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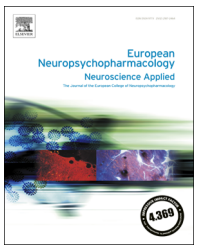

Metacognitive impairment in active cocaine use disorder is associated with individual differences in brain structure

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Abstract
Dysfunctional self-awareness has been posited as a key feature of drug addiction, contributing to compromised control over addictive behaviors. In the present investigation, we showed that, compared with healthy controls ($n=13$) and even individuals with remitted cocaine use disorder ($n=14$), individuals with active cocaine use disorder ($n=8$) exhibited deficits in basic metacognition, defined as a weaker link between objective performance and self-reported confidence of performance on a visuo-perceptual accuracy task. This metacognitive deficit was accompanied by gray matter volume decreases, also most pronounced in individuals with active cocaine use disorder, in the rostral anterior cingulate cortex, a region necessary for this function in health. Our results thus provide a direct unbiased measurement – not relying on long-term memory or multifaceted choice behavior – of metacognition deficits in drug addiction, which are further mapped onto structural deficits in a brain region that subserves metacognitive accuracy in health and self-awareness in drug addiction. Impairments of metacognition could provide a basic

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mechanism underlying the higher-order self-awareness deficits in addiction, particularly among recent, active users.

1. Introduction

Drug addiction is characterized by pervasive and reliable neurocognitive impairments (Goldstein et al., 2004; Woicik et al., 2009). Recently, we posited that an underappreciated neurocognitive impairment in drug addiction involves dysfunctional self-awareness of higher-order neurocognitive functions including behavioral monitoring and self-perception of illness severity (Goldstein et al., 2009). At the core of this self-awareness deficit may be functional and structural abnormalities of anterior prefrontal cortical (aPFC) structures, including the rostral subregion of the anterior cingulate cortex (rACC) [Brodmann Areas (BA) 24, 32)] extending into the adjacent ventromedial prefrontal cortex (BAs 10, 11, 25) (Moeller and Goldstein, 2014). Support for these hypotheses largely derived from comparing individuals with cocaine use disorder (CUD) to healthy controls on a self-awareness measure that is based on a mismatch between actual ongoing choice for viewing drug-related pictures with retrospective self-report of this choice, with implications for increased drug-seeking behavior and decreased social-emotional functioning (Moeller et al., 2012, 2014, 2010). Nevertheless, achieving a mechanistic understanding of this self-awareness deficit requires tapping into basic metacognitive functioning, thereby removing potential ambiguities associated with multifactorial choice behavior and other higher-order constructs. A basic metacognitive task could enable direct translation of self-awareness and insight deficits across psychopathologies (van der Meer et al., 2013) and potentially even across species (Lak et al., 2014; Lucantonio et al., 2014).

In the present study, we tested for metacognitive deficits in individuals with CUD using a basic visuo-perceptual task. In particular, we capitalized on recent computational models of metacognitive accuracy to allow an unbiased measure of the participants' sensitivity to their own performance (meta-*d'*), defined as the degree to which participants' objective performance during basic perceptual judgments maps onto their self-reported confidence in such basic perceptual performance (Fleming et al., 2014, 2010). These models can circumvent the difficulty in objectively measuring self-awareness in the lab (Fleming and Lau, 2014), reducing reliance on higher-order processes such as long-term memory that could contribute to potentially inaccurate retrospective reporting (Moeller et al., 2010). We hypothesized that CUD participants, particularly active/recent users of cocaine (Moeller et al., 2010), would display impairments in basic metacognitive accuracy, which in turn would be associated with gray matter volume (GMV) decreases in the aPFC (Fleming et al., 2014, 2010). Structural integrity of this region is of core importance for both self-awareness and basic metacognition (Fleming et al., 2014, 2010; Moeller et al., 2014).

2. Experimental procedures

2.1. Participants

Twenty-two individuals with CUD (15 men) and 13 matched healthy controls (7 men) participated in this research (Table 1). Participants were recruited through advertisements, local treatment facilities, and word of mouth; all provided written informed consent in accordance with the Mount Sinai Institutional Review Board. Exclusion criteria were: (A) history of head trauma or loss of consciousness (>30 min) or other neurological disease of central origin (including seizures); (B) abnormal vital signs at time of screening; (C) history of major medical conditions, encompassing cardiovascular (including high blood pressure), endocrinological (including metabolic), oncological, or autoimmune diseases; (D) history of major psychiatric disorder [for CUD, exceptions to this criterion included other substance use disorders (SUDs) and/or comorbidities that are highly prevalent in this population (e.g., post-traumatic stress disorder); for healthy controls, an exception was nicotine dependence]; (E) pregnancy as confirmed with a urine test in all females; (F) contraindications to the magnetic resonance imaging (MRI) environment; (G) except for cocaine in the CUD participants, positive urine screens for psychoactive drugs or their metabolites (amphetamine or methamphetamine, phencyclidine, benzodiazepines, cannabis, opiates, barbiturates and inhalants); and (H) alcohol intoxication, verified by trained research staff who have extensive experience with recognizing signs of intoxication in CUD participants and confirmed by breathalyzer.

Participants underwent a comprehensive diagnostic interview, consisting of: (A) Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996); (B) Addiction Severity Index (McLellan et al., 1992), a semi-structured interview instrument used to assess history and severity of substance-related problems in seven problem areas (medical, employment, legal, alcohol, other drug use, family-social functioning, and psychological status); (C) Cocaine Selective Severity Assessment Scale (Kampman et al., 1998), measuring cocaine abstinence/withdrawal signs and symptoms (i.e., sleep impairment, anxiety, energy levels, craving, and depressive symptoms) 24 h within the time of interview; (D) Severity of Dependence Scale (Gossop et al., 1992); and (E) Cocaine Craving Questionnaire (Tiffany et al., 1993). This interview identified the following cocaine-related diagnoses: current CUD (n=8) and CUD in sustained or partial remission (n=14). Because in previous studies self-awareness deficits were accentuated in active cocaine users testing positive for cocaine in urine (i.e., active users) (Moeller et al., 2010), we split our cocaine sample *a priori* by cocaine urine status. These subgroups included those with cocaine positive urine screens (though not currently intoxicated), objectively indicating recent cocaine use within 72 h (n=8: CUD+), and those with cocaine negative urine screens who did not use cocaine within 72 h of the study (n=14: CUD−). These sample sizes (including for controls: n=13), albeit relatively small, are consistent with prior studies of this metacognitive accuracy task in a different clinical population with GMV lesions of the aPFC (Fleming et al., 2014). Furthermore, this sample size is consistent with the anticipated effect sizes in CUD participants. Specifically, we previously showed evidence of an insight deficit (i.e., unawareness of drug-choice) in CUD+ and associations of such impairment with drug-relevant outcomes (e.g., withdrawal symptoms indicative