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Hyperactivation to pleasant interoceptive stimuli characterizes the transition to stimulant addiction☆

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ABSTRACT

Aims: Altered interoception, how the brain processes afferents from the body, may contribute to the urge to take drugs, and subsequently, the development of addiction. Although chronic stimulant dependent individuals exhibit attenuated brain responses to pleasant interoceptive stimuli, it is unclear whether this deficit exists early-on in the process of transition to stimulant addiction.
Methods: To this end, we compared problem stimulant users (PSU; $n = 18$), desisted stimulant users (DSU; $n = 15$), and stimulant naïve comparison subjects (CTL; $n = 15$) during functional magnetic resonance imaging (fMRI) while they anticipated and experienced pleasant soft touch (slow brushstroke to the palm and forearm).
Results: Groups did not differ in behavioral performance or visual analog scale ratings of soft touch stimuli. fMRI results indicated that PSU exhibited greater right anterior insula, left inferior frontal gyrus, and right superior frontal gyrus activation than DSU and CTL during the anticipation and experience of soft touch. Moreover, during the experience of soft touch, PSU demonstrated higher bilateral precentral gyrus/middle insula and right posterior temporal gyrus activation than DSU and CTL.
Conclusions: In contrast to chronic stimulant dependence, individuals who have recently developed stimulant use disorders show exaggerated neural processing of pleasant interoceptive stimuli. Thus, increased processing of body-relevant information signaling pleasant touch in those individuals who develop problem use may be a predictive interoceptive biomarker. However, future investigations will need to determine whether the combination of probing pleasant interoception using neuroimaging is sufficiently sensitive and specific to help identify individuals at high risk for future problem use.

1. Introduction

Of the one million people who use cocaine and amphetamine recreationally (SAMHSA, 2012), about 20% progress to stimulant dependence (Lopez-Quintero et al., 2011). Although researchers have identified neural substrates linked to chronic addiction (Goldstein and Volkow, 2011; Koob and Le Moal, 2005), identifying brain mechanisms altered during the transition to stimulant addiction is also important for the development of early intervention strategies.

Interoception, the processing and integration of afferent signals from inside the body in response to both internal and external stimuli, has been implicated in addiction (Craig, 2002; Naqvi and Bechara, 2010; Paulus et al., 2009; Verdejo-Garcia and Bechara, 2009). Chronic users may experience attenuated bodily signals to external natural rewards and aversive/stressful events (Paulus and Stewart, 2014; Verdejo-Garcia et al., 2012), reflecting reduced insular cortex function (Craig, 2002). While middle/posterior insula (MI/PI) receives somatosensory activity from thalamocortical pathways, anterior insula (AI) integrates this information with emotionally salient activity to produce a bodily prediction error, motivating fronto-cingulate mechanisms to eliminate homeostatic imbalances (Craig, 2002, 2009; Paulus et al., 2009). An individual's degree to approach or avoid a stimulus, including drugs of abuse, may result from this error (Paulus et al., 2009), the difference between an experienced versus expected internal state. When considering drug consumption, individuals with substance use disorders may not appropriately engage insular cortex

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to signal potential aversive outcomes. Instead, these individuals might derive incentive motivation from anticipation of pleasant states. In comparison, others have proposed that decreased striatal responses to natural rewards (Everitt and Robbins, 2005; Kelley and Berridge, 2002; Volkow et al., 2010) in conjunction with attenuated insular processing may result in drug-seeking to maintain perceived bodily homeostasis.

To explore compromised neural mechanisms of addiction, our lab has employed a Soft Touch paradigm, wherein participants anticipate and receive soft brush strokes to the forearm and palm during functional magnetic resonance imaging (fMRI; May et al., 2013; Migliorini et al., 2013). Gentle slow brushstrokes along forearm/palm skin, rated as subjectively pleasant, are detected by afferent fibers projecting to insular cortex (Bjornsdotter et al., 2010; Gordon et al., 2013; Löken et al., 2009, 2011). Chronic methamphetamine dependent adults exhibit lower AI and dorsal striatum activation than controls while anticipating and experiencing Soft Touch (May et al., 2013), results consistent with the notion that chronic addiction is associated with attenuated neural processing of non-drug related pleasant interoceptive feeling states. In contrast, during the experience of Soft Touch, adolescents with current alcohol/marijuana use disorders display lower PI activation in conjunction with greater AI and ventral striatum activation than controls, indicating reduced somatovisceral processing, but heightened emotional feeling states and reward sensitivity, respectively (Migliorini et al., 2013). These studies suggest that interoceptive processing dysfunctions may not be stable during the clinical course of addiction. Instead, drug-using individuals may transition from a primary positive reinforcement mechanism (seeking pleasant experiences) to a negative reinforcement mechanism (avoidance of aversive experiences; Koob and Le Moal, 2005) together with compulsive use patterns (Everitt and Robbins, 2005).

Although a substantial literature has described the nature of striatal changes as a function of addiction development (Chambers et al., 2003; Everitt and Robbins, 2013; Volkow et al., 2012), less is known about how/why insular regions change as a function of substance use. Moreover, research is warranted to clarify whether altered insular/striatal activations to pleasant interoceptive stimuli are a function of the type of drug used, indicators of a general predisposition to experiment with drugs, or markers of problem use. The present study examined these issues by recruiting an initial cohort of young adult recreational stimulant users who, three years later, either progressed to problem stimulant use (PSU) or desisted stimulant use (DSU). Groups were matched with stimulant-naïve healthy comparison subjects (CTL). Participants completed the Soft Touch paradigm during fMRI. We hypothesized that PSU would exhibit greater AI and striatum activation than DSU and CTL during the experience of Soft Touch, consistent with prior work in adolescents with recent-onset alcohol/marijuana substance use disorders (Migliorini et al., 2013), as opposed to insular/striatal attenuation evident in chronic stimulant users (May et al., 2013).

2. Methods

2.1. Participants

The study protocol was approved by the University of California, San Diego Human Research Protections Program and was carried out in accordance with the Declaration of Helsinki. All subjects provided written informed consent. Recreational, non-dependent stimulant users were recruited and defined by methods described in previous studies (Reske et al., 2011; Stewart et al., 2013). Among this original cohort ($n = 184$), users were contacted three years after their initial lab visit (93% follow-up rate: 171 followed up; 10 unreachable; 3 refused to participate). Each user underwent a standardized three-year follow-up interview to examine extent of interim drug use, allowing us to identify participants who developed problems associated with stimulant use and others who had desisted using. Thus, two stimulant user groups were formed for the present study, termed problem stimulant users (PSU) and desisted stimulant users (DSU). Of the 171 participants who completed the three-year follow-up protocol, 38 met criteria for the PSU group, whereas 83 met criteria for the DSU group. Table S1 demonstrates that PSU who consented to participate in the present study ($n = 18$) possessed greater years of education at the initial visit than PSU who did not participate ($n = 20$). Table S2 indicates that DSU who consented to participate ($n = 15$) reported a greater number of cocaine uses at the initial visit than DSU who were not enrolled in this study ($n = 68$). Otherwise, stimulant users who were enrolled in the present study did not differ in demographic or initial visit drug use variables from those who were not enrolled.

PSU were a priori defined by (1) continued stimulant (dextroamphetamine, cocaine, methylphenidate) use since the initial visit and (2) endorsement of 2+ DSM-IV (American Psychiatric Association, 2000) criteria of stimulant abuse or dependence as determined by the Semi Structured Assessment for the Genetics of Alcoholism II (SSAGA II; Bucholz et al., 1994) occurring together ≥ 6 contiguous months since the initial visit ($M = 4.83$ criteria; $SD = 1.98$; range: 2–8). Within PSU, 56% met criteria for cocaine abuse, 50% met criteria for amphetamine abuse, 28% met criteria of cocaine dependence, and 33% met criteria for amphetamine dependence. DSU were defined as having (1) no 6-month periods of 6+ stimulant uses and (2) no stimulant abuse/dependence or other substance dependence in the interim three-year period. Stimulant-naïve CTL were recruited from the general population and endorsed no lifetime substance dependence (see Fig. S1 for schematic overview). No participants were current regular nicotine smokers.

The final cohort consisted of 18 PSU (9 female), 15 DSU (6 female), and 15 CTL (7 female), all right handed (Edinburgh Handedness Inventory; Oldfield, 1971). At the time of the three-year follow-up interview, participants were in their mid-twenties ($M = 24.47$ years, $SD = 1.64$) with three years of college education ($M = 15.72$ years, $SD = 1.17$). Groups were matched on age, education, gender, and ethnicity (see Table S3). Groups did not differ on percentage of participants meeting criteria for alcohol abuse (PSU = 61%, DSU = 47%, CTL = 27%; $\chi^2(2) = 3.92$, $p = .14$), alcohol dependence (PSU = 17%, DSU = 7%, CTL = 0%; $\chi^2(2) = 3.06$, $p = .21$), or marijuana dependence (PSU = 17%, DSU = 0%, CTL = 0%; $\chi^2(2) = 5.33$, $p = .07$). However, a higher percentage of PSU and DSU met criteria for marijuana abuse than CTL (PSU = 56%, DSU = 67%, CTL = 7%; $\chi^2(2) = 12.60$, $p = .002$), although PSU and DSU did not differ from each other. Participants completed two more sessions: (1) clinical interview; and (2) fMRI Soft Touch paradigm.

2.2. Clinical interview session

Interviewers administered the SSAGA II and diagnoses were based on consensus meetings (clinicians and trained study personnel). Exclusion criteria for all groups were: (1) metal/other factors precluding fMRI; (2) head injuries or loss of consciousness >5 min; (3) medication for any psychiatric disorder (past 3 years); (4) diagnosed neurological disorder; (5) lifetime psychosis or antisocial personality disorder; (6) current and/or past six month episodes of anxiety disorders or unipolar depression; and (7) positive urine toxicology screen for substances other than marijuana (given that marijuana is present in urine up to six weeks after use).

The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was administered to obtain verbal intelligence quotient (IQ). Personality constructs known to correlate with substance use disorders were administered, including the Sensation Seeking Scale (SSS; Zuckerman, 2007), Barratt Impulsiveness Scale (Barratt and Patton, 1983), State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983), and Beck Depression Inventory II (BDI-II; Beck et al., 1996). Baseline visit/interim stimulant and marijuana uses were calculated for PSU and DSU based on the number of sessions each substance was used. Baseline visit uses consisted of cumulative drug sessions up until that visit, whereas interim uses consisted of only drug sessions completed during the time of the baseline visit until the time of the three-year follow-up interview.

2.3. fMRI session

2.3.1. Urine testing. Subjects were asked to abstain from drugs for 72 h. Twelve subjects tested positive for marijuana ($n = 7$ PSU; $n = 5$ DSU; PSU and DSU did not differ in number of subjects testing positive: $\chi^2(1) = .11$, $p = .74$). No participants tested positive for any other substance.

2.3.2. Soft Touch stimulus. Trained research assistants used a hand held soft boar bristle brush (OXO International Ltd., NY) on pre-measured and marked 4 cm long regions of skin on the ventral surface of the left forearm and palm (Löken et al., 2009; Olausson et al., 2000; Vallbo et al., 1993). Each brush stroke was performed at a velocity of 2 cm/s in a proximal to distal direction with a force equal to the weight of the brush.

2.3.3. Soft Touch paradigm. Participants engaged in a continuous performance task (CPT) with cued stimulus presentation designed to focus attention on visual stimuli while maintaining a stable cognitive load. This task was chosen to keep participants engaged while not being too complex that it would distract from external stimuli. A screen presented a left or right black arrow surrounded by a colored rectangle in successive 3 s intervals (see Fig. 1A). Subjects responded to the arrow orientation by pressing a left or right button. The arrow remained on the screen for the entire 3 s during which a button could be pressed at any time. Colored rectangle backgrounds signified one of three conditions: (1) *baseline* (gray) during which no tactile stimulus was expected or administered (variable duration averaging 9 s: three

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