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Cocaine-conditioned odor cues without chronic exposure: Implications for the development of addiction vulnerability

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ABSTRACT

Adolescents are highly vulnerable to addiction and are four times more likely to become addicted at first exposure than at any other age. The dopamine D1 receptor, which is typically overexpressed in the normal adolescent prefrontal cortex, is involved in drug cue responses and is associated with relapse in animal models. In human drug addicts, imaging methods have detected increased activation in response to drug cues in reward- and habit-associated brain regions. These same methods can be applied more quantitatively to rodent models. Here, changes in neuronal activation in response to cocaine-conditioned cues were observed using functional magnetic resonance imaging in juvenile rats that were made to over-express either D1 receptors or green fluorescent protein by viral-mediated transduction. Reduced activation was observed in the amygdala and dopamine cell body regions in the low cue-preferring/control juvenile rats in response to cocaine cues. In contrast, increased activation was observed in the dorsal striatum, nucleus accumbens, prefrontal cortex, and dopamine cell bodies in high cue-preferring/D1 juveniles. The increase in cue salience that is mediated by increased D1 receptor density, rather than excessive cocaine experience, appears to underlie the transition from aversion to reward in cue-induced neural response and may form the basis for habit-forming vulnerability.

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1. Introduction

The neural networks that underlie reward valuation and goal-directed behavior involve prefrontal cortex (PFC) innervation to the nucleus accumbens (NAc) (Griffiths et al., 2014). More specifically, D1 receptors on prelimbic PFC (plPFC) inputs to the NAc core modulate cocaine self-administration and reinstatement associated with relapse (McFarland et al., 2004; McLaughlin and See, 2003; Olsen and Duvauchelle, 2006; Rebec and Sun, 2005). D1 receptor over-expression naturally occurs without drug exposure during adolescent development (Brenhouse et al., 2008). Adolescent rats (postnatal day 44) have 4-fold higher expression of D1 receptors on plPFC glutamate neurons projecting to the NAc relative to juvenile (postnatal day 27) and adult (>90 days) rats (Brenhouse et al., 2008). This over-expression of D1 may render adolescents more vulnerable to drug-associated cues that are linked to addictive processes (Kalivas et al., 2005). Similar over-expression of D1 mRNA has been observed in human PFC during adolescence (Rothmond et al., 2012), suggesting that similar processes exist between rat and human development. Typical adolescent rats both take more cocaine (Wong et al., 2013) and show increased place preferences to cocaine-associated cues than adults (Badanich et al., 2006; Brenhouse et al., 2008); these adolescent preferences are reversible with plPFC microinjections of the D1 antagonist SCH-23390 (Brenhouse et al., 2008). To further confirm the role of D1 in adolescent responses to cocaine, we developed a lentiviral vector that over-expresses D1 receptors on glutamate neurons to approximate adolescent levels in adult rats. Behaviorally, adult rats that over-express D1 on glutamate neurons take more cocaine and show increased place preferences to cocaine-associated cues relative to control rats expressing green fluorescent protein (GFP) (Sonntag et al., 2014).

Magnetic resonance imaging (MRI) in rats provides a translational opportunity to assess brain function because this approach offers similar assessment methods to those used in humans. Blood oxygenation

Abbreviations: BLA, basolateral amygdala; BOLD, blood oxygenation level determination; DSTR, dorsal striatum; fMRI, functional magnetic resonance imaging; NAc, nucleus accumbens; PFC, prefrontal cortex; pharmacoMRI, pharmacological magnetic resonance imaging; ROI, region of interest; SNc/r, substantia nigra pars compacta/reticulata; VTA, ventral tegmental area.

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level dependent (BOLD) scans have been used to study activation patterns in response to drug-associated cues in adult humans and in animals. In human cocaine addicts, drug cues consistently increase BOLD responses in the striatum (STR), basolateral amygdala (BLA), ventral tegmental area, anterior and prefrontal cortex (PFC), hippocampus, and nucleus accumbens (NAc) (Garavan et al., 2000; Grusser et al., 2004; Jasinska et al., 2014; Lukas et al., 2013; Maas et al., 1998). With repeated and uncontrollable drug use, dorsal striatal responses to drug cues are elevated (Dalley et al., 2011; Volkow et al., 2006). Functional MRI (fMRI) responses in adult rodents exposed to drug-associated cues following chronic cocaine intake show remarkable anatomical faithfulness to these human fMRI changes (Johnson et al., 2013; Liu et al., 2013a). Because these responses are both reliable and robust, genetically modified animals could provide mechanistic insight into the underlying pharmacological basis for cue responses at the network level.

Imaging paradigms in small animals have been developed to determine structural and functional changes (reviewed by Febo, 2011), with the latter including indirect measures of BOLD (Huang et al., 2011), receptor expression/function with pharmacoMRI (Becerra et al., 2013; Chen et al., 2005), and more recently, resting state activation (Tian et al., 2006). These methodologies can be applied in normal, drug-exposed (Andersen et al., 2008; Reneman et al., 2001; van der Marel et al., 2014) or genetically-modified (e.g., Huang et al., 2011) animals and used to observe network changes in brain activity (discussed by Borsook et al., 2006).

To date, however, the majority of these applications have been restricted primarily to analyses with the region of interest (ROI) approach and not voxel-wise methodologies. Our first goal was to use whole brain, voxel-wise analysis in rats to reveal unexpected BOLD responses to cocaine-associated cues. Furthermore, its application in animals that have a genetic over-expression of D1 receptors in the plPFC produces a behavioral phenotype of animals that show reinstated responses to cocaine (McFarland et al., 2004). Developmental, preclinical imaging studies (Bouet et al., 2012; Chen et al., 2010; van der Marel et al., 2014) have utilized a region-of-interest (ROI) analytical approach, and not the voxel-wise, whole brain analysis that is commonly used in human studies. BOLD responses in juvenile control rats (with a lentiviral vector expressing GFP) that typically have low preferences for cocaine-associated environments and D1 expression on plPFC neurons (Brenhouse et al., 2008), may reveal brain regions involved in reduced addiction vulnerability. In this sense, a secondary goal of this study was to determine how a precocial increase in plPFC D1 receptors in pre-adolescent rats may be related to the increased vulnerability to use drugs of abuse that occurs during adolescence (Stanis and Andersen, 2014).

The current study used fMRI to determine how D1 dopamine receptor over-expression within the plPFC uniquely impacts widespread responses to cocaine-associated cues in a developmental context. Specifically, we compared the cue-based BOLD response in juvenile animals that showed minimum behavioral preferences for cocaine-associated environments and cues to the response in juveniles that over-expressed D1 by viral-mediated transfer. This approach allowed us to determine the responsiveness within neural circuitry that is key in the transition between low and high risk for addiction. The current study is the first to use whole brain voxel-wise BOLD responses to cocaine-conditioned cues in immature animals manipulated for low and high salience with only two exposures to cocaine; previous animal studies used a region of analysis approach (Johnson et al., 2013; Liu et al., 2013a) in animals chronically exposed to cocaine.

2. Materials and methods

2.1. Subjects

Sprague-Dawley litters of rats (n = 8 for each group) were obtained from Charles River Laboratories (Boston, MA) at 12 postnatal days of age (P12); only male pups were used, with one pup per litter for each condition. Pups were P16 at the time of surgery. Pups were weaned from the dam at P21 and housed with same-sex littermates. Rats were housed with food and water available ad libitum in constant temperature and humidity conditions on a 12-hr light/dark cycle (light period 0700–1900). The experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (NIH), and were approved by the Institutional Animal Care and Use Committee at McLean Hospital.

2.2. Lentiviral injections

Male rats were anesthetized with a ketamine/xylazine mixture (80/12 mg/kg, respectively). A lentiviral vector (0.6 μL) that targets glutamate neurons by the Calmodulin Kinase II alpha [CK] promoter and expresses either green fluorescent protein (CK.GFP) or D1 dopamine receptors (CK.D1) was produced by the Massachusetts General Hospital Vector Core (Sonntag et al., 2014). Approximately 10^6 transducing units were injected bilaterally into the prelimbic PFC at stereotaxic coordinates (AP: +2.7, ML: 0.5; DV: −2.7) for P16 rats (Sherwood and Timeras, 1970). Screening for place preferences to cocaine-associated cues began 8 days after surgery to allow for viral expression (Fig. 1a). Expression stability and placement were confirmed by histology (Sonntag et al., 2014) within the plPFC (Fig. 1c shows GFP or D1 expression) or the subjects were excluded from analysis.

2.3. Odorant presentation

Place conditioning chambers had a custom built olfactometer (Lowen and Lukas, 2006) that bubbled filtered room air through two flasks, one containing phenethyl alcohol ("rose" scent), and the other acetophenone ("almond" scent) at a final flow rate of 10 mL/min for each odorant. All tubing throughout was PTFE to minimize stray odors. Each side chamber had an odorant presented into one corner and vented through the opposite corner using the laboratory vacuum system; the side chambers were kept at negative pressure to prevent odor mixing.

2.4. Place conditioning

An unbiased place conditioning protocol was used to establish behavioral preferences or aversions to cocaine cues, as previously published (Andersen et al., 2002). Other operant paradigms, including self-administration, are not suitable for developmental studies in subjects this young because they require extensive training. Briefly, separate groups of juvenile rats (P24) were habituated to the 3-chambered apparatus (Med Associates, St. Albans, VT) for 30 min on Day 1 to establish no baseline preferences for odor-associated environments (defined as spending >18 of 30 min on one side). Initially, these chambers differed by color (black, gray, white), and floor (grid, smooth, and bars). On Days 2 and 3, a 60-minute cue conditioning session was conducted to saline in the morning (where the odor becomes a conditioned stimulus that predicts "no drug" [CS−]) and 10 mg/kg cocaine in the afternoon (a CS odor that predicts drug [CS+]). The 10 mg/kg dose of cocaine was selected because juvenile rats typically do not show place preferences for environments associated with this dose (Brenhouse et al., 2008). The pairing of odor–drug conditions was randomized within group. On Day 4 rats were permitted to freely explore the entire apparatus for 30 min in a drug-free state to determine behavioral preferences to drug-conditioned odor/environments. Place conditioning scores are expressed as time spent on the drug side − time spent on the saline side (in s) on test day.

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