



Improvement of Emotional Empathy and Cluster B Personality Disorder Symptoms Associated With Decreased Cocaine Use Severity

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Aims: Chronic cocaine users display impaired social cognitive abilities, reduced prosocial behavior, and pronounced cluster B personality disorder (PD) symptoms all contributing to their social dysfunctions in daily life. These social dysfunctions have been proposed as a major factor for maintenance and relapse of stimulant use disorders in general. However, little is known about the reversibility of social cognitive deficits and socially problematic personality facets when stimulant use is reduced or ceased. Therefore, we examined the relation between changing intensity of cocaine use and the development of sociocognitive functioning and cluster B PD symptomatology over the course of 1 year.

Methods: Social cognition, social decision-making, and cluster B PD symptoms were assessed in 38 cocaine users (19 with increased and 19 with decreased use) and 48 stimulant-naive healthy controls at baseline and at 1-year follow-up. Cocaine use severity was objectively determined by quantitative 6-month hair analyses. The categorization of the two cocaine user groups was based on a combination of absolute (± 0.5 ng/mg) and relative ($\pm 10\%$) changes in the cocaine hair concentration between baseline and the 1-year follow-up. Social cognition was assessed using the Multifaceted Empathy Test (MET) and the Movie for the Assessment of Social Cognition (MASC). A combined Distribution/Dictator Game was applied for assessing social decision-making. Cluster B PD symptoms were measured by a Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) PD questionnaire according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).

Results: Increased cocaine use was linked to worsened empathy, while decreased cocaine use went along with improved emotional empathy. Moreover, whereas decreased cocaine use was associated with reduced severity of self-reported cluster B PD symptoms, these symptoms remained largely stable in *increasers*. In contrast to a significant reduction of prosocial behavior at baseline in the combined cocaine user group, specifically *decreasers* were not statistically distinguishable from controls at the follow-up.

Conclusions: Sociocognitive deficits and cluster B PD symptoms of chronic cocaine users are adaptable over time as they covary with the increase or decrease in cocaine use. Hence, abstinence orientation and training of social cognition and interaction might improve social functioning, and should therefore be important therapeutic elements in cocaine addiction treatment.

Keywords: cocaine, stimulants, social cognition, empathy, Theory-of-Mind, social decision-making, cognition, personality disorder

INTRODUCTION

Neurocognitive deficits such as impaired attention, memory, and executive functions related to chronic cocaine use are well documented (1–3) and a risk factor for poor treatment outcomes (4, 5). While some studies investigated the linkage between these neurocognitive deficits and cocaine abstinence (6), only one study yet investigated the longitudinal relationship between cognitive impairments and changing cocaine use (7). In sum, these studies indicate that basal cognitive deficits in cocaine users seem to be largely drug-induced, remain stable during the first weeks of abstinence but likely improve after some months (8).

While nonsocial cognitive functions have been studied well during the last two decades, the systematic assessment of sociocognitive functioning in cocaine users has only recently emerged. Per definition, the concept of social cognition comprises not only abilities enabling the dynamic interaction with our social environments and include emotional and mental perspective-taking functions such as emotion recognition, emotional empathy (EE), and *Theory-of-Mind*, but also interactive abilities such as social decision-making (SDM), moral behavior, and social network behavior (9, 10). As daily-life social functioning strongly depends on intact social cognition and as the deteriorative impact of sociocognitive impairments on development, progress, and prognosis on other psychiatric disorders such as schizophrenia is well known (11), a close relationship between sociocognitive functioning and the origin and course of stimulant use disorders has been proposed (12–15). Accordingly, we previously demonstrated smaller social networks (16), reduced EE (16), altered SDM (17), stronger detachment from social norms (14), and impaired emotion recognition from voices (18) in recreational and dependent cocaine user groups. Moreover, dependent cocaine users made more errors than controls in a video-based *Theory-of-Mind* task, with recreational cocaine users performing intermediate between the two groups (16). Finally, cocaine users show also blunted neuronal responses to implicit and explicit forms of social reward (19, 20). Notably, all these studies were implemented with a cross-sectional design, but no study has investigated the longitudinal development of sociocognitive functioning so far. Thus, it is unclear if sociocognitive impairments are predisposed or drug-induced and if they are reversible upon prolonged abstinence or reduction of drug use.

As social cognition is the sum of those processes that allow individuals to interact in interpersonal contexts (21), disturbed sociocognitive functioning leads to aberrant social behavior and, in excessive forms, to deviant personality characteristics and impaired interpersonal functioning (22, 23). Notably, cocaine-addicted individuals show an increased risk for concurrent cluster B personality disorders (PDs), mainly of the antisocial and borderline types (24, 25). A cluster B PD comorbidity is largely influential for cocaine addiction severity and treatment outcomes including pronounced executive function deficits (26), more intense cocaine intake, lower rates of treatment applications, and decreased probability of cocaine addiction remission (27, 28). Additionally, it was demonstrated that impulsivity and gambling decision-making, which are both closely related to cluster B PD pathologies (22, 29), covary with changes in the intensity of cocaine use over 1 year (30). Nonetheless, the longitudinal relation between cocaine use intensity and cluster B PD symptomatology has also not been investigated to date.

In sum, only little is known about the temporal dynamics between cocaine use intensity and sociocognitive functioning. Hence, in order to investigate whether the described sociocognitive impairments and comorbid cluster B PD symptomatology in chronic cocaine users are modulated by the increase or decrease in cocaine abuse, we performed a longitudinal study with an interval of 1 year. Thereby, we compared 48 psychostimulant-naïve controls with 19 cocaine users with decreased use (*decreasers*) and 19 cocaine users with increased use (*increasers*) after a 1-year interval. To objectively assess the severity and change in cocaine use and to control for co-use of other drugs, we performed quantitative hair and urine toxicology analyses at baseline and follow-up. Considering our previous results from the present sample that changes in basal cognitive functions and impulsivity clearly covary with cocaine use intensity over time (7, 30), we hypothesized that escalating cocaine use is also associated with aggravation of sociocognitive impairments and more cluster B PD symptoms within 1 year. *Vice versa*, we also expected that reduced cocaine use is linked to a reduction of sociocognitive deficits and cluster B PD symptomatology. To test these hypotheses, we expect significant time \times group interactions specifically between *decreasers* and *increasers*. Given that at baseline cocaine users displayed significant alterations in EE, social network size, prosocial behavior in money distribution games, *Theory-of-Mind*, and cluster B PD symptoms (14, 16, 17), the longitudinal analysis was focused solely on these parameters.

METHODS

Participants

From a baseline sample of 234 participants (96 healthy stimulant-naïve controls, 138 cocaine users) (3, 16, 17), 48 healthy stimulant-naïve controls and 38 chronic cocaine users were included in the present longitudinal study. This subsample has been published twice previously but with different outcome measures (7, 30). From the baseline sample, 102 participants could not be measured at the follow-up because of unavailability (i.e., not responding to the invitation, loss of interest, lack of time, death), 27 participants had to be excluded from the final analyses as hair analyses revealed drug use not allowed by our exclusion criteria (e.g., polysubstance use, change in drug preferences), and 19 cocaine users did not meet our cocaine use criteria [see also the cocaine user group assignment below; for further recruitment and selection details, please see Ref. (7)].

At baseline, general exclusion criteria were clinically significant somatic diseases, neurological disorders, head injuries, family history of schizophrenia/obsessive-compulsive disorder/bipolar disorder, or any medication affecting the central nervous system. Additional exclusion criteria for controls were *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) axis I psychiatric disorders (excluding nicotine dependence) and regular illegal drug use (>15 lifetime occasions, except for recreational cannabis use). Additional exclusion criteria for cocaine users were a history of heroin use, polysubstance use, or DSM-IV axis I psychiatric disorders (except for cocaine, nicotine, cannabis, and alcohol abuse/dependence, attention deficit hyperactivity disorder, and a previous episode of an affective disorder). At baseline, inclusion criteria for cocaine users were cocaine use of >0.5 g per month, cocaine as primary drug, and an abstinence duration of <6 months. Participants were asked to abstain from illegal substances for at least 72 h and from alcohol for 24 h before the test sessions. Compliance with these instructions was controlled by urine screenings (semiquantitative enzyme multiplied immunoassay method). The study was approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed-consent statements and were compensated for their participation.

Cocaine User Group Assignment

The categorization of the two cocaine user groups was based on changes of cocaine concentration in hair samples as determined by liquid chromatography–tandem mass spectrometry [for technical details, see Ref. (3)]. If possible, 6-cm hair samples were drawn covering the previous drug use of approximately 6 months. Cocaine users were categorized based on a combination of absolute (± 0.5 ng/mg) and relative (>10% increase/decrease) changes in the hair concentration of cocaine_{total} between baseline and the 1-year follow-up (7, 30, 31). According to these criteria, cocaine users were divided into three equally sized groups: 19 cocaine *increasers* [mean \pm SD: $+30.4 \pm 61.9$ ng/mg (+297%), range: $+0.5$ to $+268.5$ ng/mg (+20% to +5,374%)], 19 cocaine *decreasers* [-10.6 ± 26.7 ng/mg (–72%), -116.9 to -0.6 ng/mg (–100% to –12%)], and 19 users with a relatively low and stable

cocaine use pattern who did not meet both criteria [-0.1 ± 0.5 ng/mg (–2%), -1.9 to $+0.5$ ng/mg (–100% to +720%)], and, thus, were not further analyzed in this study [for further details, see Ref. (7)].

Procedure

At baseline, self-reported drug use was assessed with a structured and standardized Interview for Psychotropic Drug Consumption (32), attention deficit hyperactivity disorder (ADHD) symptoms were assessed with the ADHD Self-Rating Scale (ADHD-SR) (33), and the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) (34) was carried out by trained psychologists.

The test battery was assessed at baseline and follow-up and included the Multifaceted Empathy Test (MET) (35) assessing EE, the Movie for the Assessment of Social Cognition (MASC) (36) for the measurement of *Theory-of-Mind*, a Distribution/Dictator Game (37, 38) for the determination of prosocial behavior, the Social Network Questionnaire (SNQ) (39) measuring the social network size, and the SCID-II questionnaire (40) in order to ascertain cluster B PD symptoms. More detailed test descriptions published already in our previous work (16, 17) are given in **Methods S1**.

Statistical Analysis

Effect sizes and power analyses were calculated with G*Power 3.1 (41). As our previous analyses showed an effect size of $p\eta^2 = 0.12$ (Cohen's $f = 0.37$) and a power of 99% for the significant interaction in the domain of working memory between *decreasers* and *increasers* (two groups, $p < .05$, two measurements) for the present sample (7), we assumed a more conservative effect size of $p\eta^2 = 0.06$ ($f = 0.25$) and calculated a still acceptable power of 86% for the detection of significant interactions in sociocognitive functions in the present sample.

In order to reduce data quantity [see also Ref. (17)], we computed an SDM composite score that was derived by averaging z -transformed payoffs for the other player in the Distribution and Dictator Game (payoffs B) according to the means and standard deviations of the control group. Because of a strong correlation of the explicit and implicit EE scores from the MET in the total sample ($r = 0.86$, $p < .001$), we further integrated both parameters by adding them up into a single MET EE score. The SCID-II Cluster B symptom score was calculated by summing up the dimensional values from histrionic, narcissistic, borderline, and antisocial PD.

Group differences in demographic data and drug use patterns were analyzed by means of Pearson's chi-squared tests, analyses of variance (ANOVA), or independent Student's t -tests. For the longitudinal analysis and in order to investigate group differences over all groups, we performed a multiple linear regression (forced entry) with the test score change values ($\Delta = t_2 - t_1$) as dependent variables and four preselected independent variables: age, sex, ADHS-SR score, and dummy-coded (zero/one) group contrasts. The two demographic variables were included because previous findings suggest a linkage between advancing age and fairness in stimulant users (17) and due to known gender effects in social cognition/functioning (42, 43). Moreover, because ADHD has previously been linked to cognitive and sociocognitive

performance in cocaine users (3, 16, 44), this variable was further included as a predictor into the regression model. To compare the groups, cocaine *increasers* acted as the reference group. To further analyze test score changes within the single groups (value t_2 vs. value t_1), we applied dependent Student's t -tests (t_{dep}). To compare the effect of changing cocaine use, we applied independent Student's t -tests (t_{ind}) between controls and a combined cocaine user sample (CCU = *increasers* + *decreasers*) at baseline as well as between controls, cocaine *increasers*, and cocaine *decreasers* at the follow-up. Notably, at baseline, cocaine *increasers* and *decreasers* showed comparable baseline values in all reported test parameters (MET, MASC, SDM, SNQ, SCID-II Cluster B) differing only with very small effect sizes ($t_{ind}(32-35) = 0.05-0.34$, $p = .99-.74$, $d = 0.00-0.11$). In the test parameter analysis, frequency data were analyzed by the Fisher-Freeman-Halton Exact Test (FET) (45). To test for test-retest effects, we applied the Pearson product-moment correlation analyses. The confirmatory statistical comparisons were carried out on a significance level of $p < .05$ (two-tailed).

RESULTS

Demographic characteristics and drug use: As shown before (7, 30), the three experimental groups did not significantly differ regarding age, sex distribution, verbal IQ, years of education, length of study interval (Table 1), and socioeconomic status (Table S1). Still, cocaine-using groups showed significantly higher BDI and ADHD-SR sum scores than controls at baseline (7, 30). Whereas at baseline both cocaine user groups showed comparable cocaine use severity, the cocaine_{total} hair concentrations for *increasers* (~3-fold increase) and *decreasers* (reduction by the factor 3.5) were significantly different at follow-up. Moreover, hair data revealed a clear preference for cocaine use compared to other illegal drugs. Finally, in both user groups, 8 of 19 participants sought psychiatric or psychological treatment during the study interval. The other cocaine users did not report any related treatment between baseline and follow-up.

Emotional empathy: The introduced predictors explained a significant amount of variance of the EE change scores in the multiple regression analysis [$F(5,80) = 2.68$, $p < .05$, $R^2 = .14$; Table 2]. The strongest predictors were sex ($\beta = -0.25$, $p < .05$) and the group contrast cocaine *increasers* vs. *decreasers* ($\beta = -0.25$, $p < .05$; Figure 1). *Post hoc* analyses showed that controls and the combined cocaine user (CCU) group showed a nonsignificant difference in EE with a small to moderate effect size at baseline [$t_{ind}(84) = 1.78$, $p = .08$, $d = 0.39$]. Whereas in the 1-year interval, *increasers* slightly reduced their already hampered EE [$t_{dep}(18) = 1.19$, $p = .25$, $d = 0.27$], and cocaine *decreasers* moderately improved their ability to respond empathically [$t_{dep}(18) = 1.80$, $p = .09$, $d = 0.41$]. Notably, controls remained largely stable in EE [$t_{dep}(47) = 0.98$, $p = .33$, $d = 0.14$]. Accordingly, at follow-up, controls differed significantly from the *increaser* group [$t_{ind}(25) = 2.14$, $p < .05$, $d = 0.64$], whereas the difference between controls and *decreasers* was strongly reduced [$t_{ind}(65) = 0.40$, $p = .69$, $d = 0.11$]. Finally, at follow-up, *increasers* and *decreasers* displayed a nonsignificant group difference of moderate effect size [$t_{ind}(36) = 1.69$, $p = .10$, $d = 0.56$].

Theory-of-Mind: The applied multiple regression model could not predict the MASC total error change scores (Table 2). At the phenomenological level, both cocaine user groups displayed small test-retest improvements [*increasers*: $t_{dep}(18) = 1.12$, $p = .28$, $d = 0.26$; *decreasers*: $t_{dep}(17) = 0.60$, $p = .56$, $d = 0.14$], while the control group showed pronounced improvements [$t_{dep}(47) = 4.68$, $p < .001$, $d = 0.68$; Figure 2].

Social interaction: The multiple regression model was also not able to predict the SDM composite change score (Table 2). From the phenomenological perspective, controls and *increasers* acted less prosocial (giving less money to the opponent), while *decreasers* remained stable but, with that, came closer to the controls (Figure 3). Exploratory *post hoc* analyses confirmed that controls and CCU significantly differed at baseline [$t_{ind}(65) = 2.51$, $p < .05$, $d = 0.56$]. At follow-up, controls and *increasers* still display a moderate group difference [$t_{ind}(65) = 1.92$, $p = .06$, $d = 0.50$], whereas the group difference between controls and *decreasers* was reduced to a small effect size [$t_{ind}(64) = 0.98$, $p = .33$, $d = 0.26$]. In addition, we analyzed behavioral changes between baseline and follow-up (more prosocial decisions, more self-serving decisions, similar decision) only in cocaine users and found that about two-thirds of the *increasers* (58% = 11/19) but only one-third of the *decreasers* (33% = 6/18) showed more self-serving decisions at follow-up ($p = .40$; FET; Figure S1).

Social network size: Regarding the SNQ total network size, the multiple regression model could again not substantially predict the change scores (Table 2, Figure 4). Interestingly, during the 1-year interval, all three groups reported a substantial and moderate social network reduction of about 2.5 contacts [controls: $t_{dep}(47) = 3.75$, $p < .001$, $d = 0.54$; *increasers*: $t_{dep}(17) = 1.94$, $p = .70$, $d = 0.46$; *decreasers*: $t_{dep}(17) = 3.09$, $p < .01$, $d = 0.73$].

Cluster B PD: The regression model significantly explained the variance in cluster B PD symptom change [$F(5,77) = 3.25$, $p < .01$, $R^2 = .17$; Table 2]. This change score was best predicted by the ADHS-SR score ($\beta = -0.32$, $p < .01$) and the group contrasts cocaine *increasers* vs. *decreasers* ($\beta = 0.34$, $p < .01$) and cocaine *increasers* vs. controls ($\beta = 0.31$, $p < .01$). Importantly, the CCU group showed at baseline significantly more cluster B PD symptoms than the controls [$t_{ind}(81) = 4.40$, $p < .001$, $d = 0.96$; Figure 5]. Whereas controls [$t_{dep}(47) = 4.91$, $p < .001$, $d = 0.71$] and *decreasers* [$t_{dep}(17) = 3.55$, $p < .01$, $d = 0.84$] had significantly lower symptom scores after the 1-year interval period, the amount of symptoms for the *increaser* group remained largely stable [$t_{dep}(16) = 0.52$, $p = .61$, $d = 0.13$]. Accordingly, at follow-up, controls differed strongly from the *increasers* [$t_{ind}(19) = 4.70$, $p < .001$, $d = 1.58$] and from the *decreasers* [$t_{ind}(22) = 3.11$, $p < .01$, $d = 0.96$]. Interestingly, already after 1 year of different cocaine use, *increasers* and *decreasers* displayed a moderate to strong group difference in cluster B PD symptoms at follow-up [$t_{ind}(33) = 1.85$, $p = .07$, $d = 0.63$]. Of note, approximately three quarters of the *decreasers* (13/18) displayed lower cluster B PD scores, while more than half of the cocaine *increasers* (9/17) showed even more symptoms at follow-up ($p < .05$; FET; Figure S2).

Remarkably, the interaction effect on cluster B PD symptoms was mainly driven by changes in the narcissistic and borderline subscores and less by the histrionic and surprisingly also not by the antisocial subscore (see Figure S3a-d). Both the narcissistic

TABLE 1 | Demographic data and pattern of cocaine use.

	Baseline (t1)				1-year follow-up (t2) ^m							
	Controls (n = 48)	Cocaine Increaser (n = 19)	Cocaine Decreaser (n = 19)	F/χ ² /T	df, df _{err}	p	Controls (n = 48)	Cocaine Increaser (n = 19)	Cocaine Decreaser (n = 19)	F/χ ² /T	df, df _{err}	p
Age, years	30.3 (8.9)	31.5 (9.4)	31.4 (8.3)	.20 ^a	2,83	.82	–	–	–	–	–	–
Sex (f/m)	16/32	3/16	5/14	2.11 ^b	2	.35	–	–	–	–	–	–
Verbal IQ (MMVT-B) ^d	107.6 (10.0)	102.9 (9.7)	103.8 (7.1)	2.20 ^a	2,83	.12	–	–	–	–	–	–
Education, years	10.8 (1.8)	10.4 (1.8)	10.0 (1.5)	1.30 ^a	2,83	.28	–	–	–	–	–	–
ADHD-SR score (0-22)	7.7 (5.2)	13.5 (9.4)**	14.1 (6.8)**	8.83 ^a	2,83	<.001	–	–	–	–	–	–
ADHD DSM IV (y/n) ^e	0/48	4/15	3/16	7.02 ^b	2	.03	–	–	–	–	–	–
Weeks between t1 and t2	58.2 (10.1)	59.3 (12.1)	61.9 (14.5)	.69 ^a	2,83	.50	–	–	–	–	–	–
BDI score (0-63)	3.5 (3.3)	7.3 (8.0)*	8.7 (6.5)**	7.53 ^a	2,83	<.001	–	–	–	–	–	–
BDI depression (y/n) ^g	0/48	1/18	1/18	2.59 ^b	2	.27	–	–	–	–	–	–
Cocaine												
Times per week ^h	–	1.6 (1.8)	1.0 (1.3)	1.17 ^c	36	.25	–	1.1 (0.8)	0.3 (0.3)	3.85 ^c	36	<.001
Grams per week ^h	–	2.0 (2.5)	1.7 (2.3)	.41 ^c	36	.68	–	1.6 (2.5)	0.4 (0.4)	2.18 ^c	36	.04
Years of use	–	7.0 (5.5)	8.2 (5.4)	.68 ^c	36	.50	–	8.9 (5.4)	9.7 (5.2)	.45 ^c	36	.65
Age of cocaine onset	–	24.5 (8.1)	23.1 (5.2)	.61 ^c	36	.54	–	–	–	–	–	–
Max. dose (g/day) ^k	–	4.7 (4.4)	5.9 (6.4)	.71 ^c	36	.48	–	3.7 (2.5)	3.1 (2.8)	.63 ^c	36	.53
Cumulative dose (g) ^k	–	1182 (1635)	3698 (6585)	1.25 ^c	36	.22	–	91 (119)	49 (89)	1.25 ^c	36	.22
Last consumption (days)	–	18.5 (25.1)	16.8 (14.6)	.29 ^c	36	.77	–	7.0 (6.3)	81.4 (145.1)	2.23 ^c	36	.03
Cocaine craving (0-70) ^l	–	19.8 (9.5)	17.7 (7.2)	.79 ^c	36	.44	–	20.5 (10.8)	15.8 (6.2)	1.66 ^c	36	.11
Hair analysis (ng/mg) ^l	–	–	–	–	–	–	–	–	–	–	–	–
Cocaine _{total}	–	10.3 (29.2)	14.9 (32.2)	.46 ^c	36	.65	–	40.7 (76.1)	4.2 (8.2)	2.08 ^c	36	.05
Cocaine	–	8.2 (23.3)	11.4 (23.9)	.42 ^c	36	.68	–	31.7 (56.5)	3.1 (5.9)	2.19 ^c	36	.03
Benzoyllecgonine	–	1.9 (5.5)	3.1 (7.6)	.58 ^c	36	.56	–	8.3 (19.6)	1.0 (2.2)	1.62 ^c	36	.11
Cocacethylene	–	1.0 (2.8)	0.9 (2.8)	.11 ^c	36	.91	–	1.2 (2.1)	0.3 (1.0)	1.56 ^c	36	.13
Norcocaine,	–	0.2 (0.5)	0.4 (0.8)	.83 ^c	36	.41	–	0.6 (1.4)	0.1 (0.1)	1.71 ^c	36	.10
Urine toxicology (n/p) ^k	48/0	14/5	16/3	.63 ^b	1	.43	48/0	7/12	18/1	14.15 ^b	1	<.001
Alcohol^l												
Grams per week ^h	119.9 (136.8)	169.4 (129.2)	155.3 (146.4)	1.07 ^a	2,83	.35	104.3 (88.6)	259.7 (244.5)**	127.4 (141.4) ^o	7.71 ^a	2,83	<.001
Years of use	13.3 (8.8)	13.7 (7.6)	12.0 (7.3)	.23 ^a	2,83	.79	14.0 (8.7)	14.8 (7.5)	12.6 (7.9)	.34 ^a	2,83	.71
Nicotineⁿ												
Smoking (y/n) ^j	37/11	14/5	14/5	.13 ^b	2	.94	40/8	15/4	13/6	1.83 ^b	2	.40
Cigarettes per day ^h	8.7 (8.7)	12.8 (11.2)	9.5 (8.2)	1.38 ^a	2,83	.26	8.2 (8.7)	13.4 (12.0)	8.2 (7.8)	2.31 ^a	2,83	.11
Years of use	9.3 (8.3)	10.4 (8.9)	12.7 (10.3)	.95 ^a	2,83	.39	10.5 (8.8)	12.5 (8.6)	12.6 (9.9)	.56 ^a	2,83	.57
Cannabisⁿ												
Grams per week ^h	0.6 (1.6)	3.3 (8.9)	1.2 (2.3)	2.38 ^a	2,83	.10	0.5 (1.6)	2.1 (4.6)	1.1 (2.7)	2.28 ^a	2,83	.11
Years of use	4.5 (4.9)	9.5 (8.5)*	10.1 (9.7)*	5.92 ^a	2,83	.004	4.6 (5.9)	10.5 (9.8)*	8.6 (9.7)	4.64 ^a	2,83	.01
Cumulative dose (grams)	980 (3985)	3199 (5899)	2606 (6359)	1.61 ^a	2,83	.21	53.4 (180)	217.8 (526.5)	84.7 (189.6)	2.15 ^a	2,83	.12
Last consumption (days) ^j	39.3 (1.8);n = 22	10.0 (0.4);n = 14	25.4 (1.1);n = 12	2.19 ^a	2,45	.12	36.5 (1.5);n = 22	9.7 (0.4);n = 13	50.8 (2.1);n = 10	1.20 ^a	2,42	.31
Urine toxicology (n/p) ^k	42/6	15/4	14/5	2.03 ^b	2	.36	42/6	7/12	15/4	18.61 ^b	2	<.001
Amphetamineⁿ												
Grams per week ^h	0.0 (0.1)	0.1 (0.1)**	0.0 (0.1)	5.18 ^a	2,83	.008	0.0 (0.0)	0.1 (0.2)**	0.0 (0.1)	5.89 ^a	2,83	.004
Years of use	0.0 (0.0)	3.3 (4.0)**	1.3 (3.1) ^o	13.73 ^a	2,83	<.001	0.1 (0.5)	3.2 (4.9)**	2.7 (5.5)*	7.46 ^a	2,83	.001
Cumulative dose (grams)	0.0 (0.1)	56.0 (177.6)*	16.2 (35.9)	2.99 ^a	2,83	.06	0.0 (0.1)	4.4 (8.9)**	1.4 (3.5)	6.47 ^a	2,83	.002
Last consumption (days) ^j	121.6 (5.1);n = 1	73.6 (3.1);n = 10	90.9 (3.8);n = 3	.29 ^a	2,11	.75	17.5 (0.7);n = 1	35.7 (1.5);n = 8	99.8 (4.2);n = 4	1.48 ^a	2,10	.27
Hair analysis (ng/mg)	0.0 (0.0)	0.1 (0.2)*	0.0 (0.0)	4.35 ^a	2,83	.02	0.0 (0.0)	0.1 (0.2)	0.1 (0.2)	2.89 ^a	2,83	.06

(Continued)

TABLE 1 | Continued

	Baseline (t1)				1-year follow-up (t2) ^m							
	Controls (n = 48)	Cocaine Increaser (n = 19)	Cocaine Decreaser (n = 19)	F/ χ^2 /T	df, d_{err}^{\dagger}	p	Controls (n = 48)	Cocaine Increaser (n = 19)	Cocaine Decreaser (n = 19)	F/ χ^2 /T	df, d_{err}^{\dagger}	p
MDMAⁿ												
Tablets per week ^k	0.0 (0.0)	0.0 (0.1)**	0.0 (0.0) ^o	7.42 ^a	2,83	.001	0.0 (0.0)	0.4 (0.9)**	0.0 (0.0) ^o	5.54 ^a	2,83	.006
Years of use	0.3 (1.0)	3.5 (4.5)***	2.4 (4.6)*	8.42 ^a	2,83	<.001	0.2 (1.4)	3.8 (5.5)**	3.2 (5.6)*	7.78 ^a	2,83	<.001
Cumulative dose (tablets)	1.3 (4.0)	108.8 (249.7)**	18.7 (46.2)	5.71 ^a	2,83	.005	0.2 (0.8)	17.0 (49.3)*	2.8 (5.2)	3.67 ^a	2,83	.03
Last consumption (days)	5.0 (0.2);n = 1	89.9 (3.7);n = 7	40.2 (1.7);n = 4	1.63 ^a	2,9	.25	91.2 (3.8);n = 3	41.6 (1.7);n = 6	47.8 (2.0);n = 5	1.11 ^a	2,11	.36
Hair analysis (ng/mg)	0.0 (0.0)	0.3 (0.7)	0.4 (1.5)	2.23 ^a	2,83	.11	0.0 (0.0)	0.5 (0.8)***	0.1 (0.3)	7.87 ^a	2,83	<.001
GHBⁿ												
Cumulative dose (pipettes)	0.0 (0.0)	0.5 (0.7)	0.5 (1.7)	3.36 ^a	2,83	.04	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	-	-	-
Hallucinogensⁿ												
Cumulative dose (times)	0.9 (2.2)	27.9 (72.8)*	9.9 (22.9)	3.92 ^a	2,83	.02	0.0 (0.0)	1.1 (1.6)***	0.6 (1.5)	8.57 ^a	2,83	<.001
Methylphenidateⁿ												
Cumulative dose (tablets)	0.0 (0.0)	20.2 (60.4)*	0.5 (2.3)	3.76 ^a	2,83	.03	0.0 (0.1)	67.7 (239.5)	0.3 (0.6)	2.72 ^a	2,83	.07
Hair analysis (ng/mg)	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)	1.80 ^a	2,83	.17	0.0 (0.0)	0.1 (0.2)*	0.0 (0.0)	3.62 ^a	2,83	.03

Means and standard deviations. Significant p values are shown in bold.
^aANOVA (all groups, with significant Sidak post hoc test vs. control group: *p < .05; **p < .01; ***p < .001; vs. cocaine increaser: ^op < .05).
^b χ^2 -test (all groups/cocaine users only) for frequency data.
^cIndependent t-test (cocaine users only).
^dVerbal IQ was assessed by the Mehrfachwahl Wortschatz Intelligenztest (46).
^eADHD-SR, ADHD self-rating scale (cutoff DSM-IV criteria) (33).
^fSmoking habits were assessed by the Fagerstrom Test of Nicotine Dependence (47).
^gBDI, Beck Depression Inventory (cutoff \geq 18) (48).
^hAverage use during the last 6 months.
ⁱCraving for cocaine was assessed by the Brief-CCQ (49).
^jLast consumption is averaged only for persons who used the drug in the last 6 months.
^kUrine toxicology (neg/pos) are based on the cutoff value for cocaine = 150 ng/ml and for tetrahydrocannabinol 50 ng/ml (50). The χ^2 -test for cannabis includes controls and cocaine users.
^lHair samples were voluntary and data are missing for three controls.
^mParameters at follow-up refer to the 1-year period between t1 and t2.
ⁿAt baseline, average use during the last 6 months. Use frequency, duration of use, and cumulative doses are averaged within the total group.

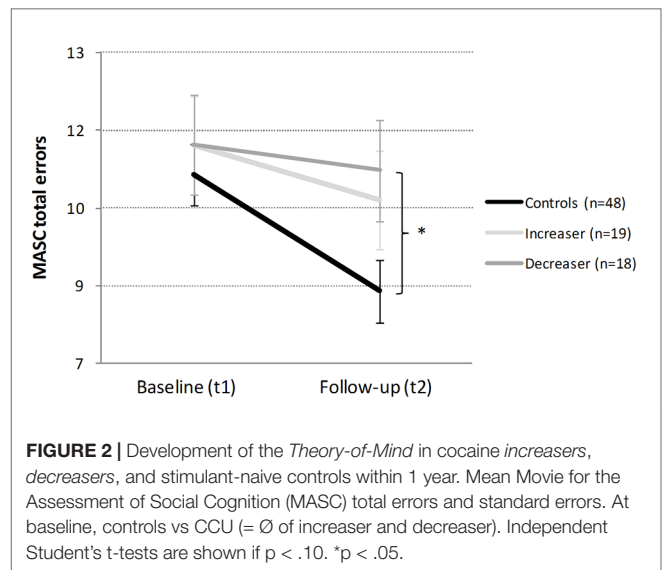
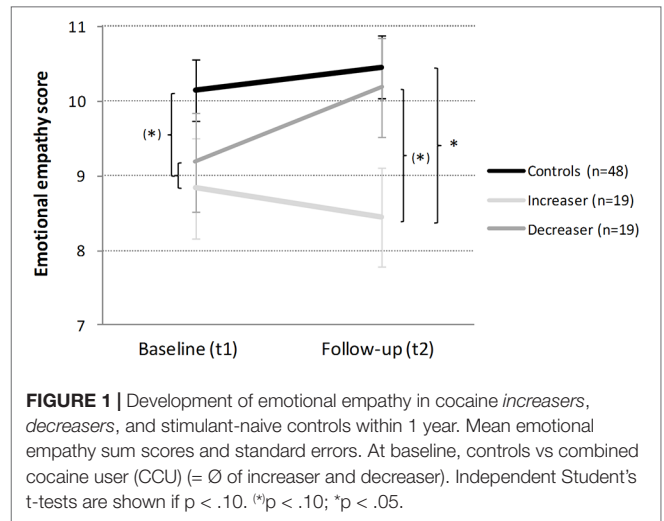
TABLE 2 | Multiple regression analyses.

	Emotional empathy			Theory-of-Mind			Social interaction			Social network			Personality disorder		
	Δ MET	SE	β	Δ MASC total errors	SE	β	Δ SDM composite score	SE	β	Δ SNQ network size	SE	β	Δ SCID-II Cluster B	SE	β
Constant	1.55	1.14		-1.85	2.02		-0.26	0.45		-0.73	2.72		-1.01	2.80	
Age	0.04	0.03	0.14	0.06	0.05	0.14	-0.01	0.01	-0.08	0.06	-0.08	0.02	0.02	0.06	0.04
Sex	-1.16	0.50	-0.25*	-0.99	0.86	-0.12	0.09	0.20	0.05	1.20	-0.05	-0.71	1.23	0.08	-0.06
ADHD-SR score	-0.05	0.03	-0.16	-0.07	0.06	-0.14	0.00	0.01	-0.01	0.08	0.05	-0.24	0.08	0.08	-0.32**
Controls vs. cocaine increaser	-0.26	0.59	-0.05	1.71	1.03	0.20	0.03	0.24	0.01	1.43	0.03	4.00	1.49	1.49	0.31**
Cocaine decreaser vs. cocaine increaser	-1.30	0.66	-0.25*	-0.51	1.17	-0.06	-0.31	0.27	-0.16	1.63	0.05	4.43	1.69	1.69	0.34**
R ²		0.14			0.10			0.03		0.01			0.17		
F		2.68*			1.67			0.57		0.22			3.25**		

Multiple linear regression with the independent variables age, sex, ADHD-SR score, and dummy coded (zero, one) group variables. To compare the groups, cocaine increaser acted as the reference group. Dependent variables are change values (Δ = value at t2 - value at t1).

B, unstandardized regression coefficient; SE, unstandardized standard error; β, standardized beta.

*p < .10; **p < .05; ***p < .001.



and the borderline subscores revealed significant regression models (Table S2), but only the borderline subscore was significantly predicted by the group contrast cocaine *increasers* vs. *decreasers* ($\beta = 0.40, p < .01$). Compared to baseline, less symptoms occurred in controls [$t_{dep}(47) = 4.99, p < .001, d = 0.72$] and *decreasers* [$t_{dep}(17) = 3.16, p < .01, d = 0.75$] at follow-up, while symptoms remained stable in *increasers* [$t_{dep}(16) = 0.18, p = .86, d = 0.04$], resulting in a strong group effect between *increasers* and *decreasers* [$t_{ind}(33) = 2.57, p < .05, d = 0.87$] at follow-up.

Change in alcohol use: As not only cocaine but also alcohol intake was increased in *increasers* (see Table 1), the change in alcohol consumption was considered in additional multiple regression models. However, alcohol change was not significant in any of the main regression models (p-values ranged from .222 to .659) shown in Table 2, while the interaction effects and also the explained variances remained stable, indicating that changes in alcohol consumption have not impacted our main results.

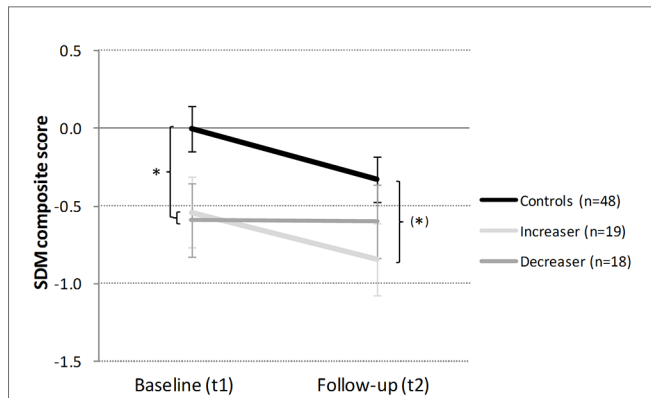


FIGURE 3 | Development of social interaction in cocaine *increasers*, *decreasers*, and stimulant-naive controls within 1 year. Mean social decision-making (SDM) composite z-scores and standard errors. At baseline, controls vs CCU (= 0 of increaser and decreaser). Independent Student's t-tests are shown if $p < .10$. (*) $p < .10$; * $p < .05$.

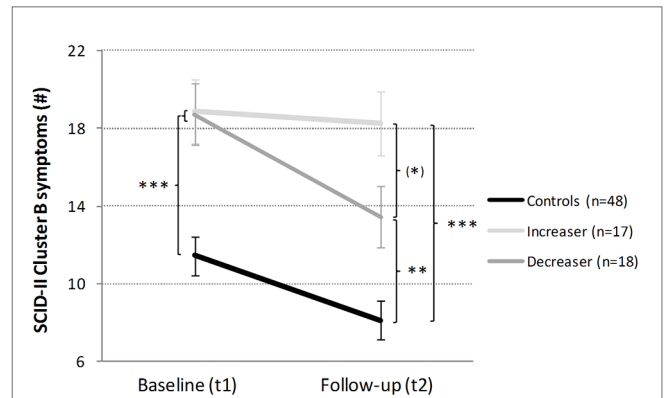


FIGURE 5 | Development of Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) Cluster B in cocaine *increasers*, *decreasers*, and stimulant-naive controls within 1 year. Mean SCID-II Cluster B symptoms and standard errors. At baseline, controls vs CCU (= 0 of increaser and decreaser). Independent Student's t-tests are shown if $p < .10$. (*) $p < .10$; ** $p < .01$; *** $p < .001$.

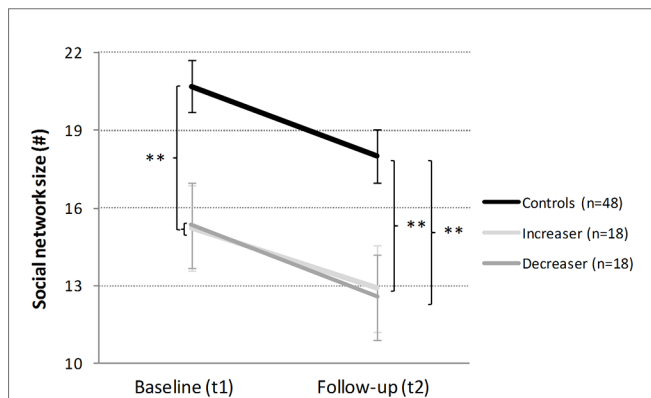


FIGURE 4 | Development of social network size in cocaine *increasers*, *decreasers*, and stimulant-naive controls within 1 year. Mean total network size and standard errors. At baseline, controls vs CCU (= 0 of increaser and decreaser). Independent Student's t-tests are shown if $p < .10$. ** $p < .01$.

TABLE 3 | One-year test-retest reliability between baseline and 1-year follow-up in controls and cocaine users.

	Controls (n = 48)	Combined cocaine users (n = 38)	Total sample (n = 86)
MET Emotional empathy score	0.66***	0.79***	0.74***
MASC total errors	0.67***	0.60***	0.63***
SDM composite score	0.48***	0.85***	0.70***
SNQ network size	0.75***	0.81***	0.80***
SCID-II Cluster B symptoms	0.68***	0.74***	0.77***

Pearson's product-moment correlation. Significance level: *** $p < .001$.

Test-retest reliability: In the total sample, all dependent variables displayed acceptable to good test-retest reliabilities (Table 3). Interestingly, in the SDM paradigm, controls and CCU differed significantly in their test-retest reliability ($z = -3.25$; $p < .001$): While in controls the SDM score showed hardly acceptable reliability ($r = 0.48$; $p < .001$), it was good in the cocaine users ($r = 0.85$; $p < .001$).

DISCUSSION

The present longitudinal study investigated the change of social cognition, social interaction, and socially relevant cluster B PD symptoms in healthy controls and relatively pure and non-help-seeking chronic cocaine users who clearly increased or decreased their cocaine consumption during a 1-year study interval. The most striking findings were that i) improved EE correlated with

decreased cocaine consumption, whereas increased cocaine use severity was linked to less EE; and ii) cluster B PD symptom burden was lowered in *decreasers*, whereas *increasers* showed stable severity in these symptoms. Additionally, during the study interval, we found an approximation between controls and *decreasers* regarding their prosocial behavior, while the large gap between *increasers* and controls remained. Moreover, neither the *Theory-of-Mind* Task (MASC) nor the social network size showed interactions with changing cocaine use, indicating that mental perspective-taking (sometimes also interpreted as *cognitive empathy*) and the number of social contacts in the last months were not affected by changing drug use during the study interval.

Importantly, the present analysis of smaller (longitudinal) subgroups from our larger cross-sectional ZuCo²St sample published previously (14, 16, 17) still showed significantly reduced prosocial behavior, a smaller social network, and strongly elevated cluster B personality symptoms in the total group of cocaine users at baseline, indicating that these indicators of social functioning were robustly altered in this population. The EE score of the MET showed only a statistical trend between cocaine users and controls at baseline, but the present effect size ($d = 0.39$) was in the range of the previously

reported effect sizes of the larger cross-sectional sample of recreational and dependent cocaine users ($d = 0.39\text{--}0.64$), suggesting rather a deficiency of power than a lack of reliability. This assumption is further supported by the fact that the MET EE score showed good test–retest reliability scores. Moreover, the MASC did not show any baseline group differences in the present subsample of cocaine users underscoring our previous conclusion that mainly very severe cocaine users with a putative ADHD comorbidity show disturbances in this task (16, 44).

While sociocognitive functions represent basic abilities in perspective-taking and interaction, more conventional psychopathology is aiming at the identification and quantification of symptoms in psychiatric disorders (51). As such, the research on the relationship between PDs and cocaine use is of special interest, as the differentiation between predispositions vs. drug-induced effects merges with the question if these pathologies are reversible or not. In our longitudinal investigation, we found that *decreasers* of cocaine consumption also significantly improved in cluster B PD symptoms during 1 year, whereas the *increasers* showed a stable PD symptom burden. This is insofar interesting as in both user groups 8 of 19 participants sought psychiatric treatment in the interval, but only *decreasers* improved in some social functions and socially relevant PD symptoms.

In general, PDs are defined as typical constellations of impaired subjective and behavioral traits that result in suffering of the affected individual and/or society (52). These personality traits are regarded as relatively stable across time and consistent across situations (diagnostically mandatory) (53–56). Moreover, cluster B PDs show a higher stability over 12 to 18 years than the other clusters (57). However, studies also found considerable variability of PD symptoms across individuals over time (58, 59), questioning the trait-like character of the disorder. An early study showed changes in PD symptoms related to treatment in substance-dependent patients (60). Interestingly, clusters A and C profited most, while cluster B changes were only observed in patients with borderline PD. In patients with cocaine addiction, cluster B PDs are the most frequent and these patients have the most severe courses of illness including worst treatment outcomes (24, 26–28, 61, 62). Therefore, cluster B PD symptoms are likely personality features that increase the risk for cocaine use and the development of an addiction. However, as seen in the present study, cluster B PD symptom load is nevertheless variable and reduction of consumption leads to a substantial improvement in these symptoms. Consequently, a reduction of cluster B PD symptom burden again increases likelihood of successful treatment, offering the patient an opportunity to leave the vicious circle of addiction.

The suggested consumption-dependent variability of social behavior as well as cluster B symptoms are well in line with our previous analyses from this sample that not only basal cognitive functions such as working memory but also self-reported impulsivity improve with a strong reduction of cocaine use, while they are worsened with increased cocaine consumption (7, 30). The present data and the previous analyses from this sample are also in accordance with our recent results from an independent

longitudinal investigation showing that decreased cortical thickness (CT) of several regions within the prefrontal cortex of cocaine users can improve after a strong reduction of cocaine use, while sustained use went along with a further decrease in prefrontal CT during the study interval (63). Importantly, the cortical changes were correlated with cognitive changes, i.e., improved CT as associated with enhanced sustained attention (63). Thus, the overall pattern of change shown by longitudinal data supports our assumption that sociocognitive impairments of cocaine users are at least in part drug-induced and that neuroplastic changes in brain regions and neurotransmitter systems involved in social cognition, social interaction, and social reward processing contribute to a further decrease in social contact and social support leading to an increase in social isolation, aggression, and depressive symptoms. This ends in a further reduction of social reward resources, ongoing social withdrawal, and the establishment of cocaine as the main source of reward resulting in the maintenance of stimulant use and recurrent relapses (15).

While EE is more a perceptive social cognition ability, social decision-making (here assessed with a combined Distribution/Dictator Game) is a form of socially interactive behavior. In our previous cross-sectional analysis sample, cocaine users cared more about efficiency than about fairness compared to healthy controls at baseline (17). This was previously interpreted as predisposition of stimulant use (15), as such fairness preferences and severity of cocaine use were not correlated (17). Intriguingly, utilitarian and opportunistic attitudes assessed with the Machiavellianism Questionnaire (MACH-IV) were also increased in cocaine users compared to controls and were shown to be stable and independent of changing cocaine use (14). However, our data indicated a shift toward improved prosocial behavior in cocaine *decreasers* indicating space for enhancement potential by treatment. Conclusively, SDM deficits in cocaine users likely have both a trait and a state component, and it might be worse to specifically target the state component in therapy in order to improve the treatment outcome.

Limitations

When interpreting the present results, some limitations of our study have to be considered: i) The total sample size is moderate for a longitudinal analysis. Moreover, the test–retest reliabilities of the applied social cognition tasks and questionnaire have a broad range (in controls: $r = 0.48\text{--}0.75$; in cocaine users: $r = 0.60\text{--}0.85$; in the total sample: $r = 0.63\text{--}0.80$). As a consequence of both, the shown interaction effects are not very strong (in terms of p-values). However, to our knowledge, these are the only existing longitudinal samples of chronic cocaine users with objectively verified increasing and decreasing cocaine use (by hair testing). Moreover, the included individuals were preferably pure cocaine users with little axis-I psychiatric comorbidities. We therefore think that the carefully selected and homogeneous sample has nonetheless sufficient explanatory power. ii) In the context of our hypotheses, we attribute the changes in behavior to the changes in cocaine consumption. However, we cannot rule out if other changes in the lives of

our cocaine users (e.g., positive or negative changes in their social environment) not assessed by our test battery may have impacted both drug use and social functioning. Future studies should therefore assess more information on the social life of cocaine users beyond simple parameters such as social network size (e.g., social media use).

Conclusions

The aim of this longitudinal study was to investigate whether cocaine use is associated with permanent or reversible alterations of social cognition and interaction as well as cluster B PD symptoms. We found that specific social dysfunctions and PD symptoms are variable over time as they seem to depend on variations in cocaine use. Thus, strong reduction of cocaine use within only 1 year seems to positively affect social dysfunctions that are assumed to be crucial factor in the maintenance of stimulant addiction (15, 64). From our perspective, the shown positive effects of reduced cocaine use clearly favor abstinence-orientated treatment approaches of cocaine addiction. Furthermore, having the strong impact of social cognitive abilities as well as prosocial behavior and attitudes on the patient–therapist relationships in mind (15), future developments in the psychotherapy of cocaine addictions should consider trainings specifically of social skills and cognitions in order to improve treatment outcome.

ETHICS STATEMENT

The study was approved by the Cantonal Ethics Committee of Zurich, Switzerland.

AUTHOR CONTRIBUTIONS

BQ and MV had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CE and BQ contributed to the

study concept and design. CE, MV, OB, KP, LH, MB, and BQ contributed to the acquisition, analysis, or interpretation of data. OB, CE, MV, and BQ contributed to the drafting of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. MV and BQ conducted the statistical analysis. ES and BQ obtained funding. KP, LH, MV, and ES contributed to the administrative, technical, or material support. ES and BQ were in charge of supervision.

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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.2019.00213/full#supplementary-material>.

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