	–0.357 (–2.061/1.347)
Ego disturbances	95%	5%	92.3%	7.7%	0.515	0.034	0.134	0.744 (–1.043/2.591)
Disturbances of affect	23.4%	76.6%	23.1%	76.9%	0.641	0.002	0.189	–0.067 (–1.330/1.196)
Disorders of drive and psychomotor activity	40.4%	59.6%	23.1%	76.9%	0.177	0.099	0.425	0.706 (–0.459/1.960)
Circadian disturbances	83.7%	16.3%	76.9%	23.1%	0.380	0.050	0.223	0.525 (–0.770/1.820)
Other disturbances	51.8%	48.2%	38.5%	61.5%	0.265	0.074	0.330	0.510 (–0.614/1.635)

(Continued)

TABLE 4 (Continued)

D	PsychAb –CSF		PsychAb +CSF		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
	Not present	Present	Not present	Present	<i>p-value</i>	Cramers V	BF 10 poisson	
AMDP criterion affectivity disorders								
Perplexity	95%	5%	92.3%	7.7%	0.515	0.034	0.134	0.777 (–0.031/2.586)
Feeling of loss of feeling	95%	5%	100%	–	0.532	0.066	0.094	–0.280 (–2.953/2.392)
Blunted affect	70.2%	29.8%	92.3%	7.7%	0.076	0.137	0.776	–1.254 (–2.958/0.450)
Fell loss of vitality	95%	5%	76.9%	23.1%	<0.05	0.204	1.428	1.792 (0.396/3.188)
Depressed mood	48.9%	51.1%	69.2%	30.8%	0.133	0.113	0.562	–0.781 (–1.967/0.394)
Hopelessness	85.1%	14.9%	92.3%	7.7%	0.417	0.057	0.171	–0.363 (–2.103/1.378)
Anxiety	61.7%	38.3%	61.5%	38.5%	0.605	0.001	0.216	0.039 (–1.082/1.159)
Euphoria	97.2%	2.8%	100%	–	0.700	0.050	0.072	0.237 (–2.457/2.930)
Dysphoria	92.2%	7.8%	92.3%	7.7%	0.732	0.001	0.126	0.323 (–1.443/2.089)
Irritability	96.5%	3.5%	84.6%	15.4%	0.109	0.158	0.530	1.675 (0.045/3.306)
Inner restlessness	85.8%	14.2%	76.9%	23.1%	0.303	0.069	0.257	0.672 (–0.632/1.975)
Complaintiveness	97.9%	2.1%	92.3%	7.7%	0.300	0.097	0.191	1.579 (–0.385/3.543)
Feelings of inadequacy	90.1%	9.9%	100%	–	0.275	0.096	0.183	–1.016 (–3.672/1.639)
Exaggerated self-esteem	100%	–	92.3%	7.7%	0.084	0.266	0.596	3.408 (0.407/6.408)
Feelings of guilt	92.2%	7.8%	100%	–	0.366	0.084	0.137	–0.754 (–3.428/1.921)
Feelings of impoverishment	97.9%	2.1%	100%	–	0.766	0.043	0.066	0.500 (–2.255/3.256)
Ambivalence	98.6%	1.4%	100%	–	0.838	0.035	0.060	0.852 (–1.964/3.667)
Parathymia	99.3%	0.7%	100%	–	0.916	0.025	0.055	1.327 (–1.722/4.377)
Affective lability	90.1%	9.9%	92.3%	7.7%	0.631	0.021	0.132	0.092 (–1.634/1.819)
Affective incontinence	100%	–	100%	–	–	–	–	–
Affective rigidity	58.9%	41.1%	76.9%	23.6%	0.165	0.103	0.452	–0.736 (–1.992/0.519)

AMDP, Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie; PsychAb-PB, psychiatric patients without peripheral blood autoantibodies; PsychAb+AB, psychiatric patients with peripheral blood autoantibodies.



the psychopathological items orientation disorder, blunted affect and affective rigidity. Another affective symptom more often present in neural autoantibody-positive psychiatric patients is a loss of vitality, if those patients presenting cerebrospinal-fluid autoantibodies are investigated in particular. Furthermore, autoantibody-positive psychiatric patients more often have a manic syndrome than those without autoantibodies, thus confirming studies showing an association between mania and autoantibodies like NMDAR antibodies (15). These results suggest that affective and cognitive dysfunction are important domains in which the psychopathology should very carefully assessed.

Psychopathology in patients with autoantibody subgroups

Our subgroup analysis showed that patients with intracellular autoantibodies were much more likely to have

attention and memory impairments compared with patients with membrane surface autoantibodies. These results are consistent with previous studies showing cognitive impairment in patients with subsets of intracellular antibodies such as recoverin antibodies, published recently (16, 17). It is likely that temporal aspects of the presence of autoantibodies and the development of cognitive dysfunction are the reason that patients with autoantibodies to intracellular antigens are more affected than those with autoantibodies to membrane surface antigens. In addition, we examined the largest group of autoantibodies to a single antigen relative to our study rather than the literature: patients with NMDAR autoantibodies ($n = 7$). Analyses of the homogenous group of patients with NMDAR antibodies compared to antibody-negative patients also showed that although there were changes in psychopathology (less memory and attention disturbances, less formal thought disorder, more ambivalence, and more feelings of loss of vitality), these cannot be regarded as meaningful due to the small number of cases.

TABLE 5 (A–F) Psychopathology of psychiatric patients presenting serum or cerebrospinal fluid neural autoantibodies versus those without them – HiTOP spectra, factors and superspectra.

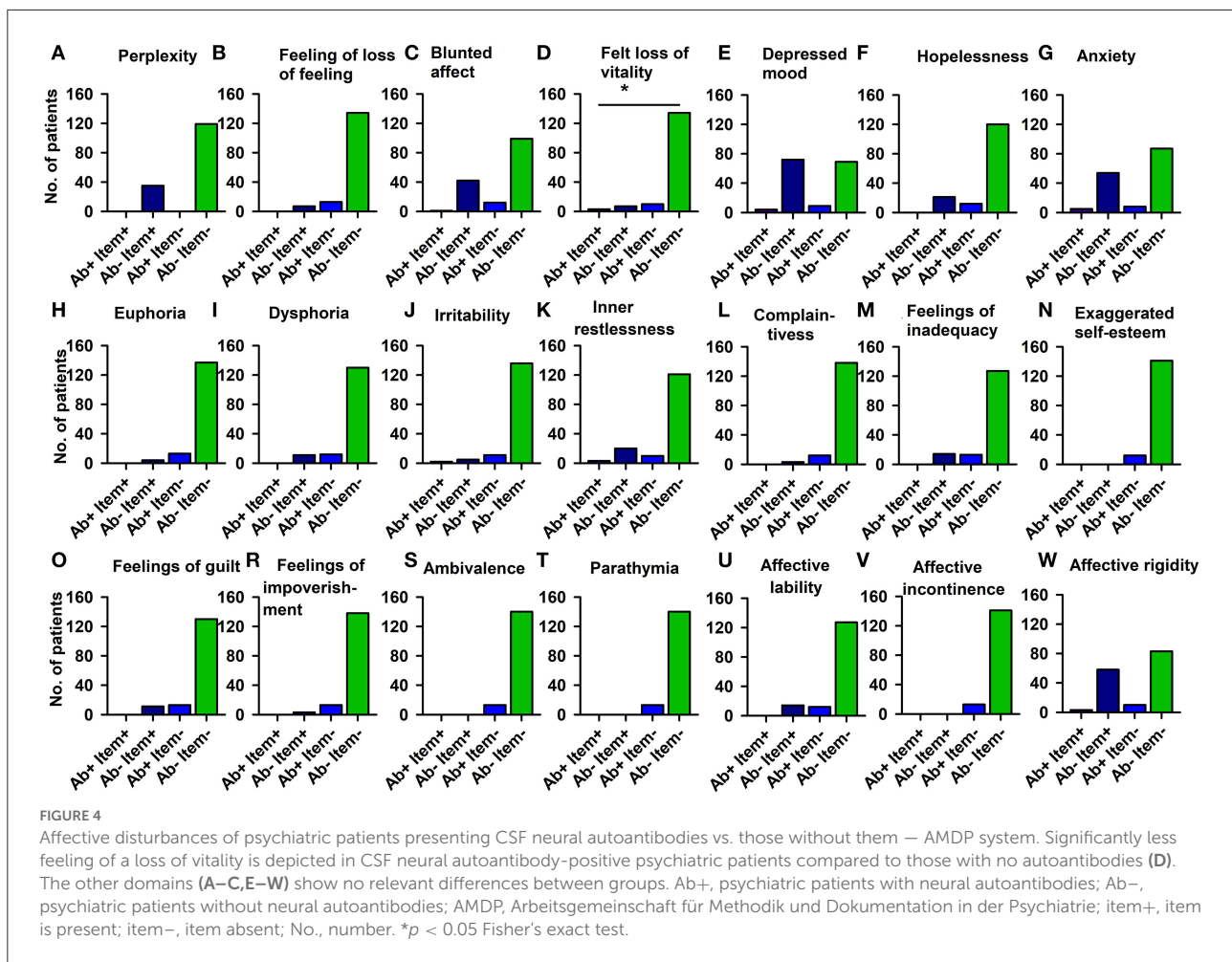
A	PsychAb –PB		PsychAb +PB		Fischer's exact test	Effect size	Cronbachs	Bayesian test	Log odds ratio
	HiTOP spectra	No present	Present	No present	Present	<i>p-value</i>	Cramers V	Alpha	BF 10 poisson
Somatoform	84.9%	15.1%	94.3%	5.7%	0.117	0.117	0.252	0.583	–0.883 (–2.247–0.482)
Internalizing	52.9%	47.1%	68.6%	31.7%	0.073	0.132	–	1.226	–0.644 (–1.433–0.145)
Thought disorder	79%	21%	82.9%	17.1%	0.407	0.040	0.163	0.209	–0.207 (–1.169–0.754)
Disinhibited externalizing	88.2%	11.8%	91.4%	8.6%	0.429	0.043	–	0.225	–0.231 (–1.451–0.990)
Antagonistic externalizing	96.6%	3.4%	100%	–	0.352	0.089	0.025	0.143	–0.898 (–3.572–1.777)
Detachment	92.4%	7.6%	100%	–	0.091	0.135	0.184	0.550	–1.673 (–4.306–0.959)
B	PsychAb –PB		PsychAb +PB		Fischer's exact test	Effect size	Cronbachs	Bayesian test	Log odds ratio
	HiTOP factors	No present	Present	No present	Present	<i>p-value</i>	Cramers V	Alpha	BF 10 poisson
Sexual problems	96.9%	3.4%	100%	–	0.352	0.089	–	0.143	–0.912 (–3.633/1.809)
Eating pathology	100%	0%	100%	–	–	–	–	–	–
Fear	89.1%	10.3%	97.1%	2.9%	0.126	0.118	0.113	0.485	–1.051 (–2.739/0.636)
Distress	60.5%	39.5%	74.3%	25.7%	0.097	0.120	–	0.933	–0.599 (–1.423/0.224)
Mania	96.6%	3.4%	94.3%	5.7%	0.413	0.051	–	0.179	0.658 (–0.928/2.244)
Substance abuse	89.1%	10.9%	94.3%	5.7%	0.290	0.074	–	0.266	–0.525 (–1.916/0.865)
Antisocial behavior	99.2%	0.8%	97.1%	2.9%	0.404	0.075	0.025	0.142	1.239 (–1.028/3.507)
C	PsychAb –CSF		PsychAb +CSF		Fischer's exact test	Effect size	Bayesian test	Log odds ratio	
	HiTOP spectra	Not present	Present	Not present	Present	<i>p-value</i>	Cramers V	BF 10 poisson	
Somatoform	87.2%	12.8%	84.6%	15.4%	0.526	0.022	0.168	0.375 (–1.067/1.817)	
Internalizing	56%	44%	61.5%	38.5	0.468	0.031	0.233	–0.196 (–1.322/0.930)	
Thought disorder	80.9%	19.1%	69.2	30.8	0.250	0.081	0.318	0.679 (–0.506/1.865)	
Disinhibited externalizing	88.7%	11.3%	92.3%	7.7%	0.566	0.032	0.139	–0.072 (–1.824/1.680)	
Antagonistic externalizing	97.2%	2.8%	100%	–	0.700	0.050	0.072	0.236 (–2.525/2.997)	
Detachment	93.6%	6.4%	100%	–	0.442	0.076	0.114	–0.544 (–3.201/2.114)	

(Continued)

TABLE 5 (Continued)

D	PsychAb –CSF		PsychAb +CSF		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
	Not present	Present	Not present	Present	<i>p-value</i>	Cramers V	BF 10 poisson	
HiTOP factors								
Sexual problems	97.9%	2.1%	92.3%	7.7%	0.300	0.097	0.191	1.677 (–0.393/3.548)
Eating pathology	100%	–	100%	–	–	–	–	–
Fear	90.8%	9.2%	92.3%	7.7%	0.665	0.015	0.129	0.129 (–1.650/1.907)
Distress	63.1%	36.9%	69.2%	30.8%	0.455	0.035	0.228	–0.229 (–1.423/0.965)
Mania	96.5%	3.5%	92.3%	7.7%	0.416	0.060	0.150	1.132 (–0.754/3.018)
Substance abuse	89.4%	10.6%	100%	–	0.249	0.100	0.202	–1.085 (–3.78/1.589)
Antisocial behavior	99.3%	0.7%	92.3%	7.7%	0.162	0.171	0.323	2.437 (0.160/4.714)
E	PsychAb –PB		PsychAb +PB		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
HiTOP superspectra	Not present	Present	Not present	Present	<i>p-value</i>	Cramers V	BF 10 poisson	
Psychosis	76.5%	23.5%	80%	20%	0.426	0.035	0.297	–0.170 (–1.098/0.758)
Emotional dysfunction	52.1%	47.9%	68.6%	31.4%	0.062	0.139	1.466	–0.677 (–1.466/0.113)
F	PsychAb –CSF		PsychAb +CSF		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
HiTOP superspectra	Not present	Present	Not present	Present	<i>p-value</i>	Cramers V	BF 10 poisson	
Psychosis	78.7%	21.3%	61.5%	38.5%	0.143	0.114	0.517	0.864 (–0.282/2.010)
Emotional dysfunction	55.3%	44.7%	61.5%	38.5%	0.448	0.035	0.238	–0.224 (–1.346/0.898)

HiTOP, Hierarchical Taxonomy of Psychopathology; PsychAb+AB, psychiatric patients with peripheral blood autoantibodies; PsychAb –PB, psychiatric patients without peripheral blood autoantibodies; PsychAb+AB, psychiatric patients with peripheral blood autoantibodies; PsychAb-CSF, psychiatric patients without cerebrospinal fluid autoantibodies; PsychAb+CSF, psychiatric patients with cerebrospinal fluid autoantibodies.



HiTOP classification vs. AMDP measurement of psychopathology associated with neural autoantibodies

No differing psychopathological features emerged when symptoms were analyzed *via* the HiTOP classification being in agreement with a recent controversy on HiTOP measurement system (18, 19) postulating disadvantages in HiTOP classification system in its current version for clinical use (18). The AMDP thus seems more suitable for assessing psychiatric symptoms potentially prominent in autoantibody-associated psychiatric syndromes. However, we could not confirm any relationship between neural autoantibody intensity and any main psychopathological feature in any of the measurement systems, as was recently demonstrated in terms of cognitive dysfunction in a subgroup of patients with psychiatric syndromes and associated autoantibodies—namely autoimmune psychosis—revealing a correlation between NMDAR autoantibody titer and cognitive dysfunction (20). Thus, our findings show that the AMDP measurement scale is

superior to the HiTOP scale in detecting differences in the psychopathology of psychiatric patients between those with and those without autoantibodies. We believe that a detailed, single symptom-oriented approach is more fruitful than an overstretched grouping of symptom domains, as small differences might prove to be extremely helpful for differentiating disease entities (autoantibody-related vs. non-autoantibody-related).

Specific psychopathology in autoantibody-associated psychiatric syndromes

The evidence of prominent orientation deficits has been reported in autoantibody-associated psychiatric syndromes (17, 21). The limbic system plays a key role in spatial orientation, which is often affected in the autoimmune encephalitis called limbic encephalitis, but it might be also functionally impaired in autoantibody-associated psychiatric syndromes leading to orientation deficits. The possibility

TABLE 6 (A–D) Autoantibody subgroup analysis.

A	Autoantibodies against intracellular antigens, <i>n</i> = 17		Autoantibodies against membrane surface antigens, <i>n</i> = 15		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
	Not present	Present	Not present	Present	<i>p</i> -value	Cramers V	BF 10 poisson	
Disturbance of consciousness								
Disturbances of orientation	35.2%	64.7%	53.3%	46.6%	0.305	0.181	1.277	0.703 (−0.664/2.070)
Disturbances of memory and attention	5.9%	94.1%	53.3%	46.7%	0.003	0.527	55.302	2.485 (0.593/4.378)
Formal thought disorders	29.4%	70.6%	53.3%	46.7%	0.169	0.243	1.882	0.944 (−0.468/2.356)
Worries and compulsions	88.2%	11.8%	80%	20%	0.522	0.113	0.702	−0.537 (−2.306/1.233)
Delusions	88.2%	11.8%	93.3%	6.7%	0.621	0.087	0.524	0.441 (−1.673/2.556)
Disorders of perception	94.1%	5.9%	86.7%	13.3%	0.471	0.128	0.599	−0.695 (−2.812/1.421)
Ego disturbances	94.1%	5.9%	93.3%	6.7%	0.927	0.016	0.42	−0.127 (−2.449/2.196)
Disturbances of affect	29.412%	70.6%	21.4%	78.5%	0.613	0.091	0.776	−0.367 (−1.913/1.179)
Disorders of drive and psychomotor activity	47.1%	52.9%	26.7%	73.3%	0.234	0.21	1.468	−0.806 (−2.214/0.602)
Circadian disturbances	94.1%	5.9%	86.7%	13.3%	0.471	0.128	0.599	−0.721 (−2.855/1.432)
Other disturbances	52.9%	47.1%	53.3%	46.7%	0.982	0.004	0.78	0.020 (−1.329/1.369)
B								
B	Autoantibodies against intracellular antigens, <i>n</i> = 17		Autoantibodies against membrane surface antigens, <i>n</i> = 15		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
	Not present	Present	Not present	Present	<i>p</i> -value	Cramers V	BF 10 poisson	
Affective disturbances								
Perplexity	94.1%	5.9%	100%	–	0.34	0.169	0.406	0.924 (−2.129/3.976)
Feeling of loss of feeling	100%	–	100%	–				
Blunted affect	76.5%	23.5%	100%	–	0.045	0.355	3.259	2.238 (−0.527/5.002)
Feeling loss of vitality	100%	–	86.7%	13.3%	0.12	0.275	1.019	−1.761 (−4.664/1.141)
Depressed mood	52.9%	47.1%	73.33%	26.7%	0.234	0.21	1.468	0.822 (−0.622/2.267)
Hopelessness	94.1%	5.9%	93.3%	6.7%	0.927	0.016	0.42	−0.129 (−2.452/2.194)
Anxiety	70.6%	29.4%	60%	40%	0.529	0.111	0.899	−0.441 (−1.861/0.978)
Euphoria	100%	–	100%	–				
Dysphoria	88.2%	11.8%	93.3%	6.7%	0.621	0.087	0.524	−0.434 (−2.534/1.667)
Irritability	94.118%	5.882%	86.667%	13.3%	0.471	0.128	0.599	0.705 (−1.439/2.849)
Inner restlessness	88.235%	11.8%	73.3%	26.7%	0.281	0.191	1.053	0.884 (−0.839/2.607)
Complaintiveness	100%	–	93.3%	6.7%	0.279	0.191	0.46	1.187 (−1.855/4.228)
Feelings of inadequacy	94.1%	5.9%	86.7%	13.3%	0.471	0.128	0.599	0.693 (1.426/2.812)
Exaggerated self-esteem	94.118%	5.9%	100%	–	0.34	0.169	0.406	0.927 (−2.109/3.964)
Feelings of guilt	100%	–	93.3%	6.7%	0.279	0.191	0.46	−1.146 (−4.129/1.836)
Feelings of impoverishment	100%	–	100%	–				
Ambivalence	100%	–	93.3%	6.7%	0.279	0.191	0.46	−1.202 (−4.302/1.898)
Parathymia	100%	–	100%	–				
Affective lability	100%	–	80%	20%	0.053	0.342	2.351	−2.165 (−4.951/0.622)
Affective incontinence	100%	–	100%5	–				
Affective rigidity	70.6%	29.4%	86.7%	21.9%	0.272	0.194	1.117	0.845 (−0.849/2.539)

(Continued)

TABLE 6 (Continued)

C	Autoantibodies against intracellular antigens, <i>n</i> = 17		Autoantibodies against membrane surface antigens, <i>n</i> = 15		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
	No present	Present	No present	Present	<i>p</i> -value	Cramers V	BF 10 poisson	
HiTOP spectra								
Somatoform	94.2%	5.9%	93.3%	6.7%	0.927	0.016	0.42	−0.134 (−2.509/2.241)
Internalizing	64.7%	35.4%	80%	20%	0.337	0.17	1.074	0.691 (−0.826/2.208)
Thought disorder	88.2%	11.8%	80%	20%	0.522	0.113	0.702	−0.533 (−2.303/1.237)
Disinhibited externalizing	88.2%	11.8%	93.3%	6.7%	0.621	0.087	0.524	0.443 (−1.646/2.533)
Antagonistic externalizing	100%	–	100%	–	–	–	–	–
Detachment	100%	–	100%	–	–	–	–	–
D								
HiTOP subfactors	Autoantibodies against intracellular antigens, <i>n</i> = 17		Autoantibodies against membrane surface antigens, <i>n</i> = 15		Fischer's exact test	Effect size	Bayesian test	Log odds ratio
	No present	Present	No present	Present	<i>p</i> -value	Cramers V	BF 10 poisson	
Sexual problems	100%	–	100%	–	–	–	–	–
Eating pathology	100%	–	100%	–	–	–	–	–
Fear	94.1%	5.9%	100%	–	0.34	0.169	0.406	−0.940 (−4.025/2.146)
Distress	64.7%	35.3%	86.7%	13.3%	0.152	0.253	1.746	−1.111 (2.760/0.538)
Mania	100%	–	93.3%	6.7%	0.279	0.191	0.46	1.175 (−1.848/4.198)
Substance abuse	94.1%	5.9%	93.3%	6.7%	0.921	0.016	0.42	0.177 (−2.213/2.447)
Antisocial behavior	94.1%	5.9%	100%	–	0.34	0.169	0.406	−0.954 (−3.982/2.075)

of a different affective psychopathology in autoantibody-associated psychiatric syndromes should be kept in mind: A blunted affect is more pronounced in antibody-negative than antibody-positive psychiatric syndromes, underlying a somewhat maintained sensation capability in an autoantibody-associated psychiatric syndrome. The psychopathology of 103 patients with Sjögren's syndrome was assessed extensively in association with autoantibodies against neuropeptides in comparison with 110 healthy controls (22). In their study, the patients with Sjögren's syndrome and autoantibodies against neuropeptides revealed different degrees of psychopathological characteristics, indicating that assessing personality traits is a potentially promising research field to target also in conjunction with autoantibody-associated psychiatric syndromes. This point was not investigated in detail in our current study. Thus, we confirm in our study patients a specific psychopathology revealing more orientation deficits, less blunted affect, and more loss of vitality, which point toward a phenotype entailing lost energy and orientation deficits in autoantibody-associated psychiatric syndromes. Our findings with mild psychopathological abnormalities in individual AMDP items, but not major AMDP domains in

psychiatric patients with autoantibodies, should be investigated in further studies with larger numbers of patients with specific autoantibody classes. Another important aspect to consider is that differences in psychopathology might not depend so much on the underlying psychiatric syndrome, as we found no differences between main syndromes apart from the manic syndrome of antibody-positive patients compared to antibody-negative patients. Thus, it is reasonable to measure a wide spectrum of psychopathologic items to be certain to detect small differences that might be of additional differential diagnostic value.

Limitations

The heterogeneous composition of our autoantibody-positive group is a potential limitation as the psychopathology associated with specific autoantibodies might be unique. Further studies with homogeneous autoantibody groups are needed to clarify this issue. Furthermore, neural autoantibody groups should be examined in separate groups, and their psychiatric diagnoses should likewise be differentiated to discover whether

certain autoantibodies play a role in specific psychiatric diseases. It would also be worthwhile to address this question in a future study with more homogeneous psychiatric-symptom constellations, and similar groups of neural autoantibodies (chosen for their supposed mechanism of action, and intra- or extracellular location of neural autoantibodies) in the hope that an immunotherapy approach would help to alleviate the symptoms of patients with a probable autoimmune basis. Another limitation is that patients with comorbidities such as other non-psychiatric disorders, developmental anomalies, or neurologic conditions were not excluded, as these are possible confounding factors. Furthermore, we cannot exclude that other factors like substance abuse or use, or anxiety might have an impact on psychopathology, not just the neural autoantibody biomarker. We thus recommend considering all these limitations in a future study to exclude confounding factors in a large cohort of autoantibody-positive psychiatric patients. Note that we refrained from multivariate testing and refer to our study's exploratory nature (we also dispensed with multivariate models because of its exploratory nature). A MANOVA is a suitable method that could be useful for a larger cohort to detect differences in psychopathology between antibody-positive and antibody-negative psychiatric patients. Another caveat is the timing of symptoms, which cannot be optimally assessed *via* a cross-sectional approach. In another study, we would prefer to assess psychopathology across its spectrum longitudinally, since in neural autoantibody diseases, symptoms often have a relapsing remitting character. A prospective study with fixed time points is necessary in future to avoid test biases regarding the timing of psychometric evaluation. Another limitation is that we only have data on the semiquantitative intensity assessment of neuronal autoantibodies and no endpoint titers of all autoantibodies, which is not a suitable biomarker to support the clinical relevance of autoantibody findings. In addition, as a further limitation of our study, it is worth noting that in the evaluation of psychopathology, the notes of doctors are used. However, this is not a prospective assessment that is carried out the same for everyone, so our study hereby draws attention to this limitation.

Conclusion

To the best of our knowledge, this is the first study to compare two methods for assessing psychopathology in autoantibody-associated psychiatric patients; we encourage the implementation of psychometry and classification of psychiatric syndromes as an important diagnostic component in the differential diagnosis of suspected autoimmune psychiatric syndromes. Thorough psychometry should be part of the diagnostic approach if an organic cause of psychiatric symptoms is suspected, and even when no organic cause of them is expected, as a patient's psychopathology may

reveal important clues to facilitate their diagnostics and care. A standard psychometric assessment scale like the AMDP seems adequate for detecting such slight differences in the phenotypical appearance of psychiatric disease associated with neural autoantibodies. The strength of our study is our detailed and novel assessment of the psychometry of patients presenting a plethora of psychopathological characteristics associated with various autoantibody-associated psychiatric syndromes. More research should be done to compare different measurement scales in assessing deep phenotypical differences between those psychiatric patients with and those without autoantibodies. The AMDP system for assessing psychopathology seems quite suitable and sensitive enough to reveal the psychopathological differences observed in psychiatric patients with and without autoantibodies, whereas the HiTOP classification system seems to be less useful for detecting autoantibody-associated differences in psychopathology. Therefore, as a general consideration of the findings, it is useful to survey the most specific psychopathology possible. Both affective psychopathology and a differential measurement of cognitive subdomains according to the AMDP system appear to be a relevant non-molecular marker for psychiatric patients diagnosed with neural autoantibodies.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the University Medical Center Göttingen. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

IG and NH wrote the manuscript. AJ and IG performed data collection. BT did part of the laboratory testing. DF and JW revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2022.945549/full#supplementary-material>

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SUPPLEMENTARY FIGURE 1

HiTOP spectra of psychiatric patients presenting serum neural autoantibodies vs. those without them. Ab+, psychiatric patients with neural autoantibodies; Ab–, psychiatric patients without neural autoantibodies; HiTOP, Hierarchical Taxonomy of Psychopathology; item+, item is present; item–, item absent; No., number.

SUPPLEMENTARY FIGURE 2

HiTOP factors of psychiatric patients presenting serum neural autoantibodies vs. those without them. Ab+, psychiatric patients with neural autoantibodies; Ab–, psychiatric patients without neural autoantibodies; HiTOP, Hierarchical Taxonomy of Psychopathology; item+, item is present; item–, item absent; No., number.

SUPPLEMENTARY FIGURE 3

Psychopathology of psychiatric patients with vs. those without neural autoantibodies—AMDP system. Ab+, psychiatric patients with neural autoantibodies; Ab–, psychiatric patients without neural autoantibodies; AMDP, Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie; item+, item is present; item–, item absent; No., number.

SUPPLEMENTARY FIGURE 4

HiTOP spectra of psychiatric patients presenting serum neural autoantibodies vs. those without them Ab+, psychiatric patients with neural autoantibodies; Ab–, psychiatric patients without neural autoantibodies; HiTOP, Hierarchical Taxonomy of Psychopathology; item+, item is present; item–, item absent; No., number.

SUPPLEMENTARY FIGURE 5

HiTOP factors of psychiatric patients presenting serum neural autoantibodies vs. those without them Ab+, psychiatric patients with neural autoantibodies; Ab–, psychiatric patients without neural autoantibodies; HiTOP, Hierarchical Taxonomy of Psychopathology; item+, item is present; item–, item absent; No., number.

SUPPLEMENTARY TABLE 1

Psychopathology of patients with NMDAR autoantibodies vs. psychiatric patients without autoantibodies.

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