Drug and Alcohol Dependence xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Cognitive and emotional impairments in adults with attention-deficit/hyperactivity disorder and cocaine use

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ARTICLE INFO

Article history:
Received 12 February 2016
Received in revised form 29 March 2016
Accepted 29 March 2016
Available online xxx

Keywords:
Stimulants
Depression
Affective disorder
Mentalizing
Emotion recognition
Chronic use

ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is an important modulator of cognitive and social functioning in cocaine addiction but it is unclear whether ADHD symptoms and cocaine use display mutually aggravating interaction effects on cognition, social functioning, and depressive symptoms. Therefore, we investigated the interaction of cocaine use and adult ADHD on social and non-social cognition and depressive symptoms.

Methods: Twenty-four cocaine users with (CU+ADHD) and 30 without ADHD (CU-ADHD), 29 cocaine-naïve ADHD patients, and 40 cocaine-naïve healthy controls underwent comprehensive neuropsychological testing including assessment of social cognition (cognitive/emotional empathy and Theory-of-Mind). Additionally, depressive symptoms were measured with the Beck Depression Inventory.

Results: The effect size of global cognitive impairment was largest in CU+ADHD (d = 1.22 vs. controls) followed by CU-ADHD (d = 0.74), and cocaine-naïve ADHD patients (d = 0.33). A similar pattern appeared regarding depressive symptoms (CU+ADHD: d = 1.47; CU-ADHD: d = 0.49, ADHD: d = 0.34). In the measures of Theory-of-Mind (CU+ADHD: d = 0.76; CU-ADHD: d = 0.06, ADHD: d = 0.01) and cognitive empathy (CU+ADHD: d = 0.80; CU-ADHD: d = 0.39, ADHD: d = −0.11) only CU+ADHD showed moderate to large impairments. Moreover, two-way analyses of covariance revealed a significant interaction effect of the factors ADHD and cocaine use on depressive symptoms ($p < 0.05$) and Theory-of-Mind ($p < 0.05$) but not on global cognitive performance (p=0.64).

Conclusions: When occurring together, cognitive impairments associated with both ADHD and cocaine use are largely additive, whereas both factors seem to mutually potentiate one another with respect to mood and mental perspective-taking disturbances. Given the high comorbidity between ADHD and cocaine use, longitudinal studies are needed to investigate the origin of these potentiated impairments.

1. Introduction

With an estimated 17 million past-year users cocaine remains one of the most used illicit drugs worldwide (United Nations Office on Drugs and Crime, 2015). Because of its negative health consequences and addictive potential, cocaine use represents a major issue in public health (Nutt et al., 2007). Attention-deficit/hyperactivity disorder (ADHD) is another major public health issue (Ballon et al., 2015), with an estimated worldwide prevalence of about 5% in children (Polanczyk et al., 2014) and symptoms that persist into adulthood in up to 65% of patients (Faraone et al., 2006). At more than 20%, the prevalence of adult ADHD appears to be much higher in individuals with cocaine use disorder compared with the general population (Perez de Los Cobos et al., 2011; van Emmerik-van Oortmerssen et al., 2012; Vonmoos et al., 2013a Vonmoos et al., 2013a). Furthermore, in a sample of adult patients seeking treatment for cocaine addiction, 35% were found to have ADHD (Lambert and Hartsough, 1998). These num-

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http://dx.doi.org/10.1016/j.drugalcdep.2016.03.026
0376-8716/

bers are in line with the assumption that adolescents with ADHD are about twice as likely as healthy individuals to develop a substance use disorder (Biederman et al., 1995).

Recent findings from the Zurich Cocaine Cognition Study ($ZuCo^2St$) confirmed that recreational and dependent cocaine users display considerable impairments in attention, working memory, declarative memory, and executive functions that were aggravated with increased use (Vonmoos et al., 2013a). Furthermore, recreational and dependent cocaine users showed less emotional empathy, and specifically dependent users displayed difficulties in mental and emotional perspective-taking (also called "mentalizing" or "Theory-of-Mind"), higher delay aversion, and decreased planning abilities (Hulka et al., 2014; Preller et al., 2014). In the $ZuCo^2St$, social and non-social cognition were strongly moderated by comorbid ADHD symptoms, since the combination of cocaine use and ADHD symptoms was associated with much more pronounced deficits (Preller et al., 2014; Vonmoos et al., 2013a).

Cocaine use appears to impact neurotransmitter systems in brain regions thought to be altered in ADHD patients: Chronic cocaine use has been linked to alterations in the fronto-striatal dopamine system (Beveridge et al., 2008; Garavan and Hester, 2007; Volkow et al., 2009a, 2004) and noradrenergic changes in the thalamus and locus coeruleus (Ding et al., 2010). Moreover, structural and functional changes in several areas of the prefrontal cortex have been linked to cognitive deficits in dependent cocaine users (Beveridge et al., 2008; Garavan and Hester, 2007; Goldstein et al., 2004). Remarkably, fronto-striatal dysfunctions and changes in catecholaminergic neurotransmitter systems appear to also play a crucial role in the etiology of ADHD (Brennan and Arnsten, 2008; Del Campo et al., 2011; Tripp and Wickens, 2009). In particular, disturbances in cognitive functions such as vigilance, working memory, planning, and response inhibition—as well as problems in motivational processes, such as delay aversion—are associated with both ADHD (Nigg, 2005; Willcutt et al., 2005) and cocaine use (Hulka et al., 2014; Vonmoos et al., 2013a, 2013b). In both cases, these effects have been proposed to depend on changes in the dopamine and noradrenaline system (Gould et al., 2014; Sofuoglu, 2010; Tripp and Wickens, 2009). Recently, also problems in more complex cognitive functions such as social cognition and interaction have been demonstrated in recreational and dependent cocaine users as well as in patients with ADHD (Bora and Pantelis, 2016; Hulka et al., 2013, 2014; Preller et al., 2014). Additionally, both, patients with cocaine addiction and with ADHD have an increased risk for developing depressive symptoms (Connor et al., 2003; Rounsaville, 2004; Swendsen and Merikangas, 2000).

To our knowledge, the interaction of ADHD symptoms and cocaine use with regard to cognitive and socio-cognitive functions as well as to depressive symptoms has not been investigated in detail yet. Thus, it remains unclear whether the pronounced cognitive and socio-cognitive impairments of cocaine users with ADHD symptoms arise from a combination of ADHD and cocaine use or can be explained by ADHD alone (Preller et al., 2014; Vonmoos et al., 2013a). Therefore, we recruited a group of ADHD patients without illegal drug use and compared them with cocaine users with and without ADHD and to stimulant-naïve healthy controls so as to investigate the presumed interactions between ADHD and cocaine use. We hypothesized that ADHD and cocaine use would reveal cumulative or even multiplicative effects.

2. Methods

2.1. Participants

We recruited 29 ADHD patients who reported no illegal drug use, 24 cocaine users with ADHD (CU+ADHD), 30 cocaine users without ADHD (CU-ADHD), and 40 stimulant-naïve healthy controls and matched the groups for age and sex (see Supplementary methods S1 for recruitment details). All participants had to be between 18 and 60 years old and fluent in German. Exclusion criteria for all participants were current or previous neurological disorders or head injury, any clinically significant medical disease, a family history of schizophrenia or bipolar disorder, and the use of prescription drugs affecting the central nervous system (except for methylphenidate and dexamphetamine for the ADHD group) as well as a lifetime history of opioid use. For controls and ADHD patients, further exclusion criteria were any Axis-I *DSM-IV* psychiatric disorder (with the exception of ADHD), any form of addiction (except nicotine), and regular illegal drug use (lifetime use >15 occasions, except cannabis). Specific exclusion criteria for the cocaine user groups were polytoxic drug use, any Axis-I *DSM-IV* adult psychiatric disorder (other than ADHD in CU+ADHD) with exception of cocaine, nicotine, and alcohol abuse/dependence and history of depression (acute major depression was excluded). Inclusion criteria for the cocaine user groups were cocaine use of at least 0.5 g/month, cocaine as the preferred illegal drug, and a current abstinence period of less than 6 months. All participants were asked to abstain from illegal substances for at least three days and from alcohol for at least 24 h prior to testing. Compliance was controlled by urine toxicology, and self-reported drug use was controlled by a 6-month hair testing (see Supplementary methods S2). Of the 29 cocaine-naïve ADHD patients, 24 received stimulant treatment prior to the study (23 participants received methylphenidate, 1 participant received dexamphetamine) while four patients showed no history of stimulant medication. ADHD patients were asked not to use prescription stimulants or any other medication for 24 h prior to testing. The study was approved by the Cantonal Ethics Committee of Zurich, and all participants gave written informed consent and were compensated for their participation.

2.2. Clinical assessment

Trained psychologists conducted the Structured Clinical Interview for Axis-I *DSM-IV* disorders in order to exclude participants with an Axis-I *DSM-IV* psychiatric disorder. Drug use was assessed with the Interview for Psychotropic Drug Consumption (Quednow et al., 2004). ADHD diagnoses and current severity of ADHD symptoms were evaluated with the ADHD self-rating scale (ADHD-SR) (Rosler et al., 2004) corresponding to *DSM-IV* criteria. Furthermore, the German short version of the Wender Utah Rating Scale (WURS-k) measuring ADHD symptoms present in childhood was used in the ADHD sample (Retz-Junginger et al., 2002). Depressive symptoms – as an outcome measure – were assessed with the Beck Depression Inventory (BDI) (Beck et al., 1961). Premorbid verbal intelligence was estimated with a German vocabulary test (Mehrfachwahl-Wortschatz-Intelligenztest) (Lehrl et al., 1995). Severity of tobacco dependence was measured by the Fagerström Test of Nicotine Dependence (Heatherton et al., 1991). Finally, to measure present cocaine craving in cocaine users, the brief version of the cocaine craving questionnaire (CCQ) was applied (Sussner et al., 2006).

2.3. Neuropsychological assessment

Cognitive performance was assessed with four tests from the Cambridge Neuropsychological Test Automated Battery (Strauss et al., 2006): Rapid Visual Information Processing, Spatial Working Memory, Intra/Extra-Dimensional Set Shifting, and Paired Associates Learning. Additionally, a German version of the Rey Auditory Verbal Learning Test (Helmstaedter et al., 2001) and the Letter Number Sequencing Test were administered (Wechsler, 1997). As previously published (Vonmoos et al., 2013a, 2014), 15 predefined test parameters underwent z-transformation on the basis of means

Please cite this article in press as: Wunderli, M.D., et al., Cognitive and emotional impairments in adults with attention-deficit/hyperactivity disorder and cocaine use. Drug Alcohol Depend. (2016), http://dx.doi.org/10.1016/j.drugalcdep.2016.03.026