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Abstract

Beyond impairments in attention, memory, and executive functions, chronic users of stimulant drugs also display specific disturbances in social cognition, which are contributing to social dysfunctions in their daily life. Recent studies have shown overlapping alterations in fear recognition from faces, emotion recognition from complex visual stimuli, emotional empathy, and mental and emotional perspective-taking (*Theory-of-Mind*) in stimulant users. Additionally, stimulant users often have smaller social networks and show less prosocial behaviour in game-theoretical social decision-making tasks. In social interaction and social feedback tasks during functional imaging cocaine users revealed decreased activation of the medial-frontal reward system. In conclusion, training of social reward and social cognition might improve social functioning including therapeutic relationships and, thus, enhance treatment success in stimulant addiction.

Keywords: amphetamine, cocaine, methamphetamine, methylphenidate, altruism, fairness, joint-attention, moral decision-making, mirror neurons, social reasoning, emotion perception, social interaction, neuroeconomics, game theory.

Introduction

Excessive and chronic use of stimulants, such as cocaine and methamphetamine, is associated with a broad range of medical, psychological, and social problems [1]. While cardiological, neurological, psychiatric, and cognitive comorbidities of chronic stimulant exposure have been recognized well [2-8], the systematic characterisation of social dysfunctions of stimulant users is only an emerging field of addiction research. This is surprising insofar as it has been phenomenologically described decades ago that chronic stimulant users display pronounced self-centred behaviours and difficulties with interpersonal relationships [9,10]. It is also well-known that stimulant addicted individuals show an increased risk for a concurrent antisocial personality disorder [7,11]. Experimental neuropsychology and social neuroscience approaches now provide the opportunity to better describe and understand the interplay between social functioning and the development and course of stimulant addiction.

Humans have developed specific abilities in order to understand themselves and others, to predict and influence the behaviour of others, and to dynamically interact with their social environment [12-14]. These abilities have been subsumed under the term *social cognition*, including more perceptive abilities such as emotion perception and recognition, self-awareness and self-perception, emotional empathy, and mental and emotional perspective-taking (also called *Theory-of-Mind)*, but also interactive social functions such as social gaze contact and social decision-making, and, finally, social attitudes and values such as altruism, fairness, trust, morale, stereotypes, and prejudices [12-15]. Given that social-cognitive abilities have been shown to be key factors in the development, progress, and prognosis of other psychiatric conditions such as schizophrenia [16], it was analogously suggested that social cognition and interaction may likewise play a crucial role in the origin and course of stimulant use disorders [17,18]. Accordingly, deficits in social cognition and behaviour may increase social isolation, aggression, and depression, predictably preserving the vicious circle of drug addiction [17]. Moreover, it has been suggested that repeated stimulant intake impacts the fronto-striatal reward system by enhancing the value of the drug of abuse, while simultaneously reducing the sensitivity for the rewarding nature of social contacts [18]. Recent meta-analyses [19,20] have additionally identified that chronic stimulant users display overlapping morphological changes of cortical regions previously shown to be key areas of social cognition and interaction [12,14,21]: e.g., ventromedial prefrontal cortex (VMPFC); inferior, middle, and superior frontal cortex; anterior cingulate cortex (ACC); insula; superior and middle temporal cortex; and amygdala. In the following, investigations characterizing, quantifying, and explaining disturbances of social cognition and interaction in cocaine, methamphetamine, and non-medical methylphenidate users will be reviewed with respect to different socially-related mental functions (see also **Table 1**).[1]

[1] As there are currently no systematic studies investigating social cognition and interaction in individuals with chronic amphetamine use, this substance has been omitted from this review.

Emotion recognition and cognitive empathy

Emotion recognition, also called *affect recognition*, *emotion perception,* or *cognitive empathy*, is the capability to recognise and understand the emotions of others from faces, voices, gestures, and situational contexts [22].

Numerous studies with stimulant users have employed emotional facial expression tasks, primarily based on the famous picture set of Ekman and Friesen [23]. Most of these investigations showed that cocaine and methamphetamine users were largely unimpaired in their general ability to identify basic facial affect expressions [24-30], whereas only a single study showed general impairment of facial affect recognition in a small sample (n=12) of former methamphetamine users [31]. Nevertheless, some studies revealed specific alterations in fear [32-35] and anger processing [32] from faces in regular users of cocaine or methamphetamine. Moreover, in polydrug users, fear and anger recognition performance was negatively correlated with cocaine use intensity [36]. Using a facial affect matching task, one functional imaging study showed no task-related changes but different cortical activation patterns in regions relevant for social cognition in methamphetamine users [30].

Emotion recognition tasks, in which only eye-pairs or complex emotional scenes were presented, did not detect abnormalities in cocaine users [33,37]. However, two independent groups have reported that methamphetamine users showed relatively strong alterations of "mind reading" from eye pairs [31,35], while non-medical users of methylphenidate exhibited problems with cognitive empathy regarding complex emotional scenes [38]. Moreover, it was shown that cocaine users with a comorbid attention-deficit/hyperactivity disorder (ADHD) also showed impaired cognitive empathy from complex scenes [39].

Interestingly, one study has shown that chronic cocaine users displayed problems in emotion recognition from voices (prosody) as well as in the detection of matches and mismatches between emotional faces and voices when both were presented together [24]. Notably, longer duration and higher cumulative doses of cocaine use were correlated with diminished integration of visual and facial emotions, indicating that the dysfunctional integration of different emotion modalities might be cocaine-induced [24].

Differences in study sample characteristics may account for some of the discrepant results discussed above, as most of the studies had relatively small sample sizes and often included stimulant-preferring polysubstance users with further psychiatric comorbidities. Accordingly, Ersche et al. demonstrated that fear and anger recognition deficits in cocaine users were mainly explained by their lower IQ and concurrent opioid dependence, respectively [32], while an additional impact of ADHD on cognitive empathy has recently been shown [39]. Of note, the well-powered *Zurich Cocaine Cognition Study* (*ZuCo*^{2}*St*) did not find changes in visual emotional processing but rather deficient prosodic emotion recognition in relatively pure recreational and dependent cocaine users with a low burden of psychiatric comorbidities [24,37].

Emotional empathy

Emotional empathy is defined as a person's emotional response to another person's emotional state, i.e., the ability to feel what another person feels [40]. In the *ZuCo²St,* both recreational and dependent cocaine users clearly reported lower emotional empathy as they showed less emotional responsiveness to photorealistic affective stimuli [37]. This was true for both an explicit condition ("How much do you feel with this person?") and an implicit condition ("How excited are you when looking at this picture?"). Importantly, implicit emotional empathy was correlated with weekly and lifetime cocaine dose and emotional empathy deficits were most pronounced in early age-of-onset users [37]. Interestingly, a comorbid ADHD had an additional impact on emotional empathy but did not explain the empathy impairment in general [37].

Additionally, a functional imaging study has demonstrated that methamphetamine users showed reduced emotional empathy in a cartoon-based task, which was accompanied by less activation of the orbitofrontal cortex (OFC), both temporal poles, and the right hippocampus relative to healthy controls [41] suggesting a functional impairment of the neural network processing empathy in methamphetamine users. Finally, low-dose, non-medical methylphenidate users did not display changes in emotional empathy [38].

Perspective-taking

Mental and emotional perspective-taking, also called *mentalizing* or *Theory-of-mind*, reflects the ability "*to propositionally reason from one's theory of how minds operate and how social situations affect mental states in general, in order to represent the mental state of a particular individual given a particular situation*" [14, p. 263]. Perspective-taking capacities in cocaine users have been measured in an ecologically valid way by application of a video-based test of social cognition [37]: Dependent but not recreational cocaine users committed more errors in this task indicating that worse mental perspective-taking is primarily associated with severe cocaine consumption [37], further supported by moderate correlations between task performance and several subjective and objective cocaine intake indices. Importantly, a concurrent ADHD diagnosis had a considerable impact on perspective-taking, i.e., only severe users with a comorbid ADHD displayed significant deficits [37,39], indicating that the interaction of cocaine use and ADHD on perspective-taking needs to be further investigated.

A single study in methamphetamine users investigating perspective-taking with a story-based task, found only a trend for weaker mentalizing abilities in the user group [35]. A trend for impaired perspective-taking abilities was also reported for non-medical methylphenidate users [38].

Social decision-making

Social decision-making describes the ability to process multiple alternatives and to choose an optimal course of action in a social environment, which is usually operationalised by socially interactive tasks derived from game theory [42]. Although maladaptive decision-making was proposed to be a core feature of stimulant addiction [43], decision-making in social contexts has not been examined in stimulant users prior to the *ZuCo*^{2}*St*. In this study, recreational and dependent cocaine users showed a reduction in prosocial decisions compared to controls as cocaine users preferred higher monetary payoffs for themselves in two social interaction tasks [44]. As the subsequent application of two different games (*Distribution* and *Dictator Game*) allowed distinguishing between fairness and efficiency preferences, it turned out that cocaine users cared primarily about efficiency and less about fairness in contrast to the controls. As no correlation between fairness preferences and cocaine use intensity was found, the authors proposed that self-serving behaviour might represent a predisposition for stimulant use [44]. Accordingly, it was recently shown that non-medical users of methylphenidate also display less fair decision-making in the *Dictator Game* [38].

Using the *Ultimatum Game*, Verdejo-Garcia and colleagues [27] investigated social decision-making during functional imaging in cocaine-dependent individuals with and without a comorbid personality disorder compared to controls. The acceptance rate for fair and unfair offers did not differ between the three groups. However, in comparison to the controls, the cocaine using groups showed reduced activation in the dorsolateral prefrontal cortex during evaluation of unfair offers and reduced activation in the subgenual ACC and the midbrain during rejection of these offers. Moreover, cocaine users showed increased activation in superior frontal and lateral OFC regions under the evaluation of unfair offers, which was additionally correlated with deficient facial affect recognition [27].

Moral decision-making and social attitudes

Moral decision-making is usually operationalised by presenting hypothetical moral dilemmas – often with varying levels of personal involvement – and asking for preferred choices [45]. One behavioural study has initially shown that cocaine-using polydrug-dependent individuals displayed more utilitarian choices that they themselves also perceived as less difficult [46]. However, a functional imaging study did not find differences in the behavioural responses to moral dilemmas between cocaine-dependent patients and healthy controls, although cocaine-dependent individuals displayed decreased activation of the ACC, left insula and brain stem as well as reduced functional connectivity between ACC, thalamus, insula, and brain stem [47]. Recently, it was additionally shown that cocaine-using incarcerates displayed reduced picture discrimination in the ventral ACC, VMPFC, lateral OFC, and left ventral striatum compared to non-cocaine-using incarcerates when viewing pictures that did or did not depict immoral actions [48].

Finally, in a questionnaire-based study of personality assessing 'detachment from conventional morality', cocaine and non-medical methylphenidate users both showed significantly higher scores of Machiavellianism than controls, reflecting their stronger tendency towards interpersonal manipulation and utilitarian beliefs [38,49]. Additionally, the pronounced Machiavellianism of cocaine users was stable and unrelated to changes in drug consumption at a one-year follow-up [49]. In line with this, particularly dependent cocaine users achieved lower scores in the *Cooperativeness*- and the *Dependence on approval by others*-subscales as well as higher values of *Disorderliness* in the *Temperament and Character Inventory* [49,50], indicating that they are less interested in social feedback and less compliant to social norms. Interestingly, Machiavellian traits correlated with prosocial decisions in the *Distribution Game* and also weakly in the *Dictator Game* but not with measures of empathy or perspective-taking [49], suggesting that such social attitudes are independent from social cognitive functions but nevertheless relevant for social interactions.

Social Network Size

In the *ZuCo*^{2}*St*, recreational and dependent cocaine users as well as non-medical methylphenidate users reported that they have smaller social networks, relative to controls [37,38]. Remarkably, the reported network sizes became smaller in line with increasing duration and amount of cocaine use, reflecting the social destructivity of excessive cocaine intake. A smaller social network size was also moderately correlated with lower emotional empathy, impaired perspective-taking, and symptoms of depression, ADHD, and narcissistic personality disorder, well depicting the ecologic validity of social network size assessments [37].

Social reward

Another key feature of social functioning is perceiving pleasure during social interactions. Following the assumption that changes in the processing of social reward might underlie dysfunctional social behaviour in cocaine users [18], two social interaction paradigms have been applied in order to investigate their implicit and explicit social reward processing [51,52]. In the first experiment, an interactive social gaze paradigm was employed that has been shown to stimulate reward-related brain regions in healthy volunteers [53]. Firstly, valence ratings and pupil-responses in different eye-contact conditions revealed that cocaine users show blunted emotional reactions to social gaze interactions [51]. Subsequently, cocaine users also showed less activation of the VMPFC during social gaze interaction, supporting the assumption that social eye-contact might be less rewarding for them. Importantly, the activation of the VMPFC was correlated with social network size (see section above), indicating that a blunted ability to perceive this implicit form of social reward is reflected in diminished real-life social functioning [51].

In a second experiment, explicit social reward in the context of social feedback was investigated and additionally compared with non-social (object) reward processing [52]. In fact, cocaine users also showed a reduced reward signal in the VMPFC in the context of explicit social feedback. The social reward-related activation in the VMPFC overlapped with the reduced response to object reward, which was additionally correlated with years of cocaine use. Thus, reward processing is disturbed in cocaine users, irrespective of reward type, suggesting a final common path. As the VMPFC has been proposed to be critically involved in the encoding and maintenance of reward value [54], it was proposed that chronic cocaine users suffer from a generalized impairment in value processing, likely generalizing to also affect their social lives [52].

Hyatt et al. [55] used an interactive competitive Domino game during functional imaging in order to investigate social reward in current and former cocaine users vs. controls. Surprisingly, only former but not current cocaine users showed altered activation of the dorsal caudate nucleus compared to the healthy controls, indicating changes in the reward processing related to social competition. However, as the authors did not include the VMPFC in their region-of-interest-based analysis, these results are difficult to compare with the studies on social reward discussed above [51,52].

Conclusion

Although the importance of social cognition and interaction for drug addiction is rather self-evident [56], only few studies thus far have objectified social dysfunctions in stimulant users by means of psychological methods. As demonstrated above, stimulant users show a range of specific impairments in social cognitive functions (**Table1**):

1) Cocaine users display impairments in affect recognition from fearful and angry faces, general emotion recognition from voices, and emotional empathy, while particularly dependent users show additional difficulties in mental and emotional perspective-taking. Furthermore, cocaine users behave less prosocially in social interaction tasks, they report fewer social contacts, show alterations in moral decision-making, and reveal more pronounced antisocial attitudes such as increased levels of Machiavellian personality traits. Finally, imaging studies suggest that cocaine users are less rewarded by social interactions.

2) Methamphetamine users exhibit fear recognition deficits similar to cocaine users, but appear to be more broadly impaired in emotion recognition from faces and eye-pairs. Moreover, they also display less emotional empathy than non-drug using controls.

3) Non-medical methylphenidate users display problems in emotion recognition from complex material and, similar to cocaine users, they also report smaller social networks and act more self-servingly in money distribution games.

Importantly, it is not fully clear yet how polydrug use, lifestyle differences, intellectual abilities, and psychiatric comorbidities might influence socio-cognitive deficits of stimulant users, as it has been shown, for example, that facial affect recognition deficits of cocaine users might be explained by their opioid co-consumption and lower IQ [32], while perspective-taking and cognitive empathy deficits may only appear if a comorbid ADHD is present [37,39]. However, stimulant using populations without polydrug use and comorbid axis-I psychiatric diagnoses have also been found to display several socio-cognitive dysfunctions [24,37,44,49,51,52].

Taken together, drug-related changes in social reward and social cognition may contribute to the social problems and the decay of social relationships in stimulant addicted individuals. Beyond that, although not investigated yet, it is likely that disturbances in social perception and behaviour could also compromise any therapeutic relationship, and, thus, hamper the success of addiction treatment. Accordingly, interpersonal problems related to social cognition deficits might partially account for high relapse rates found among stimulant-dependent subjects enrolled in any kind of psychological or psychopharmacological treatment developed so far [57,58]. Additionally, specific social reward deficits might also explain why social consequences of drug use (e.g., imprisonment or familial problems) do not discourage cocaine-dependent individuals to cease using the drug [51]. As general cognitive functions and impulse control abilities covary with changes in cocaine use across time, indicating that they are partially drug-induced but also reversible [59,60], we propose that some of the socio-cognitive impairments of stimulant users are also drug-induced and that these changes contribute to the maintenance of chronic stimulant use (see **Figure 1**). Therefore, a new focus on psychosocial treatments of stimulant addiction might better address these social dysfunctions in order to improve the therapeutic relationship and hence the treatment success [61]. Specifically, the rehabilitation of social reward might be a promising avenue for providing an alternative to bypass the accrual of drug-related reward system maladaptations in substance use disorders [51,62].

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Table 1: Changes in social cognition and interaction of stimulant users

Domain	Subdomain	Cocaine users	Methamphetamine users	Non-medical methylphenidate users
Emotion recognition (*Cognitive empathy*)				
	From faces			
	Total performance	→ [24-29]	↓ [31,35]	→[a]
	Happiness	→ [24-29,32-34]	→ [35]	→[a]
	Surprise	→ [24-29,32-34]	→ [35]	**(↑)**[a]
	Sadness	→ [24-29,32-34]	**(↓)** [35]	→[a]
	Fear	↓ [32-34,36], → [24-29]	↓ [35]	→[a]
	Disgust	→ [24-29,32-34]	→	→[a]
	Anger	↓ [32,36], → [24-29,33,34]	→	→[a]
	From prosody	↓ [24]	-	→[a]
	From eye pairs	→ [37]	↓ [35]	-
	From complex scenes	↓[b] [39], → [37]	-	↓ [38]
Emotional empathy		↓ [37]	↓ [41]	→ [38]
Perspective-taking (*Theory-of-Mind*)		↓[c] [37,39] ,→ [37,39]	**(↓)**[35]	**(↓)** [38]
Social decision-making		↓ [44], →[d] [27]	-	↓ [38]
Moral decision-making		↓ [46], →[d] [47]	-	-
Social network size		↓ [37]	-	↓ [38]
Machiavellianism		↑ [49]	-	↑ [38]
Social reward		↓[e] [51,52,55]	-	-

↓: significantly decreased, →: unchanged, ↑: significantly increased, (↓): trend for a decrease (p<.10), (↑): trend for an increase (p<.10), - : not investigated yet.
[a]Unpublished data [Wunderli and Quednow, personal communication].
[b]Only cocaine users with comorbid ADHD.
[c]Only in dependent cocaine users or in users with comorbid ADHD.
[d]No difference in task performance vs. controls, but changes in brain activation.
[e]As shown by less activation in reward-related brain areas.

Figure 1: The proposed role of social cognition and interaction in maintenance and relapse of stimulant use disorders.