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Impaired emotional empathy and related social network deficits in cocaine users

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Abstract

Chronic cocaine users consistently display neurochemical and functional alterations in brain areas involved in social cognition (e.g., medial and orbitofrontal cortex). Although social functioning plays a crucial role in the development and treatment of drug dependence, studies investigating social cognition in cocaine users are lacking. Therefore, we investigated mental perspective-taking (*"Theory-of-Mind"*) and emotional and cognitive empathy in recreational (RCU) and dependent (DCU) cocaine users. Furthermore, we related these measures to real-life indicators of social functioning. One-hundred cocaine users (69 RCU, 31 DCU), and 68 stimulant-naïve healthy controls were tested with the Multifaceted Empathy Test (MET), Movie for the Assessment of Social Cognition (MASC), and Reading the Mind in the Eyes Test (RMET). The Social Network Questionnaire (SNQ) was conducted to assess social network size. Furthermore, participants provided information on committed criminal offences. RCU and DCU showed less emotional empathy compared to controls (MET), whereas cognitive empathy was not impaired (MET, RMET). Additionally, DCU made more errors in mental perspective-taking (MASC). Notably, cocaine users committed more criminal offences and displayed a smaller social network and higher cocaine use was correlated with less social contacts. Diminished mental perspective-taking was tentatively correlated with more intense cocaine use as well. Finally, younger age-of-onset of cocaine use was associated with more pronounced empathy impairment. In conclusion, social cognition impairments in cocaine users were related to real-life social functioning and should therefore be considered in therapy and prevention strategies.

Keywords: Cocaine, empathy, mentalizing, theory-of-mind, criminal behavior, social network

Introduction

Owing to the high addictive potential and the negative health consequences the use of cocaine is a major public health issue (Degenhardt and Hall, 2012; UNODC, 2011). Cocaine is the second most prevalent illegal drug after cannabis in the United States and Europe (EMCDDA, 2012; HHS, 2011). The current lifetime prevalence for cocaine use in young adults is estimated at 6.3% in Europe (15-34 years) and 13.3% in the United States (18-25 years)(EMCDDA, 2012; SAMHSA, 2011). While most studies on the cognitive and behavioral consequences of cocaine use focus on dependent cocaine users (DCU), a substantial number of cocaine users show a recreational, non-dependent use pattern (EMCDDA, 2012). However, little is known about the neurobehavioral effects of recreational cocaine use, although recent studies suggest neurochemical alterations already in recreational cocaine users (RCU)(Hulka et al., 2013; Preller et al., 2013).

Social cognition is an important factor in the development, progress, and treatment of psychiatric disorders, as it was demonstrated for schizophrenia patients (Couture et al., 2006). Analogously, it was proposed that social cognition may play a crucial role in the origin and course of dependence as well as treatment success in stimulant abusers (Homer et al., 2008; Volkow et al., 2011). Deficits in social cognition may increase social isolation, aggression, and depression, which might lead to a vicious circle of drug use (Homer et al., 2008). It has been suggested that addiction impacts brain circuits enabling social functioning by reducing the sensitivity to social reinforcers and enhancing the value of the drug of abuse. Additionally, impaired social cognition may contribute to the decay of social relationships in addicted patients (Volkow et al., 2011), which might have consequences for treatment success, as higher social support is associated with longer abstinence durations (Mutschler et al., 2012).

Surprisingly, studies investigating social cognition in stimulant users are lacking, even though evidence accumulated that chronic cocaine users display neurochemical and functional alterations in brain areas critically involved in several facets of social cognition (Volkow et al., 2011). In particular, marked structural and functional alterations have been reported in the medioprefrontal cortex (MPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC), temporal cortices including insula and the temporal pole (TP), and striatal regions in DCU (Albein-Urios et al., 2013; Bolla et al., 2004; Ersche et al., 2011; Franklin et al., 2002; Kuhar and Pilotte, 1996; Makris et al., 2008; Volkow et al., 1992). These areas have been associated with social reward (Krach et al., 2010), emotional empathy (Abu-Akel and Shamay-Tsoory, 2011; Fan et al., 2012), cognitive empathy, and *theory-of-mind* (ToM)(Blair, 2005; Fan et al., 2012; Gallagher and Frith, 2003; Vollm et al., 2006). Difficulties in understanding, management, and regulation of emotions (Fox et al., 2007; 2011; Kemmis et al., 2007), changes in social decision-making (Hulka et al., in press), and altered frontolimbic responsivity to moral dilemmas (Verdejo-Garcia et al., in press) have indeed been reported in DCU, but social cognitive abilities such as ToM and empathy have not been investigated in cocaine users so far. As effective pharmacological treatments for cocaine addiction are missing (O'Brien, 2005), and social cognition and interaction might be relevant for treatment outcome in addiction, a characterization of social cognition abilities in cocaine users is crucial for the development of more effective prevention and psychotherapeutic treatment strategies.

Therefore, the present study investigates empathy and mentalizing together with real-life social network characteristics in large groups of RCU and DCU, and stimulant-naïve control subjects. Participants completed three tasks to capture different facets of empathy and ToM: the *Multifaceted Empathy Test* (MET)(Dziobek et al., 2008), the *Movie for the Assessment of Social Cognition* (MASC)(Dziobek et al., 2006), and the *Reading the Mind in the Eyes Test* (RMET)(Baron-Cohen et al., 2001). These tasks rely on more ecologically valid stimuli compared to questionnaires or text-based material to meet the demands of everyday social life. The MET is based on the multidimensional model of empathy suggesting two facets of empathy: cognitive and emotional (Blair, 2005; Davis, 1983). The cognitive aspect relates to inferring emotions, the ability to take another persons' perspective, and the understanding of another person's mental state, without necessarily being in an affective state (Baron-Cohen and Wheelwright, 2004; Walter, 2012). Cognitive empathy therefore overlaps with the constructs *affective ToM* and *mentalizing* (Frith and Frith, 2003; Walter, 2012). The emotional aspect of empathy describes a person's emotional response to another person's emotional state, i.e., the ability to feel what another person feels (Mehrabian and Epstein, 1972). The MASC was developed as a video-based test of social cognition approximating everyday life demands to further differentiate aspects of cognitive empathy and mentalizing (Dziobek et al., 2006). Finally, the RMET is an established test of attribution and decoding of mental states from the eye region of faces only (Baron-Cohen et al., 2001).

As most previous studies regarding cognitive alterations focused on dependent cocaine use, little is known about the substantial number of cocaine users showing a recreational use pattern. Changes in attention, memory, color vision, decision making, and sensorimotor gating have been reported in RCU (Hulka et al., in press; Hulka et al., 2013; Preller et al., 2013; Soar et al., 2012; Vonmoos et al., in press), but socio-cognitive abilities have not been investigated yet. Notably, examining recreational users holds some further important advantages: RCU are i) not/not yet addicted, ii) less burdened by psychiatric comorbidities (Smith et al., 2009), iii) less likely medicated with psychotropic drugs, and iv) display a reduced amount of polytoxic drug use. This is essential given that polytoxic drug abuse and psychiatric comorbidities are major confounding factors in addiction research especially with DCU (Degenhardt and Hall, 2012; Prinzleve et al., 2004). Therefore, the application of comprehensive psychiatric diagnostics and the validation of self-reported drug use by hair toxicologies in the present study results in a well-described sample of cocaine users with relatively sparse co-substance use and little psychiatric comorbidities. Consequently, the present study investigates different facets of social cognition in relatively pure recreational and dependent cocaine users compared to an age-, sex-, and IQ-matched group of healthy and psychostimulant-naïve controls. Considering previous imaging findings of altered MPFC, ACC, and striatal function in cocaine users, we expect to find impairments in social cognition in cocaine users presumably linked to real-life social dysfunction such as a smaller social network.

Methods and Materials

Participants

Thirty-one DCU, 69 RCU, and 68 stimulant-naïve control participants were included in the study (for recruitment details see **Supplementary Material Methods 1)**. Cocaine dependence was diagnosed following the Diagnostic and Statistical Manual-IV (DSM-IV) criteria (American Psychiatric Association, 1994), with only DCU fulfilling these criteria. Further inclusion criteria for the two user groups were cocaine use of at least 1g per month, cocaine as primary used illegal drug, and a current abstinence duration <6 months. Exclusion criteria for the user groups were use of opioids, polytoxic drug use, and an Axis-I DSM-IV adult psychiatric disorder with exception of cocaine, nicotine, and alcohol abuse/dependence, history of depression (acute major depression was excluded), and ADHD due to their high prevalence in cocaine users. Control subjects were excluded when they displayed any Axis-I DSM-IV psychiatric disorder including ADHD and any form of addiction (except nicotine), and regular illegal drug use (lifetime use <15 occasions) with exception of cannabis. Exclusion criteria for all participants were any neurological disorder or head injury, clinically significant medical diseases, family history of schizophrenia or bipolar disorder, or prescription of drugs affecting the CNS. All participants were asked to abstain from illegal substances for a minimum of three days and from alcohol for at least 24 hours. Self-reports were controlled by urine toxicology and 6-month hair analysis (for details **see Supplementary Material Methods 1 and 2)**. The study was approved by the Cantonal Ethics Committee of Zurich (KEK). All participants provided written informed-consent in accordance with the declaration of Helsinki and were compensated for their participation.

Procedure

The present data were collected as part of a larger study on cognitive consequences of cocaine use – the Zurich Cocaine Cognition Study (ZuCo^{2}St)(Hulka et al., in press; Preller et al., 2013; Vonmoos et al., in press). A Structured Clinical Interview for Axis-I DSM-IV Disorders (SCID-I) was carried out by trained psychologists. Furthermore, participants completed the DSM-IV self-rating questionnaire for Axis-II personality disorders (SCID-II). Participants were asked about number and type of committed criminal offences. Drug use was assessed by means of the Interview for Psychotropic Drug

Consumption (IPDC)(Quednow *et al.*, 2004). The brief version of the Cocaine Craving Questionnaire (CCQ)(Tiffany *et al.*, 1993) was applied to capture current cocaine craving. Smoking habits were assessed with the Fagerström Test of Nicotine Dependence (FTND)(Heatherton *et al.*, 1991). The Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B)(Lehrl, 1999), a standardized German vocabulary test, was carried out for estimation of premorbid verbal IQ. The Beck Depression Inventory (BDI)(Beck *et al.*, 1961) was used to assess current depression symptoms, and the ADHD self-rating scale (ADHD-SR)(Rosler *et al.*, 2004) was applied to allow for the diagnosis of ADHD in adulthood according to DSM-IV criteria. Together with a classical neuropsychological test battery and a psychophysiological measurement (as published elsewhere)(Preller et al., 2013) the participants completed the tasks described below. Further task details are described in the **Supplementary Material Methods 3**.

Tests of social cognition

MET: The MET is a reliable PC-assisted test comprising 40 photographs of people in emotionally charged situations (Dziobek *et al.*, 2008). The stimuli depict everyday life situations conveying information on emotional mental states via facial expression, body language, and context. To measure cognitive empathy (CE) subjects are asked to infer the mental state of the person in the photograph and choose which of four words provided along with the picture describes best what the person in the picture is feeling. Explicit emotional empathy (EEE) is assessed by ratings of empathic concern (“How concerned are you for this person?”) on a visual-analogue scale within a range of 1-9 (1=not concerned to 9=very concerned) while viewing the photograph. Implicit emotional empathy (IEE) is measured analogously by arousal ratings (“How calm/aroused does this picture make you feel?”, 1=very calm to 9=very aroused). MET and MASC are implemented in Presentation (Version 14.1, Neurobehavioral Systems, Albany, CA).

MASC: The MASC was developed as ecologically valid and video-based multimodal (visual and auditory input) test of social cognition (Dziobek *et al.*, 2006). Participants are asked to watch a 15-min movie and make inferences about the video characters’ mental states requiring the understanding of emotions, thoughts, and intentions, and concepts such as false belief, faux pas, metaphor, and sarcasm in an everyday-life situation (a dinner with friends). It is paused at 45 times when questions about the actors' feelings, thoughts, and intentions are asked ("How is Michael feeling?"). These questions are asked in a multiple-choice format with one correct answer and three distractors reflecting three different types of mistakes: i) insufficient mental state inferences (undermentalizing: reduced ToM), ii) excessive (overmentalizing), and iii) non-mental state inferences (physical causation, no-ToM). Therefore, the MASC provides a sum score for the errors and three subscales for different error types. To control for non-social inference, memory, and general comprehension effects, six control questions referring to physical events instead of a character's mental state are asked during the test.

RMET: The RMET involves inferring the mental state of a person from a photograph which depicts the eye region only (Baron-Cohen *et al.*, 2001). The RMET comprises 36 photographs, for which the participants are asked to choose one out of four mental state descriptors (e.g., jealous, panicked) which describes the person's feelings or thoughts best. The descriptors are varied for each item. A sum score is computed by adding up the number of correctly identified items.

SNQ: The SNQ is based on the social contact circle interview and was designed to evaluate the size of an individual's social network as well as the experienced emotional support and strain by this network (Linden *et al.*, 2007). Participants are required to write down the names of personal contacts in the areas 'household', 'family', 'work or apprenticeship', 'friends', 'neighbors', and 'others'. Only individuals with whom they were in direct contact (via personal encounters, phone calls, emails, or letters) during the previous four weeks should be included. Double entries of contacts are not allowed enabling the calculation of the total social network size. Furthermore, participants are requested to indicate how strongly they feel emotionally supported (e.g., solace and encouragement) by their social contacts on a 5-point scale (1=not at all; 5=very much). Analogously, they specify the emotional strain (e.g., feeling of being rejected) they experience by their social contacts.

Statistical analysis

Frequency data were analyzed by means of Pearson's Chi-square test and quantitative data by analyses of covariance (ANCOVA) or multivariate analyses of covariance (MANCOVA) where appropriate using PASW 18.0 (IBM, Switzerland). In all (M)ANCOVAs, group was introduced as fixed factor. As groups differed in age and years of education (YoE), these variables were introduced as covariates in the analyses. Pearson's product-moment correlations were calculated to relate drug use parameters to social cognition measures. Cumulated cocaine lifetime use was ln-transformed for statistical analyses because of the highly skewed distribution and the resulting deviation from the normal distribution (Shapiro-Wilk $W<.001$ for both user groups). For correlations between illegal drug use and social cognition measures control subjects were excluded to prevent inflating existing correlations. The confirmatory statistical comparisons of all data were carried out on a significance level set at $p<.05$ (two-tailed).

Results

Demographic characteristics

The groups did not differ with respect to IQ, sex distribution, and smoking status but DCU were older than controls and RCU **(Table 1)**. DCU had fewer YoE than controls and RCU. As expected, both user groups scored higher than controls on the BDI and ADHD-SR sum scores as well as on the antisocial personality disorder (PD), and the narcissistic PD scale of the SCID II. Nicotine use (FTND sum score) was higher in DCU than in RCU and controls. Furthermore, RCU and DCU reported more criminal offences than controls.

The hair samples revealed a clear domination of cocaine compared to other illegal drugs as strived for by the inclusion criteria **(Table 2)**. DCU showed a more than 8-fold higher concentration of cocaine and metabolites in the hair samples compared to recreational users. A considerable amount of participants were tested positive in urine toxicologies. However, we decided not to exclude them but to investigate the acute and post-acute effects of the drugs.

Multifaceted Empathy Test (MET)

A MANCOVA (with age and YoE as covariates) performed for the dependent variables CE, EEE, and IEE revealed a significant main effect for group ($F(6,324)=2.63$, $p<0.02$). Groups differed on the EEE ($F(2,163)=7.94$, $p<0.01$) and IEE scales ($F(2,163)=5.40$, $p<0.01$)(**Figure 1A**), while no difference was found for CE ($F(2,163)=0.98$, $p=0.38$)(**Figure 1B**). Sidak-corrected pairwise comparisons revealed a significant difference between controls and RCU ($p<0.02$, $d=0.45$) between controls and DCU ($p<0.05$, $d=0.49$) in EEE. Similarly, in IEE a significant difference was found between controls and DCU ($p<0.01$, $d=0.64$), and controls and RCU ($p<0.05$, $d=0.39$).

As expected, the scores on the antisocial and narcissistic PD scales were significantly correlated with EEE and IEE (**Table 3**), but introducing antisocial or narcissistic PD as a covariate did not change the main results. Craving did not influence the results as cocaine users with high craving, low craving, and controls did not reveal a significant main effect for group (**Supplementary Material Figure 1**). Furthermore, controls showed more empathy than both, cocaine users with and without ADHD ($p<0.04$, $d=0.40$-0.68)(**Supplementary Material Figure 2**), and cocaine users with high and low BDI scores ($p<0.05$, d=0.39-0.62)(**Supplementary Material Figure 3**) on the EEE and IEE scale, indicating that even cocaine users with low ADHD and depression symptoms display deficits in emotional empathy.

The impact of the age of cocaine use onset (AoO) was investigated by a MANCOVA (additionally corrected for cumulated cocaine use), with cocaine users split according to their AoO (AoO≤18: n=27, AoO>18, n=73) compared to controls (n=68). This revealed a main effect for group ($F(6,322)=3.18$, $p<0.01$) with groups differing in EEE ($F(2,162)=10.41$, $p<0.01$) and IEE ($F(2,162)=15.53$, $p<0.001$). Controls differed from cocaine users with early AoO on the EEE and IEE scale (all $p<0.01$, d=0.90). On the IEE scale, cocaine users with early AoO differed from cocaine users with AoO>18 ($p<0.01$, d=0.63), whereas cocaine users with AoO>18 did not differ from controls on both scales (all $p>0.21$)(**Figure 2**). No group differences were found for CE ($F(2,162)=0.36$, $p>0.70$). Moreover, cocaine users with positive urine samples did not differ from users with negative samples ($p>0.69$, d=0.01-0.29) on either MET scale. Finally, cocaine users with MDMA co-use (n=33) did not differ from users without MDMA co-use (n=67) in the global MANCOVA $F(3,96)=1.24$, $p>0.30$).

Reading the Mind in the Eyes Test (RMET)

An ANCOVA (with age and YoE as covariates) did not reveal any significant differences between groups regarding the RMET sum score ($F(2,163)=0.55$, $p>0.58$; mean [SD] for controls: 25.47 [3.82]; RCU: 25.09 [3.43], DCU: 24.16 [3.85]).

Movie for the Assessment of Social Cognition (MASC)

An ANCOVA (corrected for age and YoE) of the MASC total errors yielded a main effect for group ($F(2,164)=3.41$, $p<0.05$). Sidak-corrected pairwise comparisons revealed a significant difference between DCU and controls ($p<0.05$, $d=0.55$), while RCU did not differ from DCU ($p=0.17$, $d=0.46$) and controls ($p=0.97$, $d=0.09$)(**Fig. 3A)**. A MANCOVA with different types of error as dependent variable revealed a significant main effect for group ($F(6,324)=2.41$, $p<0.03$), with groups differing on the excessive ToM scale ($F(2,163)=4.62$, $p<0.01$). Sidak-corrected pairwise comparisons showed that DCU made more errors with regard to excessive ToM than RCU ($p<0.02$, $d=0.61$) and controls (*p*<0.02, *d*=0.58). RCU did not differ from controls (*p*=0.99, *d*=0.03)(**Fig. 3B**). Groups did not differ with regard to performance in the control items (F(2,163)=1.85, p=0.16) and introducing control items as a covariate in the analysis did not reveal different results. Introducing narcissistic and antisocial PD as a covariate did not change group differences for MASC total errors.

ANCOVAs testing the influence of recent cocaine use, craving, depressive symptoms, and AoO did not reveal significant group differences (all p>0.09), suggesting that these variables did not critically influence the results. However, cocaine users with ADHD performed significantly worse than controls (p<0.01, d=0.72) and cocaine users without ADHD (p<0.02, d=0.63). Cocaine users without ADHD did not differ from controls (p>0.92, d=0.09)(**Supplementary Material Figure 4)**. Nevertheless, introducing ADHD-SR sum score as an additional covariate did not change the main group effect.

Social Network Questionnaire (SNQ)

Social network data were available for 65 controls, 62 RCU and 27 DCU. Differences between groups for the social network size were analyzed with an ANCOVA (corrected for age and YoE), resulting in a significant main effect for group (F(2,149)=6.34, *p*<0.01). Both, RCU (*p*<0.01, d=0.52) and DCU (*p*<0.01, d=0.70) reported a smaller social network than controls (**Fig. 4A**). A MANCOVA with group and scale (emotional support/strain) as fixed factors revealed a significant main effect for scale (F(1,139)=9.48, *p*<0.01) and a significant group*scale interaction (F(2,139)=4.04, *p*<0.02)(**Fig. 4B**), suggesting that especially DCU experienced less emotional support and more emotional strain than controls.

An ANCOVA (additionally corrected for cumulated cocaine use) with cocaine users split according to their AoO compared to controls (n=65) revealed a significant main effect for group (F(2,149)=5.39, p<0.01): controls differed significantly from cocaine users with AoO≤18 (*p*<0.02, d=0.66) and cocaine users with AoO>18 (*p*<0.03, d=0.44)(**Supplementary Material Figure 5).**

Correlation analyses

Social network size was weakly correlated with test outcomes on the MET, MASC, and RMET, indicating that impaired social cognition goes along with worse real-life social functioning. Moreover, amount of criminal offences was slightly associated with the MET IEE score, which might reflect a negative relationship between emotional empathy and adherence to social norms. As expected, the scores on the antisocial and narcissistic PD scales were correlated with emotional empathy. Interestingly, MET emotional empathy scores and MASC were largely independent from each other, while MET cognitive empathy and MASC were interrelated and both associated with RMET performance (**Table 3**), indicating that they all share a common cognitive component (e.g., emotion recognition), whereas these more cognitive scores and the emotional empathy measures are largely distinct functions.

Furthermore, the MASC total errors were tentatively associated with cumulative cocaine use (ln-transformed), duration of cocaine use, and cocaine/norcocaine in the hair toxicology, Finally, social network size was negatively correlated with duration and amount of cocaine use (**Table 4**).

Discussion

The present study demonstrates that recreational and dependent use of cocaine is associated with impairments in specific empathy and mentalizing abilities, which interfere with real-life social functioning. Comprehensive psychiatric diagnostics and hair toxicology allowed the analysis of as pure as possible cocaine users with little psychiatric comorbidities. Compared to stimulant-naïve control persons, these cocaine users showed less emotional empathy, whereas cognitive empathy and emotion recognition was not altered. Only dependent users additionally displayed impaired mentalizing functions in the MASC that were correlated with higher cocaine intake. Moreover, both cocaine user groups reported a smaller social network than controls and this real-life indicator of social functioning was correlated amount and duration of cocaine use and tentatively associated also with several social cognition measures. In addition, also the number of committed criminal offences was slightly correlated with emotional empathy. Taken together, this is, to our knowledge, the first study demonstrating relevant emotional empathy and mentalizing impairment in cocaine users affecting real-life social behavior.

The emotional empathy deficits shown here are in line with previous studies reporting difficulties in the emotion regulation subscale of the Mayer-Salovey-Caruso-Emotional-Intelligence-Test in DCU (Fox et al., 2007; 2011). Importantly, decreased emotional empathy but intact cognitive empathy was previously reported also in patients with narcissistic PD (Ritter et al., 2011), whereas patients with autism displayed the reversed pattern (Dziobek et al., 2008; Gleichgerrcht et al., 2012). However, narcissistic symptoms, often comorbid with cocaine use as also shown here, cannot alone explain the emotional empathy deficits, as statistical control for these symptoms did not change the results. Additionally, narcissistic symptoms were not very pronounced in our sample in comparison to earlier studies, probably due to the strict exclusion criteria regarding psychiatric comorbidities (Ritter et al., 2011). Finally, our finding that cocaine users do not differ from controls in their performance on the RMET is also in line with Kemmis et al.(2007), who reported no differences on the RMET score between controls, occasional, and regular cocaine users as well.

The MASC is a test to sensitively detect subtle deficits in mentalizing abilities in contrast to other less ecologically valid ToM tests (Dziobek et al., 2006). Here, DCU performed worse than controls, while RCU did not show any disturbance. DCU made more errors with regard to ‘overmentalizing’ (overinterpretive perspective-taking). These results suggest that a subtle deficit in mental perspective-taking may arise from unusual compensation strategies, rather than the loss of cognitive empathy and ToM abilities per se, as they did not make more ‘no-ToM’ or ‘insufficient ToM’ errors in the MASC (Sharp et al., 2011). Thus, dependent cocaine users probably try to take the perspective of others but over-interpret social signs. A previous fMRI study showed that the MASC engages the MPFC (Wolf et al., 2010), an area associated with the integration of social information (Van Overwalle, 2009), amongst other regions related to social cognition. As alterations in this brain region were repeatedly reported for cocaine users (Bolla et al., 2004; Ersche et al., 2011; Volkow et al., 1992), it is likely that subtle deficits in mentalizing are associated with MPFC alterations. Therefore, mainly the integration of social information – which is highly necessary to solve the multimodal MASC – might be challenging for dependent users. Moreover, the pattern of ‘overmentalizing’ together with emotional but not cognitive empathy deficits in cocaine users may suggest a deficit in the ability to process emotional feedback in complex scenarios, supporting theories of reduced sensitivity to social rewards (Volkow et al., 2011). Furthermore, difficulties in mentalizing seem to be associated with duration of cocaine use, cumulated cocaine use, and cocaine and norcocaine in the hair, suggesting that problems in mental perspective-taking might be partially cocaine-induced. On the other hand, mentalizing deficits may also predispose addictive cocaine use in particular as only dependent individuals showed these deficits.

Cognitive and affective aspects of empathy are behaviorally distinguishable and rely on dissociable, but overlapping, brain networks. In functional imaging studies, emotional empathy engages the ventral striatum, the amygdala, the TP, the ACC, the OFC, and the anterior insula (Abu-Akel and Shamay-Tsoory, 2011; Bernhardt and Singer, 2012), whereas cognitive empathy depends on the MPFC and the superior temporal gyrus (Vollm et al., 2006). Addicted cocaine users have been reported to show alterations in the ventral striatum, as well as the MPFC, ACC, the TP, and OFC (Albein-Urios et al., 2013; Bolla et al., 2004; Ersche et al., 2011; Kuhar and Pilotte, 1996; Makris et al., 2008; Volkow et al., 1992), and these alterations might be associated with our current finding of impaired empathy. As emotional empathy is already impaired in recreational users, changes in the relevant brain regions (e.g., ventral striatum, OFC, insula, TP), might be more strongly related to cocaine use than changes in areas associated with cognitive ToM (e.g., MPFC). As these regions are also involved in social reward processing (Katsyri et al., 2012) this would support the hypothesis that neuroadaptations in brain reward systems make drug users more responsive to the abused drug and also reduce sensitivity to non-drug reinforcers such as social interaction (Volkow et al., 2011). This might have a negative impact on general social competence and might explain why social consequences such as imprisonment or familial problems may fail to detain drug addicted people from using the drug (Volkow et al., 2011).

Most importantly, our data suggest a relationship between test outcomes and real-life social functioning: Participants showing more empathy and better mentalizing abilities had a larger social network. In addition, social network size was correlated with duration and amount of cocaine use. This implies that cocaine use and the associated deficits in empathy and mentalizing may have consequences in real life, such as fewer social contacts and less emotional support. Alternatively, a smaller social network might reduce opportunities to adequately learn and practice social abilities, leading to impairments in social cognition and an increase in cocaine use. However, longitudinal studies are needed to disclose causality. Additionally, DCU committed more criminal offences than controls and the number of criminal offences was weakly correlated with empathy measures. These relationships are especially important, as real-life social behavior and social environment are important factors in onset and therapy of drug use (Ramirez et al., 2012; Shortt et al., 2007). Therefore, therapeutic and prevention approaches focusing on the improvement of social skills and involving the social environment should be intensified to improve the impact of treatment strategies against cocaine addiction.

Furthermore, the age in which cocaine use starts seems to influence emotional empathy and the number of social contacts, with users who began using cocaine before the age 18 showing less empathy than controls. Since we corrected the analyses for cumulated cocaine use, this finding is unlikely to be influenced by longer cocaine use in the early onset group. It is also in line with previous studies, reporting an association between earlier onset of cocaine dependence and elevated motor impulsivity and therefore identifying an early onset of use as particularly dangerous (Prisciandaro et al., 2012). Early onset of drug use may be particularly harmful, because structural, neurochemical, and functional brain development continues during adolescence, which is therefore a period in which the system is highly vulnerable to toxic influences (Crone and Dahl, 2012; Jager and Ramsey, 2008). Moreover, puberty is also a critical time period, when complex social-cognitive skills such as mentalizing evolve and social-affective skills such as empathy advance (Crone and Dahl, 2012). Alternatively, social impairments may have preceded drug use and possibly represent a vulnerability to start using drugs. Furthermore, due to their illegal drug use, cocaine users may experience less social support and possibilities to acquire and train social abilities.

One limitation of our study is the lack of an objective measure of the duration of abstinence beyond urine toxicology. Thus, we were unable to investigate the true effect of abstinence duration on empathy and ToM. However, it would have been nearly impossible to control for abstinence in our ambulant and voluntary study setting.

In sum, our study provides first evidence that dependent and already also recreational cocaine users show deficits in emotional empathy, whereas only dependent users additionally show subtle impairments in cognitive empathy and mentalizing. These results suggest that cocaine users are less emotionally responsive to other people's emotional state and less able to mirror emotions compared to healthy controls. Empathy is crucial to our emotional and social lives (Bernhardt and Singer, 2012) and therefore, these deficits could account for antisocial behavior, especially as social cognition impairments are related to real-life social behavior such as a smaller social network and more criminal offences. The characterization of social cognition abilities in cocaine users is crucial for the development of effective prevention and treatment strategies, as social cognition predicts treatment success in psychiatric disorders (Couture et al., 2006; Homer et al., 2008). Furthermore, it should be considered that treatment approaches requiring strong emotional empathy (e.g. classic treatment modalities like community reinforcement approaches) may not be particularly effective in stimulant users. Thus, treatment success might benefit from trainings designed to improve social cognition and empathy, resembling those designed for schizophrenia patients (Lahera et al., 2012; Rus-Calafell et al., 2012) before classic treatment approaches are conducted. Finally, prevention strategies should be intensified towards delaying the onset of cocaine use, as a young age of onset is associated with greater deficits in empathy and real-life social behavior.

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Author contributions

KHP gathered and analyzed the data, and wrote the first draft of the manuscript. BBQ designed the study, revised and edited the manuscript, and bears responsibility for data acquisition and analyses. ID designed two of the tests and revised the first draft of the manuscript. LMH, MV, and DJ contributed to data acquisition and/or revised the first draft of the manuscript. MRB conducted the hair analyses. ES revised the first draft of the manuscript.

Declaration of interest

All authors declare no conflict of interest.

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Table 1 Demographic data (means and standard deviation)

	Control group (n=68)	Recreational cocaine users (n=69)	Dependet cocaine users (n=31)	Value	df/df_{err}	p
Male/female participants (n)	47/21	49/20	24/7	χ2 = 0.73[b]	2	0.70
Age	29.81 (9.13)	28.09 (6.60)	34.81 (10.22)*,°°	F = 6.85[a]	2/165	**<0.01**
Years of education	10.62 (1.67)	10.35 (1.91)	9.47 (1.18)**,°	F = 4.95[a]	2/165	**<0.01**
Verbal IQ	104.87 (9.66)	103.17 (9.28)	101.81 (11.23)	F = 1.15[a]	2/165	0.32
Smoker/nonsmoker (n)	51/17	55/14	24/7	χ2 = 0.43[b]	2	0.81
FTND sum score (0-10)[d]	2.45(2.26)	3.35 (2.22)	4.79 (2.52)**,°	F = 8.58[a]	2/127	**<0.001**
Craving for cocaine (0-70)	-	19.14 (8.64)	20.55 (11.65)	T = 0.67[c]	98	0.50
Antisocial PD (SCID II, 0-15)[e]	2.40 (2.12)	4.39 (3.23)**	4.39 (3.83)**	F = 8.91[a]	2/159	**<0.001**
Narcissistic PD (SCID II, 0-16)[e]	3.06 (2.48)	4.43 (2.56)*	5.11 (3.49)**	F = 7.226[a]	2/159	**<0.001**
ADHD-SR sum score (0-22)	7.56 (5.05)	13.43 (9.65)**	17.00 (8.51)**	F = 17.93[a]	2/165	**<0.001**
BDI sum score (0-63)	3.66 (3.45)	7.83 (6.58)**	11.35 (8.66)**°	F = 19.08[a]	2/165	**<0.001**
Criminal offences[f]						
total	0.54 (0.98)	1.31 (2.07)	1.84 (2.12)**	F = 6.23	2/140	**<0.01**
drug related	0.21 (0.45)	0.65 (1.07)*	1.40 (1.12)**;°°	F = 15.43	2/140	**<0.001**
non-drug related	0.33 (0.89)	0.66 (1.74)	0.44 (1.19)	F = 0.68	2/140	0.51
cocaine related	-	0.24 (0.62)*	0.80 (0.71)**,°°	F = 19.73	2/140	**<0.001**
non-cocaine related	0.54 (0.98)	1.05 (1.93)	1.04 (1.88)	F = 1.86	2/140	0.16
forfeit	0.47 (0.89)	1.13 (1.98)	1.28 (1.54)	F = 3.76	2/140	**0.03**
conviction	0.07 (0.26)	0.18 (0.61)	0.56 (1.23)**,°	F = 5.16	2/140	**<0.01**

Significant p values are shown in bold. Means and standard deviation of means in parenthesis.
FTND, Fagerstrom Test of Nicotine Dependence (in smokers only); PD, Personality Disorder; SCID, Structured Clinical Interview for DSM-IV Disorders; ADHD-SR, ADHD self rating scale; BDI, Beck Depression Inventory
[a]ANOVA (across all groups), [b]χ2 test (across all groups) for frequency data or [c]Independent T-Test (cocaine users only)
[d]FTND measured in smokers only, [e]SCID-II available for 67 controls, 67 RCU, 28 DCU, [f]Criminal offences data available for 57 controls, 62 RCU, 25 DCU
* indicates post-hoc (Sidak) vs control group p<0.05
** indicates post-hoc (Sidak) vs control group p<0.01
° indicates post-hoc (Sidak) vs recreational cocaine users group p<0.05
°° indicates post-hoc (Sidak) vs recreational cocaine users group p<0.01

Table 2 Pattern and amount of drug use: Results of the Psychotropic Drug Interview, urine toxicology, and hair samples

	Control group (n=68)	Recreational cocaine users (n=69)	Dependet cocaine users (n=31)	Value	df/df_{err}	p
Cocaine						
times per week	-	1.10 (1.08)	2.63 (2.46)	T = 4.34[c]	98	**<0.001**
grams/week	-	1.11 (1.43)	6.72 (14.72)	T = 3.15[c]	98	**<0.01**
years of use	-	6.32 (4.06)	9.66 (6.42)	T = 3.16[c]	98	**<0.01**
maximum dose (24h)	-	3.43 (2.45)	9.48 (8.57)	T = 5.42[c]	98	**<0.001**
last consumption (days)	-	27.45 (37.35)	21.62 (35.58)	T = 0.73[c]	98	0.47
cumulative dose (grams)	-	504.32 (751.12)	5325.44 (9505.37)	T = 4.21[c]	98	**<0.001**
urine toxicology (pos/neg)	-	10/58	14/17	χ2 = 10.75[b]	1	**<0.01**
hair sample (pg/mg)						
COC	-	2670.15 (4600.40)	22324.84 (32083.52)	T= 4.97[c]	97	**<0.001**
BEC	-	537.57 (913.16)	4710.65 (7284.00)	T = 4.67[c]	97	**<0.001**
ECO	-	258.71 (298.16)	1918.71 (3583.17)	T = 3.82[c]	97	**<0.001**
NOC	-	61.60 (99.77)	570.16 (733.30)	T = 5.64[c]	97	**<0.001**
MDMA						
pills/week	-	0.08 (0.26)	0.36 (1.79)	T = 1.26[c]	98	0.21
years of use	1.66 (11.15)	2.29 (3.62)	2.92 (5.19)	F = 0.30[a]	2/165	0.74
last consumption (days)	-	111.28 (110.63) (n=22)	81.00 (48.43) (n=8)	T = 0.74[c]	28	0.46
cumulative dose (pills)	0.97 (2.96)	31.91 (86.66)	140.23 (387.41)**;°	F = 6.90[a]	2/165	**<0.01**
hair sample (pg/mg)	1.78 (14.46)	509.68 (1462.43)**	218.55 (633.69)	F = 4.58[a]	2/162	**0.01**
Cannabis						
grams/week	0.56 (1.47)	0.95 (2.08)	1.20 (3.68)	F = 1.00[a]	2/165	0.37
years of use	5.45 (6.82)	7.54 (5.91)	9.78 (10.06)*	F = 4.08[a]	2/165	**0.02**
last consumption (days)	33.10 (46.98) (n=30)	19.81 (30.39) (n=45)	66.55 (218.64) (n=17)	F = 1.38[a]	2/88	0.26
cumulative dose (grams)	821.85 (3433.07)	1001.10 (1742.07)	3259.86 (5957.33)**,°	F = 5.62[a]	2/165	**<0.01**
urine toxicology (pos/neg)	10/58	15/53	10/21	χ2 = 4.04[b]	2	0.13

Table 2 Pattern and amount of drug use: Results of the Psychotropic Drug Interview, urine toxicology, and hair samples (cont.)

	Control group (n=68)	Recreational cocaine users (n=69)	Dependet cocaine users (n=31)	Value	df/df_{err}	p
Amphetamine						
grams/week	-	0.06 (0.11)	0.04 (0.18)	$T = 0.60^c$	98	0.56
years of use	0.01 (0.06)	1.53 (2.97)**	1.49 (3.12)*	$F = 8.85^a$	2/165	**<0.001**
last consumption (days)	-	61.25 (51.84) (n=25)	78.38 (75.42) (n=6)	$T = 0.67^c$	29	0.51
cumulative dose (grams)	0.19 (1.42)	17.02 (44.38)*	21.49 (61.88)*	$F = 4.59^a$	2/165	**0.01**
hair sample (pg/mg)	0.9 (7.39)	84.85 (257.79)*	57.74 (166.85)	$F = 3.69^a$	2/162	0.03
GHB						
cumulative dose (pipettes)	-	1.64 (9.39)	1.24 (2.85)	$T = 0.23^c$	98	0.82
Halluzinogenes						
cumulative dose (times)	1.46 (6.88)	6.45 (14.73)*	6.57 (11.70)	$F = 3.83^a$	2/165	**0.02**
Alcohol						
grams/week	119.11 (126.73)	176.53 (115.95)	192.32 (256.31)	$F = 3.38^a$	2/165	**0.04**
years of use	13.23 (9.39)	10.98 (5.22)	13.92 (9.31)	$F = 2.01^a$	2/165	0.14
Nicotine						
cigarettes per day (CPD)	9.18 (9.92)	12.43 (9.00)	15.70 (13.98)*	$F = 4.43^a$	2/165	**0.01**
years of use	9.05 (9.75)	9.39 (6.38)	13.98 (9.24)*,°	$F = 4.07^a$	2/165	**0.02**

Significant p values are shown in bold. Means and standard deviation of means in parenthesis.
Consumption per week, duration of use, and cumulative dose are averaged within the total group. Last consumption is averaged only for persons who used the drug in the last 6 months. In this case, sample size (n) is shown.
Pg/mg = picogram/milligram. The hair analysis was performed on two hair samples (each 3 cm in length) per participant capturing drug use over the last six months. Concentrations were averaged over the two samples. If the hair sample was not long enough, only one sample was analyzed (3 cm, 3 months). MDMA = 3,4-methylenedioxy-N-methylamphetamine; methylenedioxy-amphetamine, Cut-off value for cocaine = 500 pg/mg, for amphetamines and MDMA = 200 pg/mg
[a]ANOVA (across all groups), [b]$\chi 2$ test (across all groups) for frequency data or [c]Independent T-Test (cocaine users only)
* indicates post-hoc (Sidak) vs control group p<0.05
** indicates post-hoc (Sidak) vs control group p<0.01
° indicates post-hoc (Sidak) vs recreational cocaine users group p<0.05
°° indicates post-hoc (Sidak) vs recreational cocaine users group p<0.01

Table 3 Correlations between test outcomes, real-life measures of social functioning, and clinical measures in 100 cocaine users, 68 controls and (total n=168).

		MET CE	MET EEE	MET IEE	MASC total errors	RMET Sum score	SNQ total network size	BDI sum score	ADHD-SR sum score	Antisocial PD (SCID II)	Narcissistic PD (SCID II)
MET EEE	controls										
	cocaine user										
	total										
MET IEE	controls		**0.91**								
	cocaine user		**0.85**								
	total		**0.89**								
MASC total errors	controls	-0.29									
	cocaine user	**-0.35**									
	total	**-0.32**									
RMET Sum score	controls	0.24			**-0.40**						
	cocaine user	**0.36**			**-0.35**						
	total	**0.30**			**-0.38**						
SNQ total network size	controls										
	cocaine user										
	total		0.18		-0.16	0.16					
BDI sum score	controls										
	cocaine user				0.23						
	total			-0.16	**0.21**		-0.20				
ADHD-SR sum score	controls					0.24		**0.51**			
	cocaine user				**0.28**			**0.53**			
	total		**-0.20**	-0.15	0.18		-0.17	**0.60**			
Antisocial PD (SCID II)	controls			**-0.32**							
	cocaine user		-0.22			-0.24			0.21		
	total		**-0.28**	**-0.29**		**-0.21**			**0.30**		
Narcissistic PD (SCID II)	controls		**-0.31**	-0.28				0.26	**0.44**		
	cocaine user								**0.38**	**0.40**	
	total	-0.19	**-0.24**				-0.17	**0.28**	**0.45**	**0.40**	
Criminal offences total	controls										
	cocaine user									**0.43**	
	total			-0.17					**0.21**	**0.44**	

Correlations with p<0.01 are shown in bold, correlations with p>0.05 are not shown

ADHD-SR, ADHD Self-Rating scale; BDI, Beck Depression Inventory; PD, Personality Disorder; SCID, Structured Clinical Interview for DSM-IV Disorders; SNQ, Social Network Questionnaire, MET, Multifaceted Empathy Test; CE, Cognitive Empathy; EEE, Explicit Emotional Empathy; IEE, Implicit Emotional Empathy; MASC, Movie for the Assessment of Social Cognition; RMET, Reading the Mind in the Eyes Test; CCQ, Cocaine Craving Questionnaire.

Table 4 Correlations between drug use measures and test outcomes in cocaine users

	MASC total errors	RMET Sum score	SNQ total network size	BDI sum score	ADHD-SR sum score	Criminal offences total
Cocaine						
grams/week						
years of use	0.25		**-0.30**			
cumulative dose (grams)	0.24		-0.25	0.25	0.24	
hair sample (pg/mg)						
COC	0.20					
NOC	0.22					
Cannabis						
grams/week						**0.30**
cumulative dose (grams)						0.23
MDMA						
pills/week		-0.23				
cumulative dose (tablets)		**-0.28**				
Alcohol						
grams/week					0.21	
Nicotine						
years of use	0.22		-0.27			
Cocaine craving (CCQ)				**0.32**	0.23	0.20

Correlations are calculated for cocaine users only, correlations with $p<0.01$ are shown in bold, correlations with $p>0.05$ are not shown
Only measures with significant correlations are shown
ADHD-SR, ADHD Self-Rating scale; BDI, Beck Depression Inventory;
SCID, Structured Clinical Interview for DSM-IV Disorders; SNQ, Social Network Questionnaire;
MASC, Movie for the Assessment of Social Cognition;
RMET, Reading the Mind in the Eyes Test; CCQ, Cocaine Craving Questionnaire.

Figure Legends

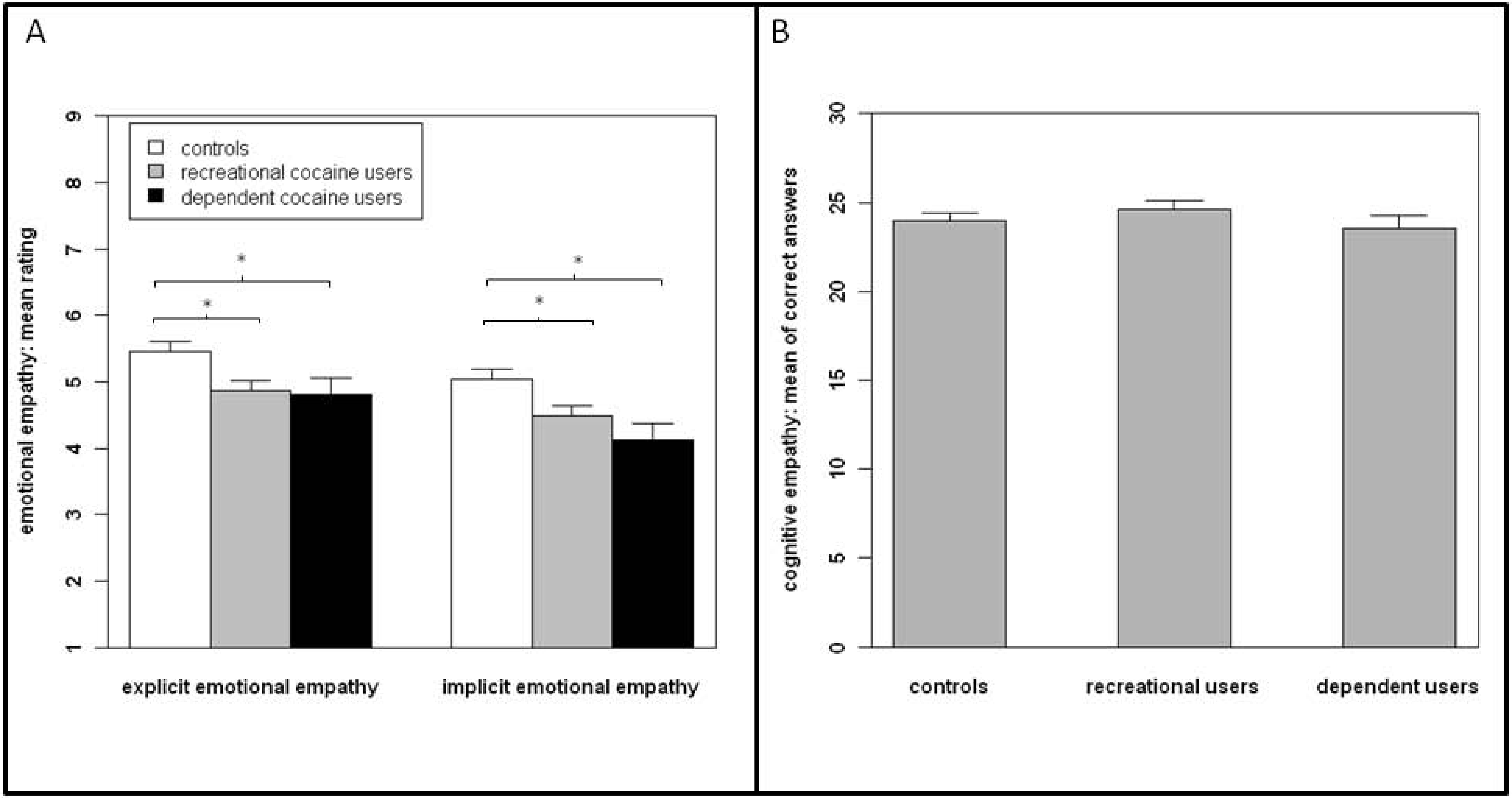
Fig 1 - Mean explicit (EEE) and implicit emotional empathy ratings (A) and mean of correct answers on the cognitive empathy (CE) scale (B) of the multifaceted empathy test (MET) for recreational (n=69) and dependent cocaine users (n=31), and healthy control participants (n=68). Recreational and dependent cocaine users show less IEE and EEE than controls. No differences are found for CE. Error bars refer to SEM. *indicates significant difference between groups ($p<.05$)

Fig 2 - Mean explicit and implicit emotional empathy ratings of the multifaceted empathy test (MET) in cocaine users with an age of onset (AoO) of cocaine use ≤18 (n=27) and >18 (n=73), and controls (n=68). Cocaine users with an AoO≤18 showed less explicit and implicit emotional empathy than controls and less implicit empathy than cocaine user with an AoO >18. Error bars refer to SEM. *indicates significant difference between groups ($p<.05$)

Fig. 3 – Mean total errors (A) and mean of error types (B) for the assessment of social cognition (MASC) for recreational (n=69) and dependent cocaine users (n=31), and healthy control participants (n=68). Dependent cocaine users made more errors in total than controls and more errors regarding overmentalizing (excessive theory-of-mind [ToM]) than controls and recreational cocaine users. Error bars refer to SEM. *indicates significant difference between groups ($p<.05$)

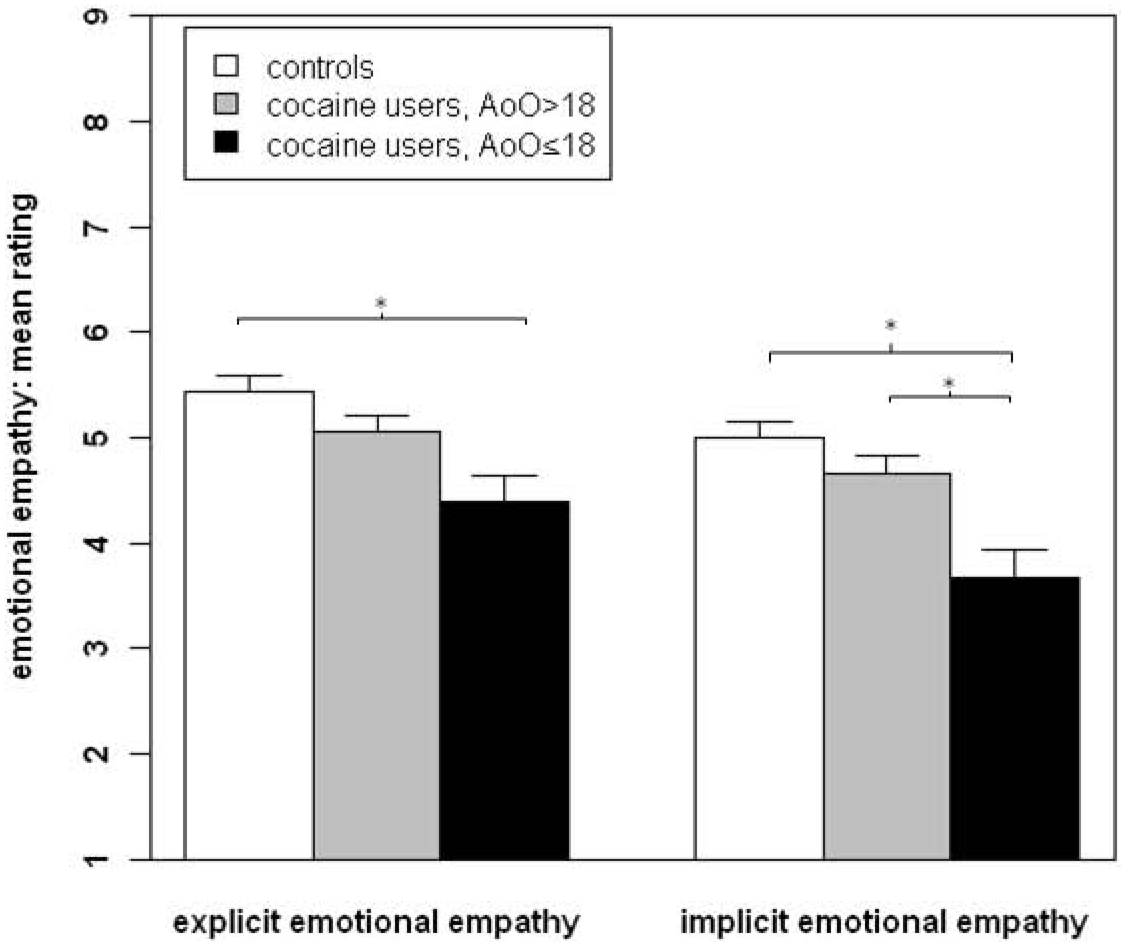
Fig. 4 – Mean of total contacts (A) and mean of emotional support and strain ratings (B) assessed with the social network questionnaire (SNQ) for recreational (n=62) and dependent cocaine users (n=27) and healthy control participants (n=65). Controls reported more total contacts than recreational and dependent cocaine users. Furthermore, a significant interaction ($p<0.05$) was found for group*emotional support/strain. Error bars refer to SEM. *indicates significant difference between groups ($p<.05$); (*) indicates trend towards significance ($p<.08$)

Figure 1



A
B
controls
recreational cocaine users
dependent cocaine users
emotional empathy: mean rating
explicit emotional empathy
implicit emotional empathy
cognitive empathy: mean of correct answers
controls
recreational users
dependent users

Figure 2



controls
cocaine users, AoO>18
cocaine users, AoO≤18
emotional empathy: mean rating
1
2
3
4
5
6
7
8
9
*
*
*
explicit emotional empathy
implicit emotional empathy

Figure 3

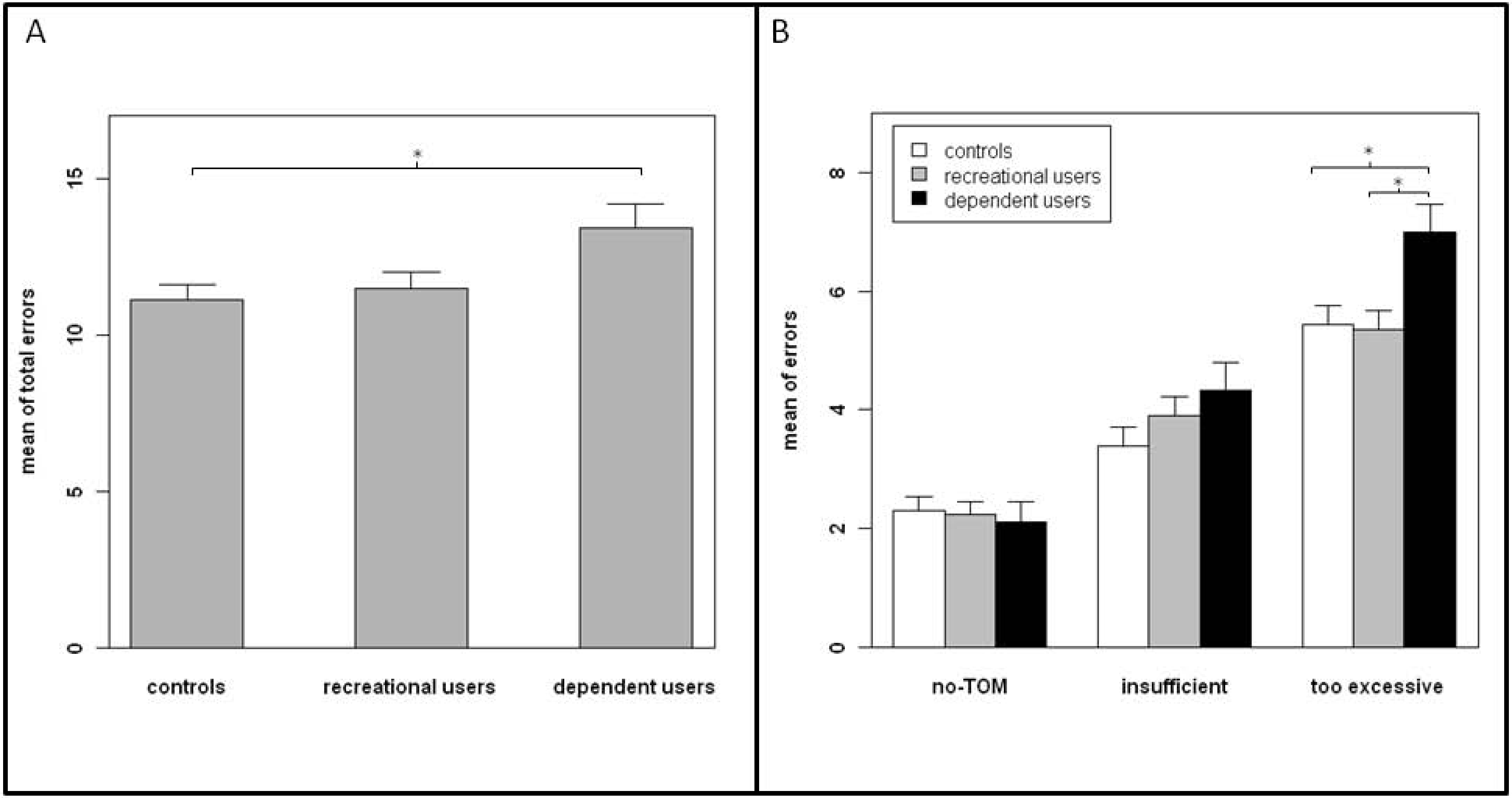
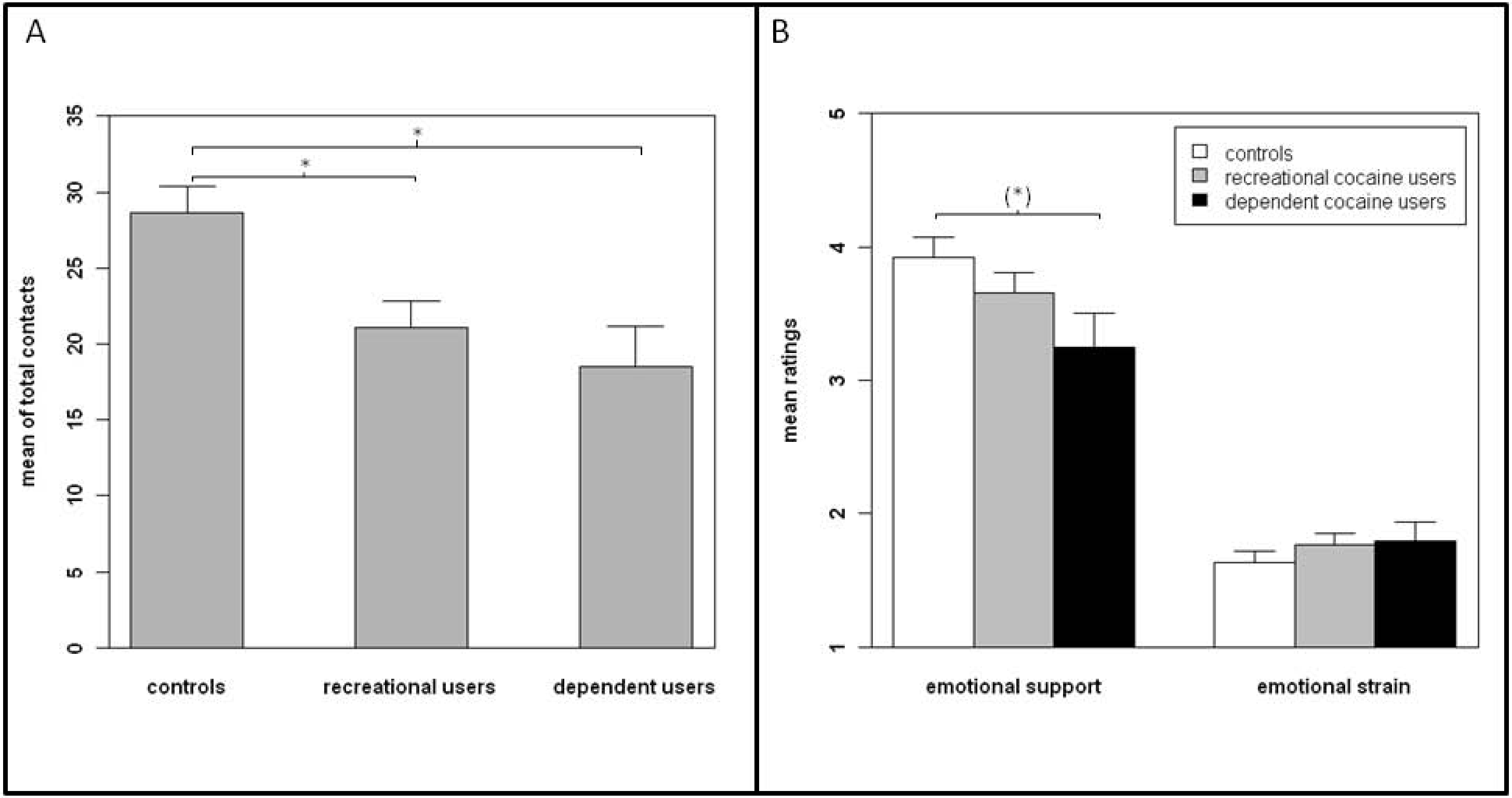

A
B
*
mean of total errors
0
5
10
15
controls
recreational users
dependent users
controls
recreational users
dependent users
*
*
mean of errors
0
2
4
6
8
no-TOM
insufficient
too excessive

Figure 4


A
mean of total contacts
0
5
10
15
20
25
30
35
*
*
controls
recreational users
dependent users
B
mean ratings
1
2
3
4
5
(*)
controls
recreational cocaine users
dependent cocaine users
emotional support
emotional strain

Supplementary Material

Impaired emotional empathy in cocaine users is related to social network deficits

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Methods 1: Recruitment and selection

Subjects were recruited by means of advertisements in local newspapers, drug prevention and treatment centers, psychiatric hospitals, online media, and by word of mouth. Participants were considered eligible for the study if they were aged between 18 and 60 years and had sufficient German language skills. Eight-hundred-four potential participants completed an initial telephone screening, whereof 240 subjects participated in the study. Fourty-six participants had to be excluded afterwards because of hair analyses revealing illegal drug use not declared in the interviews (e.g., opioids, excessive MDMA use) or lack of cocaine use. Further 26 participants were excluded due to matching reasons (age, IQ, education, and smoking) between groups (17 controls, 9 cocaine users). Therefore, 168 datasets were included in the analysis. Hair samples were provided by 165 subjects, as hair analysis was not possible by reason of an insufficient amount of hair for three participants (2 controls, 1 recreational cocaine user). Urine toxicology was not possible for one recreational cocaine user.

Methods 2: Urine and hair toxicologies

Urine toxicology analyses comprised the compounds/substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany).

To characterize drug use over the last six months objectively, hair samples were collected and analyzed with liquid chromatography-tandem mass spectrometry (LC-MS/MS). If participants' hair was long enough, one sample of six cm hair (from the scalp) was taken and subsequently divided into two subsamples of three cm length. The following compounds were assessed: cocaine, benzoylecgonine, ethylcocaine, norcocaine, amphetamine, methamphetamine, MDMA, 3,4-methylenedioxy-N-ethylamphetamine (MDEA), 3,4-methylenedioxyamphetamine (MDA), morphine, codeine, methadone EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; primary methadone metabolite), tramadol, and methylphenidate.

For our routine protocol for drugs of abuse analysis, a three step washing procedure with water (2 minutes shaking, 15 ml), acetone (2 min., 10 ml) and finally hexane (2 min., 10 ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5 ml, 16 hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33% (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5, MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of high-performance LC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1 mM ammonium formate buffer adjusted to pH 3.5 with formic acid (eluent A) and acetonitrile containing 1 mM ammonium formate and 1 mM formic acid (eluent B). The analysis was performed in multiple reaction monitoring mode with two transitions per analyte and one transition for each deuterated internal standard, respectively.

Methods 3: Task details

MET: The task is designed to differentiate two facets of empathy: cognitive (CE) and emotional empathy (EE). EE can be sub-divided in explicit emotional empathy (empathic concern, EEE) and implicit emotional empathy (arousal, IEE), where IEE may be less prone to social desirability. CE, IEE, and EEE are assessed for each photograph in a pseudorandomized order. Correct responses in the CE condition are scored as one point, therefore a sum score for CE is computed, whereas average rating scores are calculated for IEE and EEE. The MET has been shown to detect deficits in CE in patients with autism spectrum disorders (ASD) (Dziobek *et al.*, 2008), and deficits in EE in patients with narcissistic personality disorder (Ritter *et al.*, 2011). Internal consistency of the MET scales ranged from Cronbach's α=0.71 to α=0.92 (Dziobek *et al.*, 2008).

MASC: The MASC has been shown to reliably detect even subtle mindreading difficulties amongst others in healthy individuals of normal IQ (Hassenstab *et al.*, 2007; Smeets *et al.*, 2009), and patients with schizophrenia (Montag *et al.*, 2011), borderline personality disorder (Preissler *et al.*, 2010), and ASD (Dziobek *et al.*, 2006). It has been reported to be more sensitive than other mindreading tests (strange stories task (Happe, 1994), RMET (Baron-Cohen *et al.*, 2001), basic emotion recognition (Ekman and Friesen, 1971)), due to the video-based and realistic nature of the stimuli (Dziobek *et al.*, 2006). The test has a good internal consistency with Cronbach's α=0.84 (Dziobek *et al.*, 2006).

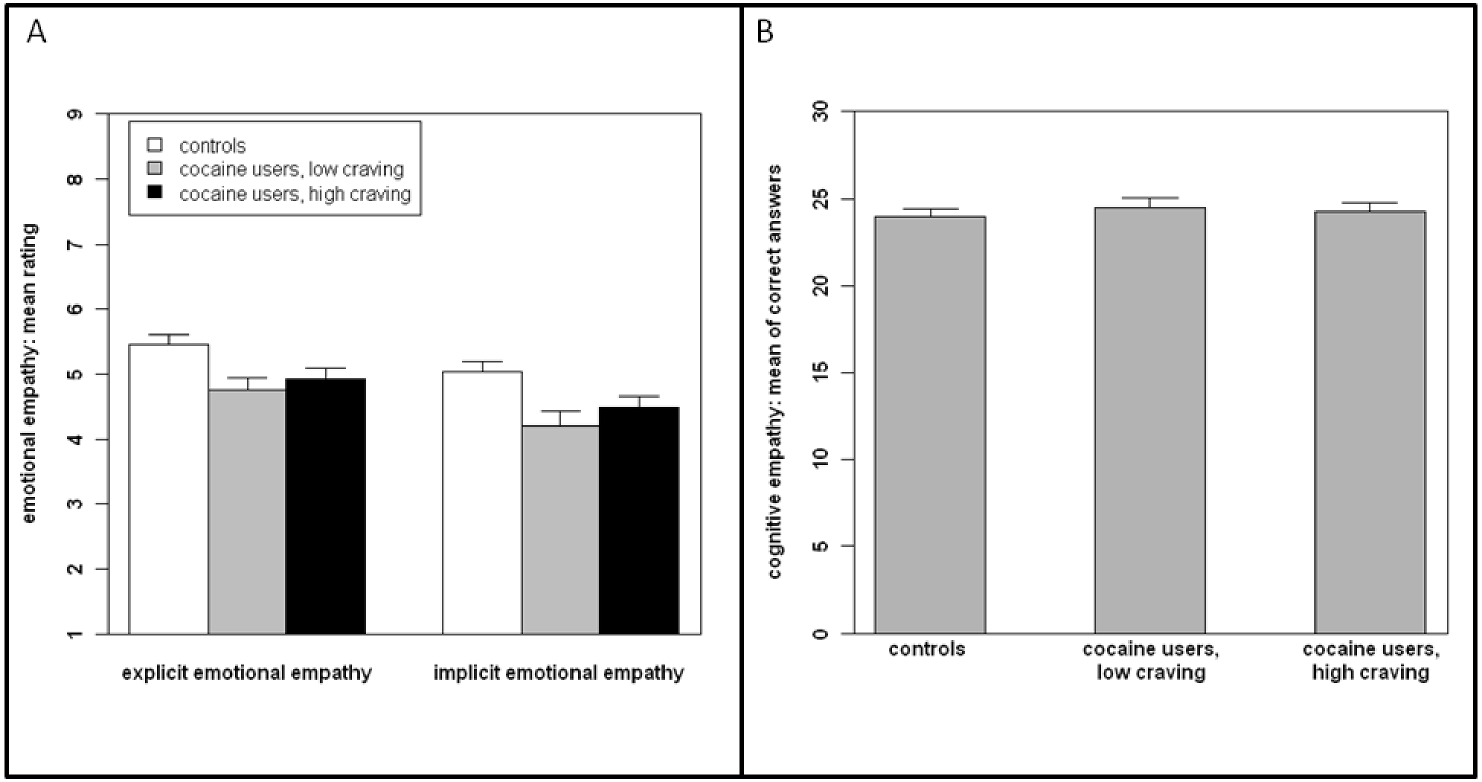

Figure 1. Mean explicit and implicit emotional empathy ratings (A) and mean correct answers on the cognitive empathy scale (B) of the multifaceted empathy test (MET). To test the influence of craving, cocaine users were divided into users with low (CCQ<16, n=41) and high craving (CCQ≥16, n=59) by median split. A MANCOVA (corrected for age and years of education) comparing cocaine users with high craving , low craving, and controls did not reveal a significant main effect for group ($F(6,324)=1.92$, $p<0.08$). Error bars refer to SEM.

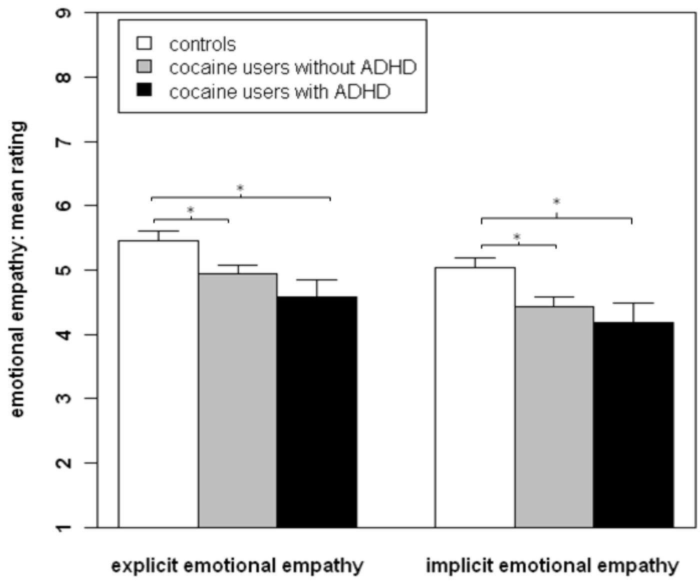

Figure 2. Mean explicit and implicit emotional empathy ratings of the multifaceted empathy test (MET). A MANCOVA (corrected for age and years of education) for ADHD subgroups (cocaine users fulfilling DSM-IV criteria for ADHD (n=22) vs. cocaine users not fulfilling these criteria (n=78) vs. controls (n=68) revealed a significant main effect for group (F(6,324)=2.84, p<0.01) with groups differing in EEE (F(2,163)=5.68, p<0.01) and IEE (F(2,163)=4.91, p<0.01). Controls showed more empathy than both, cocaine users with and without ADHD, on the EEE (p<0.03, d=0.40-0.68) and IEE scale (p<0.04, d=0.42-0.59). No significant differences were found between cocaine users with and without ADHD (p>0.55, d=0.16-0.27). No group differences were found for CE (F(2,163)=2.53, p>0.08). Cocaine use parameters did not differ between cocaine users with and without ADHD (all p>.24). Error bars refer to SEM. * indicates significant difference between groups (p<.05).

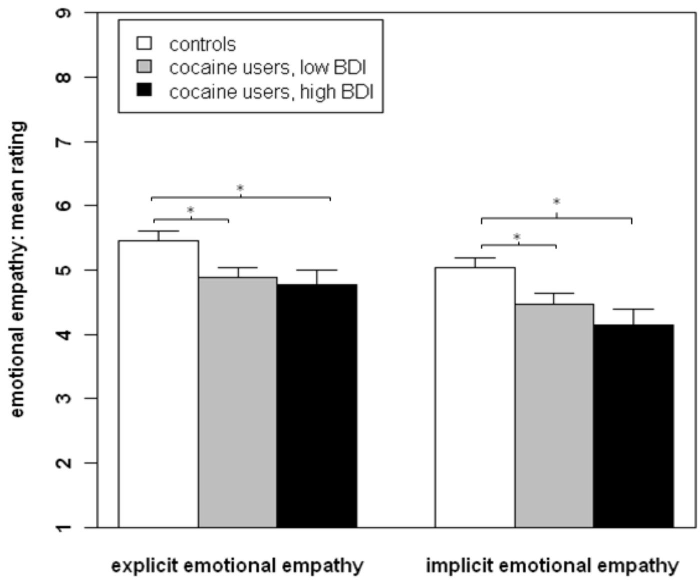

Figure 3. Mean explicit and implicit emotional empathy ratings of the multifaceted empathy test (MET). To test the influence of depressive symptoms, the user groups were split according to a predefined depression criterion (low/high, BDI<11/BDI≥11). A MANCOVA (corrected for age and years of education) for depressive subgroups (low: n=69, high: n=31) comparing them with controls (n=68) revealed a significant main effect for group (F(6,324)=2.28, p<0.04) with groups differing in EEE (F(2,163)=5.04, p<0.01) and IEE (F(2,163)=5.30, p<0.01). Controls differed from both, cocaine users with a high and low BDI score on the EEE (p<0.03, d=0.43-0.53) and the IEE scale (p<0.05, d=0.39-0.62). No significant difference was found between cocaine users with low and high BDI scores (p>0.61, d=0.22-0.43). No group differences were found for CE (F(2,163)=0.62, p>0.54). Cocaine use parameters did not differ between cocaine users low and high BDI scores (all p>.05). Error bars refer to SEM. * indicates significant difference between groups (p<.05).

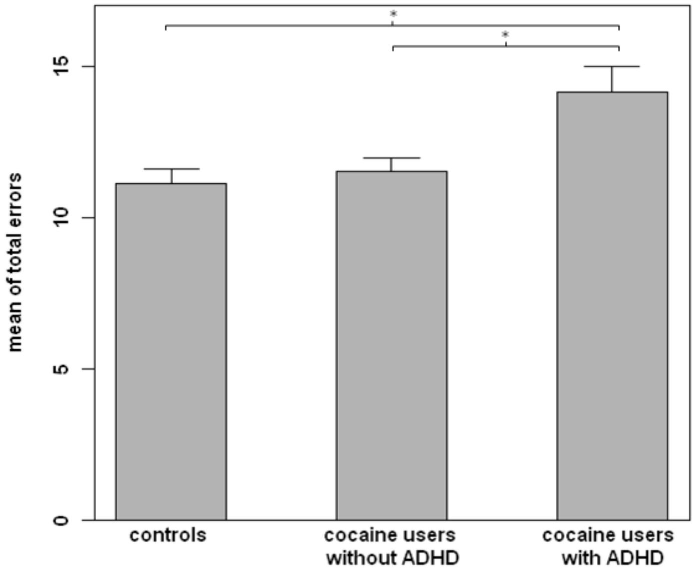

Figure 4. Mean of total errors on the movie for the assessment of social cognition (MASC). To examine the influence of ADHD, cocaine users were divided into cocaine users fulfilling DSM-IV criteria for ADHD (n=22) and cocaine users not fulfilling these criteria (n=78) and compared with controls (n=68). An ANCOVA corrected for age and years of education revealed a significant main effect for group on the MASC total errors ($F(2,163)=4.48$, $p<0.01$) with cocaine users with ADHD performing significantly worse than controls ($p<0.01$, $d=0.72$) and cocaine users without ADHD ($p<0.02$, $d=0.63$). Cocaine users without ADHD did not differ from controls ($p>0.98$, $d=0.09$). Error bars refer to SEM. * indicates significant difference between groups ($p<.05$).

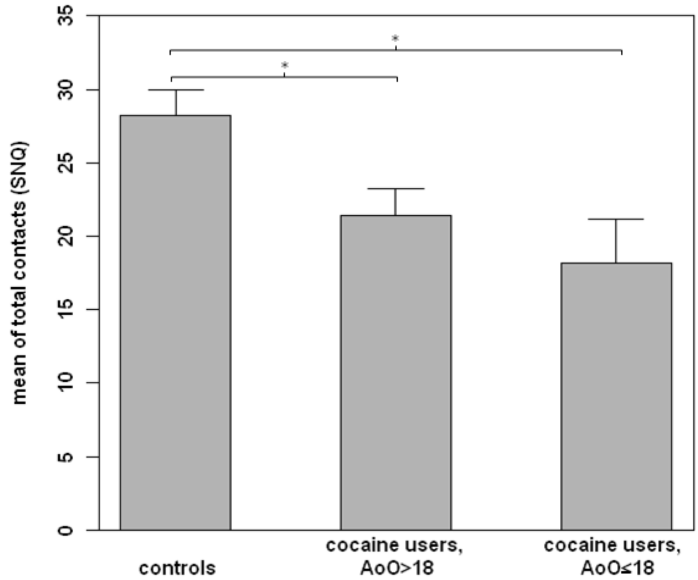

Figure 5. Mean of total contacts assessed with the social network questionnaire (SNQ) in cocaine users with an age of onset (AoO) of cocaine use ≤18 (n=24) and >18 (n=65), and controls (n=65). Cocaine users with an AoO≤18 (p<0.02, d=0.66) and an AoO>18 (p<0.03, d=0.44) reported significantly less contacts than controls. Error bars refer to SEM. * indicates significant difference between groups (p<.05)

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