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Monoamine polygenic liability in health and cocaine dependence: Imaging genetics study of aversive processing and associations with depression symptomatology☆

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ABSTRACT

Background: Gene polymorphisms that affect serotonin signaling modulate reactivity to salient stimuli and risk for emotional disturbances. Here, we hypothesized that these serotonin genes, which have been primarily explored in depressive disorders, could also have important implications for drug addiction, with the potential to reveal important insights into drug symptomatology, severity, and/or possible sequelae such as dysphoria.
Methods: Using an imaging genetics approach, the current study tested in 62 cocaine abusers and 57 healthy controls the separate and combined effects of variations in the serotonin transporter (5-*HTTLPR*) and monoamine oxidase A (*MAOA*) genes on processing of aversive information. Reactivity to standardized unpleasant images was indexed by a psychophysiological marker of stimulus salience (i.e., the late positive potential (LPP) component of the event-related potential) during passive picture viewing. Depressive symptomatology was assessed with the Beck Depression Inventory (BDI).
Results: Results showed that, independent of diagnosis, the highest unpleasant LPPs emerged in individuals with *MAOA*-Low and at least one 'Short' allele of 5-*HTTLPR*. Uniquely in the cocaine participants with these two risk variants, higher unpleasant LPPs correlated with higher BDI scores.
Conclusions: Taken together, these results suggest that a multilocus genetic composite of monoamine signaling relates to depression symptomatology through brain function associated with the experience of negative emotions. This research lays the groundwork for future studies that can investigate clinical outcomes and/or pharmacogenetic therapies in drug addiction and potentially other psychopathologies of emotion dysregulation.

1. Introduction

Gene polymorphisms that modulate serotonin signaling may increase susceptibility to multiple psychopathologies marked by heightened emotional reactivity and poor affect regulation (Buckholtz and Meyer-Lindenberg, 2012). These symptoms characterize both drug addiction and major depression, highly comorbid psychiatric illnesses (Martins and Gorelick, 2011) that exhibit shared perturbations in brain regions and circuits mediating emotional regulation (Bogdan et al., 2013; Goldstein and Volkow, 2011). Of the candidate serotonin-associated genes that modulate serotonin neurotransmission and could influence emotional dysregulation in addiction, two genes likely to play prominent roles include those encoding the serotonin transporter (*SLC6A4*) and monoamine catabolic enzyme monoamine oxidase A (*MAOA*). The commonly studied risk variants in both genes are believed to exert their effects by modulating serotonin clearance from the

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synapse (Buckholtz and Meyer-Lindenberg, 2008, 2012; Cools et al., 2008). These include a functional insertion–deletion polymorphism (i.e., sequence variation) of the *SLC6A4* promoter (5-*HTTLPR*), which produces "short" (S) and "long" (L) alleles and has been linked to depression (Kenna et al., 2012); and the repeat polymorphism (uVNTR, i.e., variable number of tandem repeats) upstream of the *MAOA* promoter, which produces common alleles with high activity (*MAOA*-H) and low activity (*MAOA*-L) and has been linked to impulsive aggression (Buckholtz and Meyer-Lindenberg, 2008) and depression (Fan et al., 2010).

Importantly, both of these polymorphisms modulate emotional reactivity, including responsiveness to aversive stimuli and experiences. In studies of 5-*HTTLPR*, study groups are often analyzed based on the presence of at least one S-allele. For example, compared with individuals homozygous for the L-allele, carriers of at least one 5-*HTTLPR* S-allele show increased startle response to noise bursts (Brocke et al., 2006). S-allele individuals also allocate more attention to fear-provoking stimuli (e.g., spiders) (Osinsky et al., 2008) and negative words (Kwang et al., 2010), and show a decreased ability to disengage attention from such stimuli (Beevers et al., 2009). A subsequent meta-analysis confirmed the association between the S-allele and attention bias to aversive stimuli (Pergamin-Hight et al., 2012). Neurally, S-allele carriers have enhanced event-related potential (ERP) responsiveness to unpleasant images (Herrmann et al., 2007) and enhanced functional magnetic resonance imaging (fMRI) response in the amygdala to aversive stimuli (meta-analysis: Murphy et al., 2013). Similarly, *MAOA*-L individuals show increased reactivity during aversive experiences, for example behaving more aggressively following provocation (Kuepper et al., 2013; McDermott et al., 2009) and showing greater dorsal anterior cingulate cortex activity (ACC) following social exclusion (Eisenberger et al., 2007). *MAOA* also modulates ERP reactivity (Williams et al., 2009) and fMRI activity in the amygdala and ACC (Alia-Klein et al., 2009; Lee and Ham, 2008; Meyer-Lindenberg et al., 2006) during the presentation of emotional faces and words. More recent research has aggregated these polymorphisms, thereby examining 5-*HTTLPR* and *MAOA* polygenic liability [defined as the aggregate burden of deleterious alleles harbored in each individual genome (Buckholtz and Meyer-Lindenberg, 2012)]. For example, the combined effects of 5-*HTTLPR*-*MAOA* in interaction with negative life events increased risk for depression in adolescence (Priess-Groben and Hyde, 2013). In addition, 5-*HTTLPR* and *MAOA* interacted to modulate fMRI signal in the subgenual ACC during a go/no-go task in health (Passamonti et al., 2008).

The goal of the current imaging-genetics study was to test whether these two serotonin gene polymorphisms modulate emotional reactivity in individuals with drug addiction, with whom these gene polymorphisms were previously associated (Bacher et al., 2011; Cao et al., 2013; Ehlers and Gizer, 2013; Fowler et al., 1996; Kenna et al., 2012). More specifically, we tested the separate and combined effects of 5-*HTTLPR* and *MAOA* on ERP-measured reactivity to unpleasant stimuli in individuals with cocaine use disorder (CUD) and healthy controls. Furthermore, to explore the possible clinical significance of these findings, we also tested whether such enhanced reactivity relates to higher depression symptomatology and/or cocaine use. Our primary ERP component of interest was the *a priori* defined late positive potential (LPP), thought to index stimulus salience (Hajcak et al., 2013, 2010; Hajcak and Olvet, 2008; Weinberg and Hajcak, 2010) and shown to be altered during passive picture viewing in CUD (Dunning et al., 2011). Drawing on the literature of these genes in healthy controls as described above, we hypothesized that (A) individuals with at least one 5-*HTTLPR* S-allele and/or *MAOA*-L would show higher LPP response to aversive images. We additionally hypothesized that (B) such reactivity would correlate with higher depression symptomatology and/or cocaine use especially in the individuals with higher monoamine polygenic liability, who presumably are at higher risk for reactivity to unpleasant stimuli.

2. Methods

2.1. Participants

Sixty-two CUD and 57 healthy controls, recruited through advertisements, local treatment facilities, and word of mouth, participated in this research. All provided written informed consent to participate in the study in accordance with the Stony Brook University Institutional Review Board. Exclusion criteria were: (A) head trauma (with a loss of consciousness for more than 30 min); (B) any psychiatric, medical, or neurological disorder requiring hospitalization or regular monitoring [except for highly frequently comorbid disorders in CUD, inclusive of additional substance use disorders, post-traumatic stress disorder (PTSD), and depression (with the latter being especially appropriate given our hypotheses)]; (C) current use of psychoactive medications (i.e., within the last six months); (D) current or past history of substance use disorder in the healthy controls (other than nicotine); and (E) positive urine screens for drugs of abuse (other than cocaine in CUD; any positive urine screens in controls).

All participants underwent a comprehensive clinical interview inclusive of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1996; Ventura et al., 1998); (B) Addiction Severity Index (ASI; McLellan et al., 1992). (For complete description of this interview, see Supplementary Material[1]). This interview determined that all 62 CUD met criteria for current cocaine dependence, 36 of whom tested positive for cocaine in urine (indicating use within 72 h prior to the study). (For current and past psychiatric comorbidities, see Supplementary Material[2]). Importantly, however, cocaine urine status did not differ by genotype (Table 1), and no participants were acutely intoxicated while performing the study procedures; these considerations broadly speak against a potential confounding influence of recent drug use on our results (but see Supplementary Materials for additional exploration of this variable[3]). We also used the clinical interview, specifically the traumatic events section from the PTSD module of the SCID and the emotional/physical/sexual abuse section of the ASI, to explore for potential interactions of 5-*HTTLPR* and *MAOA* with stressful and traumatic life events (Caspi et al., 2002; Caspi et al., 2003; Karg et al., 2011). (For results of these analyses, which did not reveal any significant effects, see Supplementary Material[4]). Study groups were generally well-matched demographically, only differing on history of cigarette smoking (Table 1) for which we controlled in the analyses. Although race did not differ as a function of genotype and diagnosis (Table 1), we nonetheless also controlled for this variable because of the potential for population stratification in the current sample (Cardon and Palmer, 2003). Depression symptomatology, which was measured with the Beck Depression Inventory (BDI; Beck, 1996) and differed between the groups as expected (Table 1), was a key variable of interest (not a covariate).

2.2. Genotyping

Using DNA extracted from peripheral blood, all participants were genotyped [by polymerase chain reaction as previously described (Shumay et al., 2011)] for the 5-*HTTLPR* and uVNTR *MAOA* polymorphisms. For 5-*HTTLPR*, individuals were grouped into those with the L/L genotype versus those with either L/S or S/S 5-*HTTLPR* genotypes; observed frequency of the major 5-*HTTLPR* genotypes were close to expected according to Hardy–Weinberg assumptions in both African Americans and Caucasians ($\chi^2 < 0.56$, *ns*). A different method of partitioning the groups, where the S/S genotype is considered particularly risky, is more common in pharmacogenomics studies examining response to antidepressants (Lesch and Gutknecht, 2005) [but see (Haase et al., 2013; Papousek et al., 2013)]. However, we decided to compare any S-allele carriers with the L/L genotype given the presumed dominant functional effects of the S-allele (Lesch et al., 1996) and following prior studies and meta-analyses (Brocke et al., 2006; Herrmann et al., 2007; Karg et al., 2011; Osinsky et al., 2008; Pergamin-Hight et al., 2012). Of particular mention is a study showing that carriers of one S-allele did not differ from those with the S/S genotype, and that both S-carrying groups differed from the L/L genotype (Kwang et al., 2010).

For *MAOA*, individuals were separately grouped into *MAOA*-L (high risk) versus *MAOA*-H (low risk) genotypes; 4 individuals (3 of them women, 2 of them CUD)

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