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Denial in methamphetamine users: Associations with cognition and functional connectivity in brain

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ABSTRACT

Background: Despite harmful consequences of drug addiction, it is common for individuals with substance use disorders to deny having problems with drugs. Emerging evidence suggests that some drug users lack insight into their behavior due to neurocognitive dysfunction, but little research has examined potential neurocognitive contributions to denial.

Methods: This study explored the relationship between denial, cognitive performance and functional connectivity in brain. The participants were 58 non-treatment-seeking, methamphetamine-dependent participants who completed the URICA precontemplation scale, a self-report measure of denial of drug problems warranting change, as well as a cognitive test battery. A subset of participants ($N=21$) had functional MRI scans assessing resting-state functional connectivity. Given literature indicating roles of the rostral anterior cingulate (rACC), anterior insula and precuneus in self-awareness, relationships between denial and resting-state connectivity were tested using seeds placed in these regions.

Results: The results revealed a negative relationship between denial and an overall cognitive battery score ($p=0.001$), the effect being driven particularly by performance on tests of memory and executive function. Denial was negatively associated with strength of connectivity between the rACC and regions of the frontal lobe (precentral gyri, left ventromedial prefrontal cortex, left orbitofrontal cortex), limbic system (left amygdala, left hippocampus and left parahippocampal gyrus), occipital lobes and cerebellum; and between the precuneus and the midbrain and cerebellum. Anterior insula connectivity was unrelated to denial.

Conclusions: These findings suggest that denial by methamphetamine users is linked with a cognitive and neural phenotype that may impede the development of insight into their behavior.

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1. Introduction

Despite the negative impact on one's health and quality of life, individuals who have drug use disorders may deny having a problem with drugs. Indeed, traditional models of addiction treatment, such as that embraced by Alcoholics Anonymous, conceptualize denial as a hallmark of the addictive process (Kurtz, 1982). More contemporary models of behavior change in addiction, such as the Transtheoretical Model (DiClemente et al., 2004; Prochaska et al.,

1992), likewise suggest that individuals who abuse substances may deny or fail to recognize the need to change their behavior, and that only through insight into the problem and intrinsic motivation can true behavioral change take place. This view is consistent with evidence suggesting that, among those who meet criteria for methamphetamine dependence, lack of perceived need for treatment is one of the most problematic barriers to treatment utilization (Kenny et al., 2011).

An emerging literature suggests that abnormalities in cognition and brain function may reduce the degree to which drug users can reflect upon and have insight into the nature of their substance abuse (see Goldstein et al., 2009). The relevant evidence has raised the possibility that denial by substance users may reflect a deficit in self-awareness and/or interoceptive monitoring, rather than, or in addition to, a conscious or subconscious attempt by the drug

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user to minimize his or her symptoms (Goldstein et al., 2009). Limited research, however, has examined potential neurocognitive contributions to denial in addiction. A preliminary study of individuals in treatment for alcohol dependence found that participants who were judged by clinicians to have more denial regarding their addiction exhibited worse performance on tests of executive functioning, memory, and processing speed than their counterparts who were thought to have less denial (Rinn et al., 2002). However, other studies of cognitive or neural contributions to denial in substance users have not been conducted.

Research has indicated that individuals who abuse drugs may have less awareness of their behavior than those who do not abuse drugs. When compared to healthy control subjects, cocaine users have shown less awareness of their choices when viewing emotional and cocaine-related images (Moeller et al., 2010), and of errors they made when performing an inhibitory control task (Hester et al., 2007). In alcohol-abusing college students, reduced awareness of drinking problems was associated with worse performance on memory tests (Blume et al., 2000). Marijuana users completing a go/no-go task while undergoing functional magnetic resonance imaging (fMRI) had less awareness of errors and less error-associated BOLD activation in the anterior cingulate cortex (ACC) and right insula than healthy control subjects (Hester et al., 2009). Similarly, cocaine users with limited insight into their choices for emotional and drug-related images exhibited less activation of the rostral ACC (rACC) during errors on an fMRI Stroop Task, and had less gray matter volume in the rACC, than participants with intact insight (Moeller et al., 2014).

Evidence from error-monitoring studies in healthy subjects has likewise suggested that the rACC and insula contribute to one's awareness of having made errors during task performance (Klein et al., 2007; Simoes-Franklin et al., 2010; Taylor et al., 2007). The anterior portion of the insula, in particular, is considered to be important in the integration of interoceptive states with environmental conditions necessary for self-awareness (Craig, 2009). In the resting state, the anterior insula and ACC act as a "salience network" that is sensitive to detecting inconsistencies in oneself or the environment, and serves to activate other brain regions for further processing of personally relevant information (Menon and Uddin, 2010).

There is also evidence that, in addition to the rACC and anterior insula, the precuneus is involved in self-awareness (see Cavanna and Trimble, 2006). In healthy participants, the level of activation of the precuneus is positively associated with the degree to which subjects are aware of internal thoughts and feelings compared to stimuli in the external environment (Vanhaudenhuyse et al., 2010). Further, transcranial magnetic stimulation of the precuneus inhibits the retrieval of judgments about oneself but not about others (Lou et al., 2004). Schizophrenic patients with low insight into their psychosis exhibit hypoperfusion of the precuneus compared with patients who have intact insight (Faget-Agius et al., 2012). Schizophrenic patients with poor insight into their condition also show less resting-state functional connectivity (RSFC) between the default mode network and the precuneus and ACC than those with greater insight (Liemburg et al., 2012). Notably, research participants who meet DSM-IV criteria for methamphetamine dependence also exhibit gray-matter deficits and task-related abnormalities in the precuneus, ACC and insula (London et al., 2005; Morales et al., 2012; Nestor et al., 2011; Thompson et al., 2004); however, the relationship between these abnormalities and denial or insight regarding their addiction has not been evaluated.

Given evidence of neurocognitive contributions to self-awareness in substance users, we evaluated whether denial of substance use problems is related to cognitive performance and RSFC of regions previously associated with self-awareness (i.e., rACC, anterior insula and precuneus) in a sample of individuals who

met criteria for current methamphetamine dependence according to DSM-IV criteria (58 participants with cognitive tests, 21 of whom also had fMRI scans). Denial was assessed with the University of Rhode Island Change Assessment (URICA) precontemplation subscale. This subscale is a measure of the degree to which participants deny having problems they wish to change, and has been conceptualized as assessing denial of problems (e.g., Dare and Derigne, 2010; Peteet et al., 1998; Zimmerman et al., 2000). Consistent with the aforementioned literature, the hypotheses tested were that denial of problems would be negatively associated with overall cognitive performance and with the strength of connectivity of the rACC, anterior insula and precuneus with regions important for decision-making and affect (e.g., prefrontal cortex, limbic regions).

2. Methods and materials

2.1. Participants

The participants were 58 currently methamphetamine-dependent subjects who were not seeking treatment, 21 of whom received an fMRI resting-state scan (Table 1). Participants were recruited using Internet and local newspaper advertisements and completed procedures in return for monetary compensation. After receiving a detailed description of the protocol, they provided written informed consent, following the guidelines of the UCLA Office for Protection of Research Subjects. Forty-eight participants completed the study as inpatients at the UCLA General Clinical Research Center (GCRC), and 10 completed the study as outpatients after closure of the GCRC. All participants tested positive for methamphetamine in urinalysis at study entry, but negative for methamphetamine and other illicit substances (amphetamine, opiates, cocaine, benzodiazepines) during cognitive and fMRI assessments, following 4–12 days of abstinence (given the long duration in which marijuana can be detected through urinalysis, brief abstinence from marijuana for outpatients was verified through saliva testing (Oratec, Grapevine, TX), with all participants endorsing at least 4 days of abstinence at testing. Abstinence for inpatients was supervised). Participants were originally recruited to complete studies of cognition and brain structure in methamphetamine dependence (e.g., Morales et al., 2012; Simon et al., 2010), and fMRI scanning in the resting state was added to this protocol in later years (e.g., Kohno et al., 2014). All participants were fluent in English and were administered the Structured Clinical Interview for the DSM-IV (SCID) for Axis I diagnosis (First et al., 1995). The exclusion criteria, based on interview and laboratory tests, were: neurological disease (e.g., stroke, head trauma with loss of consciousness >30 min); frank structural brain abnormalities on MRI; systemic disease; cardiovascular disease; pulmonary disease; HIV infection (HIV1/HIV2 antibody screen); abnormal laboratory tests (hematocrit, plasma

Table 1
Characteristics of methamphetamine-dependent participants.

	Entire sample	fMRI subsample
Sample size	58	21
Age (years)	34.14 ± 8.29 (21–52)	36.19 ± 9.30 (22–52)
Gender (# male)	37	13
Education (years)	12.57 ± 1.66 (7–18)	12.67 ± 1.68 (10–18)
Ethnicity		
Caucasian	28	7
African American	2	1
Hispanic	18	8
Asian American	3	1
Other	7	4
Days used alcohol last 30 days	4.14 ± 6.65 (0–30)	2.89 ± 4.24 (0–16)
Days used marijuana last 30 days	3.58 ± 7.34 (0–30)	3.94 ± 8.03 (0–30)
Tobacco use (# smokers)	49	18
Days used methamphetamine last 30 days	22.05 ± 7.96 (2–30)	23.00 ± 7.20 (5–30)
Grams methamphetamine used last week	3.28 ± 4.25 (0.13–28)	2.18 ± 1.89 (0.25–7)
Years of regular methamphetamine use	6.62 ± 5.94 (1–28)	6.52 ± 4.97 (1–18)

Note: Data reflect mean ± standard deviation (range); Regular methamphetamine use = using at least 3 days per week, or twice weekly binges.

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