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You are the danger: Attenuated insula response in methamphetamine users during aversive interoceptive decision-making☆

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ABSTRACT

Background: Drug dependent individuals often make drug-taking decisions when they do not feel well. Yet, few studies have examined the influence of an aversive state on decision-making related neural processing.
Methods: We investigate brain activation to decision-making during an aversive interoceptive challenge in methamphetamine users using functional magnetic resonance imaging (fMRI). Recently abstinent inpatients with methamphetamine use disorder (METH; $n=20$) and healthy comparison subjects (CTL; $n=22$) performed a two-choice prediction task at three fixed error rates (ER; 20% = reward, 50% = uncertainty, 80% = punishment) while anticipating and experiencing episodes of inspiratory breathing load during fMRI.
Results: METH exhibited higher trait anxiety in conjunction with lower anterior insula (AI) and inferior frontal gyrus (IFG) activation than CTL across trials. METH also showed lower posterior insula (PI) and anterior cingulate cortex (ACC) activation than CTL during breathing load independent of ER. For the crucial ER by interoception interaction, METH displayed lower ACC activation to punishment/loss than CTL during breathing load. Within METH, lower trait anxiety was linked to AI/IFG attenuation across trials.
Conclusions: AI/IFG attenuations in METH are suggestive of an executive functioning deficit, particularly in users with low anxiety, reflecting reduced resources allocated to choice selection. In contrast, PI/ACC reductions in METH appear specific to impairments in registering and evaluating interoceptive experiences. Taken together, inadequate activation of brain areas that are important for regulating when one does not feel well may be the neural basis for poor decision-making by METH.

1. Introduction

Methamphetamine addiction constitutes a major public health issue, linked to cardiac, pulmonary, and neurological impairments, heightened depression and anxiety, compromised decision-making, and poor quality of life (Gonzales et al., 2010). Identifying components of neural, behavioral, physiological, and experiential systems that are compromised in methamphetamine dependent individuals (METH) can facilitate innovative treatment interventions to reduce future harm to the individual and society (Shoptaw, 2014). The study of interoception, the physiological condition of the body (Craig, 2003), may aid in the search for markers of impairment. Brain regions involved in interoception may be dysregulated in addiction, contributing to the maintenance, escalation, and/or relapse of substance use (Gray and Critchley, 2007; Naqvi and Bechara, 2010; Paulus et al., 2009; Stewart and Paulus, 2013; Verdejo-Garcia et al., 2012).

Addiction may reflect a discrepancy between an individual's predicted versus actual internal state known as the bodily prediction error, an imbalance that could in turn adversely influence the degree of future drug-related approach versus avoidance behavior (Paulus and Stewart, 2014; Paulus et al., 2009). Researchers assert that the insular cortex coordinates with other brain regions to

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process and integrate somatosensory feeling states in order to guide future decisions (Bechara, 2005; Damasio et al., 1996). It has been argued (Blomqvist et al., 2000; Craig, 2003, 2014; Damasio and Carvalho, 2013) that thalamic regions deliver sensory information to posterior insula (PI) and then to anterior insula (AI), resulting in bodily feeling states that are registered by anterior cingulate cortex (ACC), initiating motivated action to regain internal homeostasis and minimize bodily prediction error (Critchley et al., 2004). METH may possess inadequate function in this relay system in response to bodily signals, which limits engagement in adaptive behavior (Paulus and Stewart, 2014).

Decision-making may be impaired in METH, particularly during conditions of interoceptive distress. Therefore, it is critical to understand the interaction between compromised interoception and cognitive control systems involving regions of the prefrontal cortex (PFC) and how this may lead to suboptimal decision-making in METH (e.g., using drugs despite negative outcomes). METH exhibit lower thalamic, AI and PFC activation than healthy comparison subjects (CTL) while making decisions within the context of pleasant interoceptive touch via soft bristle brush (May et al., 2013). Although no studies have examined decision-making in METH during the experience of aversive interoceptive stimuli, young adults transitioning to stimulant dependence exhibit lower thalamic, ACC, and PFC activation than stimulant-naïve CTL while making choices during an aversive inspiratory breathing load (Stewart et al., 2013). Moreover, AI, ACC, and PFC hypoactivations are often linked to aversive outcomes in METH. For instance, METH display lower ACC activation than CTL in response to losses (Gowin et al., 2014b). Attenuated AI activation during risky behavior with a potential for high loss also predicts future relapse in recently abstinent METH (Gowin et al., 2014a). AI and ACC hypoactivations are both linked to heightened error rates (ER) in METH (London et al., 2005). METH also exhibit lower AI, ACC, and PFC activation than CTL in situations of response conflict (Nestor et al., 2011; Salo et al., 2012) as well as AI and PFC reductions to aversive images of human suffering (Kim et al., 2011). Taken together, findings support the hypothesis that METH may not process negative consequences of drug use as prediction errors to correct and optimize future behavior (Shoptaw, 2014). This prediction is consistent with a more general deficit in METH showing attenuated PFC activation when making decisions within the context of all types of feedback—rewarding, uncertain, and punishing outcomes (Paulus et al., 2003, 2005). Therefore, METH may exhibit a general neural processing deficit characterized by reduced resources devoted to the integration of decision–outcome contingencies. In other words, for METH an aversive outcome does not necessarily result in corrective behavior.

Although METH is linked to impaired decision-making, individual differences in comorbid psychopathology, particularly anxiety, adversely impact treatment outcomes in METH (Glasner-Edwards et al., 2010). Anxiety symptoms, often heightened in METH (Gonzales et al., 2010; London et al., 2004; Salo et al., 2011), are linked to greater AI activation to aversive stimuli and risky decisions (Hartley and Phelps, 2012; Paulus and Stein, 2010; Simmons et al., 2011; Stein et al., 2007). These findings are suggestive of heightened prediction error in high anxious individuals, in direct contrast with attenuated prediction error predicted for METH. Individual differences in anxiety symptoms may moderate the neural responses of METH to interoceptive contexts, which might lead to differential relapse prevention strategies as a function of stress responses in METH.

The present study examined these issues by utilizing functional magnetic resonance imaging (fMRI) to compare neural mechanisms of decision-making during an aversive interoceptive manipulation in METH and CTL. A two-choice prediction task with varying types of feedback (20%, 50%, and 80% ERs) was employed to examine decision-making in response to rewarding, uncertain, and punishing outcomes, respectively. In addition, an inspiratory breathing load shown to activate AI and PFC during decision-making was used as an aversive interoceptive manipulation during the two-choice prediction task (Paulus et al., 2012; Stewart et al., 2013). Breathing physiology (carbon dioxide levels), behavioral performance, and subjective experience of the aversive manipulation were also measured to examine multiple facets of interoceptive processing. Furthermore, measures of emotion and personality were collected to examine individual differences in neural interoceptive processing within METH. Of interest was whether anxiety moderated AI activation within the context of aversive stimuli in METH, given that heightened anxiety has previously been linked to exaggerated AI responses to threat (Paulus and Stein, 2006).

Three hypotheses were tested in the present investigation: compared to CTL, we predicted that METH would exhibit: (1) lower PFC activation across all trials, suggestive of reduced resource allocation for executive functions more generally (Paulus et al., 2003, 2002); (2) lower thalamic and AI activation in response to the aversive breathing load manipulation, consistent with prior work showing neural attenuations in METH within the context of pleasant interoceptive stimuli (May et al., 2013); and (3) lower AI and ACC activation during the aversive interoceptive condition specifically within the context of punishment (80% ER and high losses), in line with studies showing links between attenuated AI/ACC with losses, errors, and response conflict in METH (Gowin et al., 2014a,b; London et al., 2005; Nestor et al., 2011; Salo et al., 2012).

2. Methods

2.1. Subject recruitment

The study protocol was approved by the local Human Subjects Review Board and individuals gave written informed consent prior to enrollment. METH were recruited from the inpatient Veterans Administration Alcohol and Drug Treatment Program and local recovery homes. CTL were recruited from posted fliers and internet advertisements. Individuals were phone-screened to rule out: (1) left-handedness, assessed by the Edinburgh Handedness Inventory (Oldfield, 1971); (2) fMRI contraindications (e.g., irremovable metal; pregnancy; claustrophobia); (3) traumatic head injury and loss of consciousness >5 m. Individuals who passed the phone screen were scheduled for an interview.

2.2. Clinical interview session

Participants completed a urine screen, questionnaires, and the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA; Pierucci-Lagha et al., 2005) to determine presence of DSM-V Axis I disorders, Axis II antisocial personality disorder (ASPD), and lifetime substance use. Experimenters administered the wide range achievement test (WRAT-4) to obtain verbal intelligence quotient (IQ; Wilkinson and Robertson, 2006). Subjects completed personality and symptom assessment questionnaires known to correlate with substance use disorders, including the sensation seeking scale (SSS; Zuckerman, 2007), the Barratt impulsiveness scale (BIS; Patton et al., 1995), the Beck Depression Inventory II (BDI-II; Beck et al., 1996), and the State-Trait Anxiety Inventory (STAI) trait anxiety subscale (Spielberger et al., 1983). To assess trait interoceptive responses and coping responses to stressful events, participants completed the Body Awareness Questionnaire (BAQ; Shields et al., 1989) and the COPE scale (Carver and Scheier, 1989), respectively.

Individuals were excluded from either group if they met criteria for: (1) lifetime schizophrenia, bipolar disorder, or obsessive compulsive disorder; (2) current (past six months) anxiety disorders or unipolar depression; (3) diagnosed neurological disorders; (4) ASPD; and (5) a positive urine toxicology test. METH were required to be in treatment, between 15 and 120 days sober (M = 45.47; SD = 19.76; range = 16–91; n = 1 missing data). No METH reported symptoms of withdrawal. CTL could not meet criteria for lifetime substance use disorder. Upon consensus review of diagnoses confirmed by a psychiatrist (M.P.P.), eligible participants were scheduled for the neuroimaging session.

The final cohort (Table 1) consisted of 42 participants (n = 20 METH; n = 22 CTL). All METH met criteria for current DSM-V methamphetamine use disorder. Some METH met criteria for comorbid current DSM-V use disorders: (1) alcohol (n = 8); (2) cocaine (n = 2); (3) marijuana (n = 2); (4) opiate (n = 2) (n = 2 METH had missing diagnosis sheets and were unable to be categorized). On average, METH reported 15,967.26 lifetime sessions of methamphetamine use (SD = 18,941.32; range = 414–74,310) and began using methamphetamine at 22