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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

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Contributors

AD had primary responsibility for writing the manuscript and developing its conceptual aims. MK conducted and described fMRI analyses and contributed to conceptual content. AM assisted with fMRI analyses and contributed to conceptual content. DG contributed to conceptual content. EL supervised all research procedures and contributed to conceptual content. All authors critically reviewed the manuscript and approved the final version for publication.

Conflict of Interest

All other authors declare that they have no conflicts of interest.

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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.

Keywords

cognition; insight; denial; awareness; substance abuse; connectivity

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 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. 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 to 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, Texas), 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 electrolytes, markers for hepatic and renal function); use of psychotropic medications; diagnosis of current abuse or dependence for any substance other than methamphetamine, marijuana or nicotine; and any current non-substance-induced Axis I psychiatric conditions (with the exception of one subject with current social phobia who did not receive an fMRI scan). Eight participants also met criteria for current marijuana dependence (N=6) or abuse (N=2).

2.2 Measures

2.2.1 Cognitive battery—The cognitive battery was identical to that used by Dean et al. (2012), and included measures of

2.2.2 Processing speed/attention—Trailmaking Part A (Reitan, 1958), Stroop Color and Word identification (Golden, 1978), and Digit Symbol Coding from the WAIS-R (Wechsler, 1981).

2.2.3 Learning/memory—Selective Reminding Test (Buschke, 1963) and Repeated Memory Test- Pictures (Simon et al., 2004; based on stimuli from Snodgrass and Vanderwart, 1980);

2.2.4 Working memory—Backward Digit Span (Woodcock and Johnson, 1977) and Missing Digit Span (patterned after Buschke, 1963; Simon et al., 2004).

2.2.5 Executive function—Stroop Color-Word Interference (Golden, 1978); Trailmaking Part B (Reitan, 1958), Controlled Oral Word Fluency (FAS, Borkowski et al., 1967), Logical Problems (Simon et al., 2004), and Discrimination Learning (Simon et al., 2004; similar to Concept Learning from Woodcock and Johnson, 1977).

As reported previously (Dean et al., 2012), an overall cognitive battery score was created by centering and scaling each of the test scores based on the mean and standard deviation of an age-matched control group (N=42), and then averaging the resulting standardized scores (tests on which lower scores indicated better performance were multiplied by -1 to keep the directionality of the measures consistent). Due to a change in procedures, the participants with fMRI scans (N=21) were not administered the full cognitive battery, but received only the Selective Reminding Test, Stroop Test, Trailmaking Test and Controlled Oral Word Fluency; therefore, their cognitive battery score was comprised of these tests alone. However, for participants receiving the full battery, composite scores comprised of only these tests were highly correlated with composite scores comprised of the full battery ($r=0.91$, $p<0.0001$).

2.2.6 Denial: University of Rhode Island Change Assessment-Precontemplation subscale: (URICA-P; McConaughy, 1989)—The URICA is a measure of the motivation to change one's behavior which is often applied to addictive disorders, based on the Transtheoretical Model (Prochaska et al., 1992). The model proposes that the motivation to change one's behavior undergoes a series of stages, beginning with denial or a lack of recognition that a problem exists and needs to be changed (Precontemplation), followed by increased recognition and motivation to initiate change (Contemplation, Action, Maintenance). The Precontemplation subscale has been posited to assess denial (e.g., Dare and Derigne, 2010; Peteet et al., 1998; Zimmerman et al., 2000) by measuring the explicit denial of problems (e.g., "As far as I'm concerned, I don't have any problems that need changing"; and "I'm not the problem one; it doesn't make much sense for me to consider changing"). We used it to assess the denial of methamphetamine-related problems by instructing the participants to answer the questions as it pertained to their "methamphetamine use". The scale consists of 8 items ranging from strongly disagree (1) to strongly agree (5), with higher total scores (8 to 40) indicating greater adamance that one does not have a problem that needs changing. Chronbach's alpha reliability coefficient for the Precontemplation items was acceptable at a level of $\alpha = 0.801$.

2.3 fMRI Resting-State Scanning

Imaging was performed at 3 Tesla on a Siemens Magnetom Trio MRI system. For the resting-state scan, participants were presented with a black screen for 5-min and were asked

to keep their eyes open. A set of 152 functional, T2*-weighted, echoplanar images (EPI) was acquired (slice thickness=4 mm; 34 slices; repetition time (TR)=2 s; echo time (TE)=30 ms; flip angle=90°; matrix=64 × 64; field of view=200 mm). High-resolution, T2-weighted, matched-bandwidth and magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scans were also acquired. The orientation for matched-bandwidth and EPI scans was oblique-axial to maximize brain coverage and to optimize signal from ventromedial prefrontal regions.

2.4 Data Analysis

The relationship between demographic characteristics and Precontemplation and overall cognitive scores was examined using correlations or t-tests, as appropriate. Although the Precontemplation subscale is considered to be a measure of denial of having substance use problems, it is possible that those with the highest scores were not denying but actually had the fewest drug problems. To investigate this possibility, we also tested correlations between drug use and Precontemplation. The relationship between Precontemplation and cognitive scores was evaluated with multiple regression. For all primary cognitive and fMRI analyses, age, gender, years of education and inpatient status (yes/no) were included as nuisance covariates. Functional MRI image analysis was performed using the FMRIB Software Library (FSL 5.0.2.1; www.fmrib.ox.ac.uk/fsl). The image series from each participant were first realigned to compensate for small head movements (Jenkinson et al., 2002), and high-pass temporal filtering was applied (Gaussian-weighted least-squares straight-line fitting, with sigma=33s). Images were spatially smoothed using a 5-mm FWHM Gaussian kernel, and skull-stripping was performed using the FSL Brain Extraction Tool. Registration was conducted through a three-step procedure, whereby EPI images were first registered to the matched-bandwidth structural image, then to the high-resolution MPRAGE structural image, and finally into standard MNI space, using 12-parameter affine transformations. Registration of MPRAGE structural images to standard space was further refined using FNIRT nonlinear registration (Andersson et al., 2007). Bilateral volumes of interest (VOIs) for the rACC and precuneus were anatomically derived using the Desikan-Killiany Atlas (Desikan et al., 2006). The anterior portion of the insula was defined using information from a functional parcellation study (Deen et al., 2011). Statistical analyses for each VOI were performed separately using the general linear model (GLM) in each participant's native space using FMRIB's fMRI Expert Analysis Tool (FEAT), with the above-mentioned transformation to standard space carried out on resulting statistical maps. Nuisance regressors were added to each GLM to account for sources of noise, including activation measured in the cerebrospinal fluid and two variables accounting for motion artifact: frame-wise displacement (FD) and the root mean squared change in BOLD signal (DVARs; Power et al., 2011). The mean time series of the VOIs were calculated by averaging the time series of all voxels within each VOI; this average was included as a regressor for each GLM. The relationships between functional connectivity with each VOI and Precontemplation scores were examined in group-wise, whole-brain, voxel-wise regression analyses, using Precontemplation scores as a regressor in addition to the aforementioned covariates. Each whole-brain fMRI statistic was corrected for multiple comparisons using cluster-correction with a voxel height threshold of $Z > 2.3$ and a cluster-extent threshold of $p < 0.016$ to adjust (Bonferroni) for the three separate VOI analyses.

2.5 Post-hoc Analyses

Analyses revealed that Precontemplation was negatively associated with overall cognition (see below). To determine whether this relationship was driven by performance on one or more specific cognitive domains, we examined the relationship between Precontemplation and composite scores calculated from tests in the cognitive domains previously described (calculated and statistically analyzed in an identical fashion to the overall battery score, but comprised of domain-specific tests). Further, because Precontemplation was also negatively associated with RSFC of the rACC and precuneus (below), the extent to which overall cognition attenuated these relationships was examined by including it as a covariate in the aforementioned models. Because methamphetamine use may also contribute to a lack of insight, years of regular methamphetamine use (using methamphetamine three times per week, or twice weekly binges) was included as a covariate into the base RSFC models to determine whether it altered existing relationships.

Finally, as an exploratory analysis to assess specificity of the findings with the Precontemplation scale, we evaluated the relationship between RSFC of the VOIs and scores on the Contemplation scale of the URICA, which measures the tendency for respondents to consider having a problem that warrants making a change (McConaughy, 1989). Of note, the Maintenance and Action subscales of the URICA were not evaluated because the participants were active methamphetamine users who were not seeking treatment.

3. RESULTS

3.1 Demographic analyses

When controlling for age, Precontemplation scores were *negatively* correlated with the age of onset of methamphetamine use ($r=-0.36$, $p=0.007$), indicating that higher Precontemplation scores were associated with a younger age of onset. A similar relationship was observed with respect to years of regular methamphetamine use, in which higher Precontemplation scores were associated with more years of methamphetamine use ($r=0.26$, $p=0.052$; as expected, years of regular MA use and onset were negatively correlated, $r=-0.31$, $p=0.021$). Precontemplation was not significantly related to days of methamphetamine use in the last 30 days ($r=-0.03$, $p=0.835$), times of use per day ($r=0.03$, $p=0.815$) or grams used in the week prior to study entry ($r=0.06$, $p=0.676$). Among participants who provided relevant self-report data ($N=37$), those with high Precontemplation scores (grouped by median split) had a significantly *greater* number of incidents of being arrested and charged for drug offenses, relative to those with low Precontemplation scores ($t(34)=-2.09$, $p=0.045$). These data suggested that, if anything, Precontemplation was associated with more, not fewer, drug problems, consistent with the presence of denial and/or a lack of awareness regarding one's behavior.

Precontemplation was negatively correlated with years of education ($r=-0.297$, $p=0.024$), while overall cognition was significantly lower in male than female participants ($t(56)=-3.19$, $p=0.002$) and inpatient participants than outpatient participants ($t(56)=2.04$, $p=0.046$). Other demographic and drug use characteristics showed no significant associations with Precontemplation or cognition (e.g., ethnicity, days of marijuana use or abuse/dependence

diagnosis, days of alcohol use, smoking status, p 's>.05). With respect to exploratory analyses, as expected, Precontemplation scores were negatively correlated with Contemplation scores ($r=-0.29$, $p=0.027$).

3.2 Cognition and Denial

Precontemplation scores were negatively related to overall cognitive function ($\beta=-0.425$, $t(57)=-3.513$, $p=0.001$, Figure 1), and this relationship was unchanged when additionally controlling for years of methamphetamine use ($p=0.002$; excluding the subject with social phobia also had no effect, $p=.001$). In post-hoc analyses, Precontemplation was significantly negatively related to learning/memory ($\beta=-0.392$, $t(56)=-2.833$, $p=0.007$) and executive functioning ($\beta=-0.327$, $t(57)=-2.646$, $p=0.011$), while it was negatively related to processing speed/attention at a trend level ($\beta=-0.231$, $t(57)=-1.706$, $p=0.094$).

Precontemplation was unrelated to working memory ($\beta=-0.155$, $t(36)=-0.846$, $p=0.404$), although the sample size tested for working memory was relatively small ($N = 37$) because these tests were not administered in the portion of participants who received fMRI scans. In exploratory analyses, overall cognitive performance was not significantly related to the Contemplation subscale ($\beta=-0.184$, $t(57)=-1.34$, $p=0.186$).

3.3 RSFC and Denial

Relationships between Precontemplation scores and RSFC of the rACC and precuneus are presented in Table 2. Noteworthy negative relationships were exhibited between Precontemplation and strength of connectivity of the rACC with the precentral gyri, left middle temporal gyrus, ventromedial PFC (vmPFC), left orbitofrontal cortex (OFC), left amygdala, left hippocampus, left parahippocampal gyrus, occipital lobes, and cerebellum ($p<0.016$, whole-brain, cluster corrected; Figure 2). Strength of connectivity between the precuneus and the midbrain/brainstem and cerebellum was also negatively related to Precontemplation ($p<0.016$). Anterior insula connectivity was not significantly related to Precontemplation scores ($p>0.016$). No areas of positive relationship were found between the VOIs and Precontemplation.

When controlling for cognitive battery scores, the aforementioned relationships between Precontemplation and RSFC of the rACC and precuneus were not attenuated. However, when controlling for years of methamphetamine use, the negative relationships between Precontemplation and connectivity strength of the rACC with limbic regions (parahippocampal gyrus, hippocampus, amygdala) and some frontal regions (vmPFC, OFC) were no longer significant, nor was the relationship between Precontemplation and RSFC between precuneus and midbrain (p 's>0.016). Table 2 denotes which clusters were altered by covarying for years of methamphetamine use (see † symbols). Demonstrating possible shared and independent relationships between RSFC of the VOIs, Precontemplation and years of methamphetamine use, Figures 2 and 3 show differences in results when controlling and not controlling for years of methamphetamine use, as well as the independent relationship between years of methamphetamine use and connectivity.

In exploratory analyses, Contemplation scores were positively related to RSFC strength between the rACC and cerebellum ($x=34$, $y=29$, $z=23$) and left superior frontal gyrus

($x=54, y=95, z=47$). Similarly, Contemplation scores were positively related to RSFC between the Precuneus and ACC ($x=44, y=58, z=58$), left parietal operculum ($x=69, y=46, z=44$), and right middle frontal gyrus ($x=60, y=82, z=51$; $p's < 0.016$); these results remained significant when controlling for methamphetamine use. Contemplation was unrelated to RSFC of the anterior insula ($p > 0.016$). Of note, in contrast to Precontemplation, no significant negative relationships were found between Contemplation and connectivity of the VOIs.

4. DISCUSSION

The results obtained here suggest that denial in methamphetamine users is associated with a neurocognitive phenotype that may impede insight into one's behavior. Specifically, in methamphetamine-dependent participants, denial was negatively associated with overall cognitive function, with the effect particularly driven by performance on tests of memory and executive function. Further, denial was negatively correlated with connectivity strength between the rACC and regions of the frontal lobe (precentral gyri, vmPFC, left OFC), limbic system (left temporal lobe, left amygdala, left hippocampus and left parahippocampal gyrus), occipital cortex and cerebellum; and between the precuneus and the midbrain and cerebellum. These relationships were specific to denial, as the tendency to consider one's substance use potentially problematic and in need of change (Contemplation) was *positively* associated with connectivity between the rACC and precuneus with other cortical regions. Given previous evidence for a role of the rACC and precuneus in self-awareness (see Cavanna and Trimble, 2006; Goldstein et al., 2009), these findings support the hypothesis that some "denial" may reflect a deficit in self-awareness apart from, or in addition to, a conscious or subconscious attempt to minimize one's symptoms (Goldstein et al., 2009).

The finding that denial is associated with a weakness in RSFC of the rACC in methamphetamine-dependent subjects is consistent with a report regarding cocaine users (Moeller et al., 2014), indicating that subjects with low insight into their preferences for emotional and drug-related images had less error-related activation of the rACC during performance of an inhibitory control task, and less gray matter volume in the rACC, than participants with intact insight. The current results suggest that stimulant users with low insight may also exhibit a general weakness in connectivity between the rACC and regions important for decision-making (vPFC, OFC; Mesulam, 2000), memory (hippocampus, parahippocampal gyrus; Mesulam, 2000) and emotional reactivity (amygdala; Mesulam, 2000). Given evidence implicating the role of the rACC in conflict-monitoring and evaluating the personal relevance of stimuli (Moeller and Goldstein, 2014; Nestor et al., 2011; Simoes-Franklin et al., 2010), judgments made by stimulant users with low insight may reflect poorer integration between neural substrates important for detecting inconsistencies and making value-laden decisions. This view supports conceptualizations of error awareness as a manifestation of neural networks working in concert, incorporating specialized modules for attention, motivation, conflict-monitoring and cognitive control (Taylor et al., 2007).

The present findings of a negative relationship between denial and precuneus connectivity with midbrain and cerebellum extend previous evidence for a link between precuneus

activity and self-awareness (Cavanna and Trimble, 2006). It is unclear precisely how this connectivity contributes to awareness of substance abuse problems, but it is noteworthy that the midbrain and cerebellum have both been associated with learning about the difference between actual versus predicted outcomes. The cerebellum has been hypothesized to encode error signals when cognitive events differ from internal predictive models (similar to error detection in motor control; Popa et al., 2014), while dopaminergic neurons in the midbrain have been shown to track differences between predicted versus actual rewards (i.e., prediction error; Tobler et al., 2005). As such, reduced connectivity between the precuneus, cerebellum and midbrain may confer difficulties in adjusting behavior to information, which violates preconceived expectations.

Some of the relationships between denial and RSFC of the rACC and precuneus were attenuated when covarying for years of regular methamphetamine use. The relationships affected included RSFC between rACC and limbic and frontal regions (hippocampus, amygdala, vmPFC, OFC), as well as RSFC between precuneus and midbrain. Independent of denial, years of methamphetamine use was negatively related to strength of RSFC between rACC and the OFC, and between precuneus and midbrain (as well as ventrolateral PFC). It is therefore possible that relationships between denial and RSFC of these regions, in particular, were spurious. Alternatively, it is also possible that toxicity from methamphetamine use led to reduced RSFC of these regions and denial/poor insight, such that the effects are naturally confounded. Such a causal hypothesis has been supported in a study of rodents which found that cocaine administration impaired both function in the OFC and behavioral markers of insight, with insight restored by subsequent normalizing (optogenetic activation) of the OFC (Lucantonio et al., 2014).

RSFC in several regions was negatively related to denial irrespective of methamphetamine use. These relationships included RSFC of rACC with bilateral precentral gyri, bilateral occipital cortex, and right middle frontal gyrus (rMFG); and RSFC of precuneus with regions of cerebellum and brainstem. The persistence of these relationships after controlling for methamphetamine use suggests that weak connectivity between these regions may predate drug abuse and promote denial of drug-related problems after addiction is established. While reduced connectivity with the rMFG may implicate some aspect of decision-making (Cao et al., 2015), it is less immediately clear how connectivity with regions important for vision (occipital lobes; Mesulam, 2000) and motor processing (precentral cortex; Mesulam, 2000) may play a role in denial. Additional research is needed to determine whether these patterns of connectivity play a causal role in denial or alternatively represent epiphenomena.

Reduced connectivity of the rACC and precuneus has been observed in studies of other addictive disorders. For example, compared with healthy control subjects, cocaine users showed weaker RSFC between the rACC and the amygdala, hippocampus, parahippocampal gyrus, insula and temporal cortex (Gu et al., 2010). In another study, cocaine users showed weaker RSFC between the ACC and striatum than controls, and RSFC was negatively associated non-planning impulsivity (Wisner et al., 2013). In addition, subjects with a pathological gambling disorder displayed weaker RSFC between the precuneus and the

default mode network than control subjects, with the strength of RSFC inversely associated with the severity of gambling symptoms (Jung et al., 2014).

A recent study found that Precontemplation scores were associated with larger gray matter volume of the left dorsomedial prefrontal cortex in treatment-seeking cocaine users (Moreno-Lopez et al., 2014). Given that these subjects were treatment-seeking, it would be useful to determine whether the results generalize to non-treatment-seeking individuals, in whom Precontemplation may be more indicative of denial. While few other studies have examined relationships between denial and the brain in addiction, the cortical and limbic regions identified in the current study have been variously associated with other abnormalities in methamphetamine users. Compared to healthy control subjects, methamphetamine-dependent participants have exhibited hypoactivity of the ACC associated with inhibitory control deficits (Nestor et al., 2011), increase in cerebral glucose metabolism in the precuneus during early abstinence (Berman et al., 2007), gray matter deficits in the ACC, OFC, precuneus, amygdala and hippocampus (Morales et al., 2012; Thompson et al., 2004), and aberrant relative glucose metabolism in the ACC, OFC and amygdala associated with inattention and mood disturbances (London et al., 2005; London et al., 2004). Future studies are needed to investigate mechanisms by which these abnormalities may, in isolation or combination, contribute to reduced insight/denial.

Significant relationships between anterior insula connectivity and denial were not identified in this study, despite previous research relating the anterior insula to awareness (Craig, 2009). Notably, parallel results have been obtained from cocaine-dependent participants, in which those with low insight into their behavior did not significantly differ in gray matter volume or error-related activation of the insula, compared with those with intact insight (Moeller et al., 2014). These results may suggest that insight into drug abuse, as measured here, is not largely attributable to insula activity. Alternatively, it is possible that insula activity is more critical for situational aspects of insight (rather than generalized at rest), such as the awareness of interoceptive and external craving cues (see Naqvi et al., 2014).

The results relating denial to cognition in this study extend previous research documenting memory and executive deficits in alcohol-abusing individuals with low insight/denial (Blume et al., 2000; Rinn et al., 2002). Given the relationships between these domains and functioning in multimodal association cortex (PFC, parietal cortex) and limbic regions (e.g., hippocampus) (Strauss, 2006), it is possible that function in some of the structures associated with denial also contribute to reduced cognitive function. However, when overall cognitive function was included as a covariate in analyses, it did not attenuate the relationships with rACC and precuneus connectivity. This suggests that potential neuronal commonalities of denial and cognition may not be evident in the resting state, although they might be evident when participants are placed under task demands.

Limitations of this research should be noted. This study is correlational and cannot determine whether the identified relationships between denial and connectivity are causal in nature, nor whether methamphetamine use has potentially caused poor insight. In addition, the sample size of the RSFC analyses was modest (N=21), and further studies are recommended to help establish the generalizability of the results, particularly as some of the

null findings may be attributable to insufficient power (e.g., anterior insula). Nonetheless, the results suggest that denial in drug abuse may have important neurocognitive correlates, which could potentially influence the effectiveness of behavioral treatments intended to promote awareness and the desire to change drug use behavior.

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Highlights

- It is common for drug abusers to deny having problems with drugs
- In methamphetamine abusers, denial is associated with cognitive dysfunction
- Denial is linked to weaker brain connectivity in regions vital to self-awareness
- The cognitive and neural phenotype of denial may impede insight development

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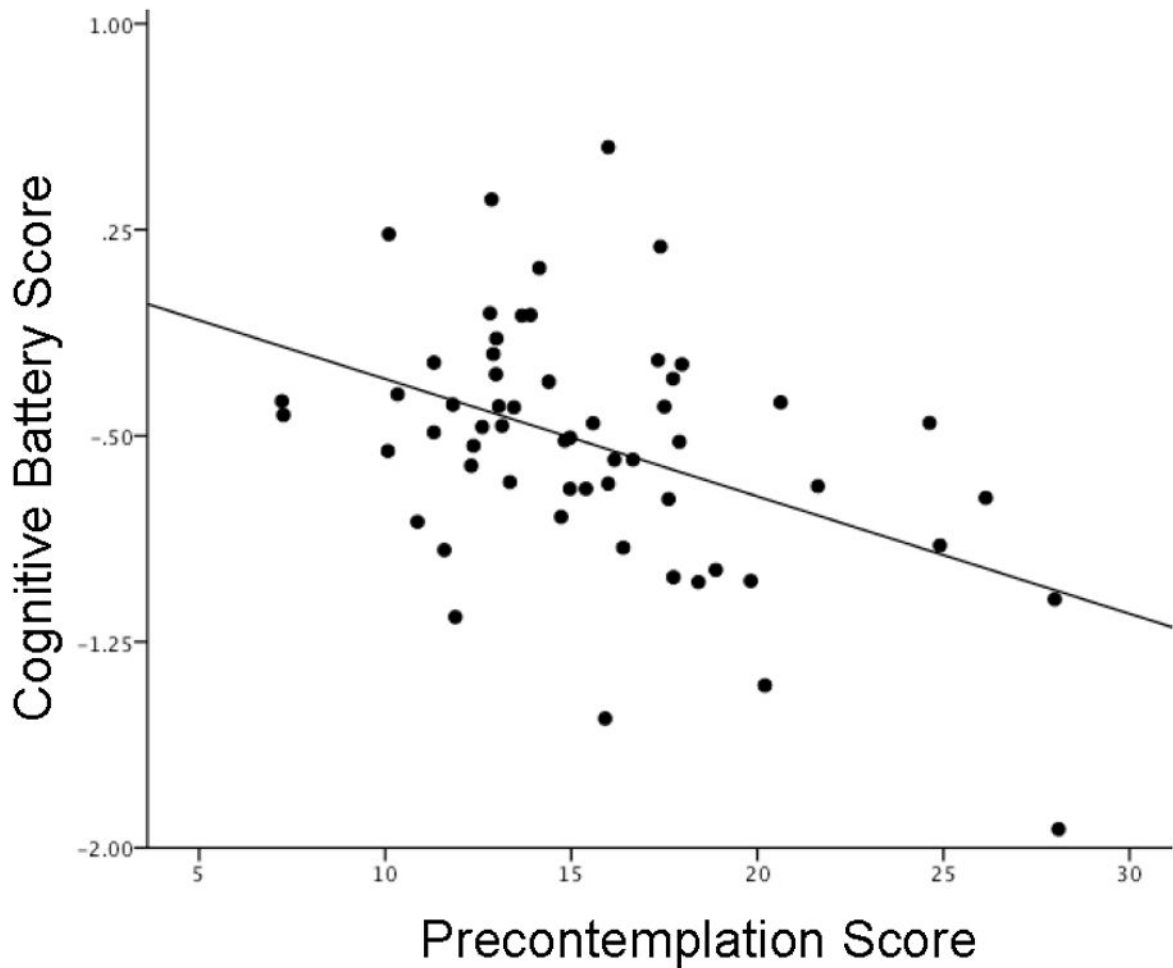


Figure 1.

The relationship between Precontemplation scores and overall cognitive performance in methamphetamine-dependent participants.

Note: $N = 58$. Higher Precontemplation scores reflect greater adamance that one does not have a problem with drug use that requires changing. Overall cognitive scores (z-scores) are normalized to an age-matched healthy control group ($N = 42$), in which higher scores (more positive) reflect better performance. Results and the figure have been adjusted for age, gender, inpatient status and years of education ($p = 0.001$).

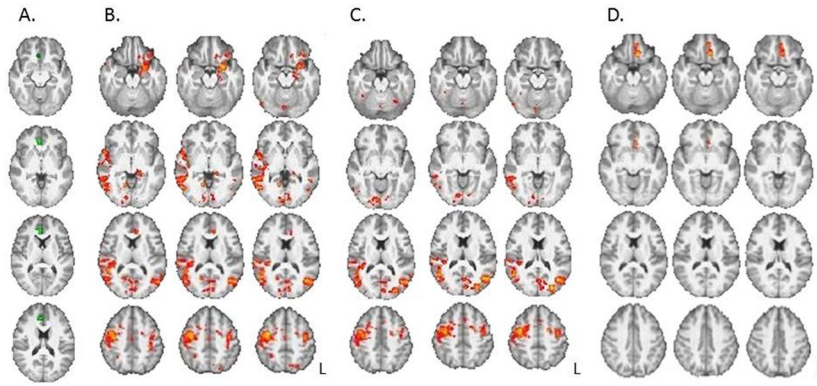


Figure 2.

Relationships between resting-state connectivity strength of the rostral anterior cingulate cortex and Precontemplation scores (B, C) and years of regular methamphetamine use (D). **A.** Rostral anterior cingulate cortex (rACC) seed (in green). **B.** Connectivity maps show negative relationships between Precontemplation scores and connectivity strength between rACC and amygdala, parahippocampal gyrus, medial and lateral orbital frontal cortex, bilateral precentral gyrus, temporal lobe, bilateral occipital cortex and cerebellum. **C.** After covarying for years of regular methamphetamine use, relationships between Precontemplation and connectivity of the rACC were attenuated, with remaining relationships in precentral cortex, occipital cortex and right middle frontal gyrus. **D.** The relationship between connectivity strength of the rACC with years of methamphetamine use, independent of Precontemplation. All results controlled for age, gender, inpatient status and years of education (p 's < 0.016 , whole-brain cluster corrected). L = left hemisphere.

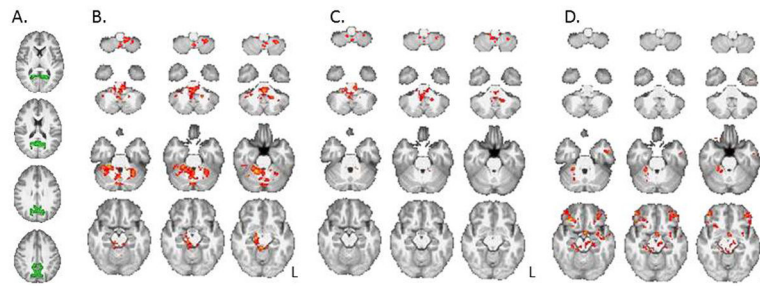


Figure 3. Relationships between resting-state connectivity strength of the precuneus and Precontemplation scores (B, C) and years of regular methamphetamine use (D). **A.** Precuneus seed (in green). **B.** Negative relationships between Precontemplation scores and connectivity strength between the precuneus and midbrain, brainstem and cerebellum. **C.** After covarying for years of regular methamphetamine use, relationships between Precontemplation and connectivity of the precunues were attenuated, with remaining relationships in cerebellum and brainstem. **D.** The relationship between connectivity strength of the precuneus with years of methamphetamine use, independent of Precontemplation. All results controlled for age, gender, inpatient status and years of education (p 's < 0.016, whole-brain cluster corrected). L = left hemisphere.

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.

Table 2

Connectivity of brain regions related to Precontemplation scores

Brain region	Cluster size (voxels)	X ^a	y	z	Z statistic
<i>Rostral Anterior Cingulate Seed</i>					
Cluster #1^b	5843				
† Precentral Gyrus (R)	38	-6	60	4.08	
† Middle frontal Gyrus (R)	38	12	28	2.61	
Cluster #2	2396				
Lingual Gyrus (R)	14	-58	0	4.11	
† Occipital Cortex (R/L)	58	-64	-4	3.83	
† Middle Temporal Gyrus (L)	-52	-48	0	3.02	
Cluster #3	906				
†† Precentral Gyrus (L)	-40	-14	52	3.52	
Postcentral Gyrus (L)	-36	-32	44	3.16	
Cluster #4	841				
Amygdala (L)	-22	-2	-18	4.21	
Hippocampus (L)	-14	-10	-26	3.57	
Parahippocampal Gyrus	-14	-34	-6	3.24	
Ventromedial PFC	-12	26	-18	3.01	
Orbital Frontal Cortex	-28	18	-26	3.00	
Cluster #5	603				
†† Cerebellum	28	-64	-54	3.28	
Cluster #6	602				
†† Anterior Cingulate Cortex	12	16	34	3.35	
<i>Precuneus Seed</i>					
Cluster #1	3329				
† Cerebellum	16	-46	-24	3.95	
Brainstem/Midbrain	12	-20	-14	3.76	
† Brainstem/Pons	0	-36	-40	3.56	

Z-statistic maps were thresholded using cluster-corrected statistics with a height-threshold of $Z > 2.3$ and cluster-forming threshold of $p < 0.016$, covariates include age, sex, years of education and inpatient status.

^a x, y, z reflect coordinates for peak voxel or for other local maxima in MNI space.

^b Clusters are numbered and presented in order of decreasing size.

[†] Regions that remained significant after controlling for years of regular methamphetamine use.

^{††} Regions extending beyond original cluster after controlling for years of methamphetamine use.