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Association of dopamine gene variants, emotion dysregulation and ADHD in autism spectrum disorder

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ABSTRACT

The aim of the present study was to evaluate the association of dopaminergic gene variants with emotion dysregulation (EMD) and attention-deficit/hyperactivity disorder (ADHD) symptoms in children with autism spectrum disorder (ASD). Three dopamine transporter gene (*SLC6A3/DAT1*) polymorphisms (intron8 5/6 VNTR, 3′-UTR 9/10 VNTR, rs27072 in the 3′-UTR) and one dopamine D2 receptor gene (*DRD2*) variant (rs2283265) were selected for genotyping based on *à priori* evidence of regulatory activity or, in the case of *DAT1* 9/10 VNTR, commonly reported associations with ADHD. A sample of 110 children with ASD was assessed with a rigorously validated *DSM-IV*-referenced rating scale. Global EMD severity (parents' ratings) was associated with *DAT1* intron8 ($\eta p^2 = .063$) and rs2283265 ($\eta p^2 = .044$). Findings for *DAT1* intron8 were also significant for two EMD subscales, generalized anxiety ($\eta p^2 = .065$) and depression ($\eta p^2 = .059$), and for *DRD2* rs2283265, depression ($\eta p^2 = .053$). *DRD2* rs2283265 was associated with teachers' global ratings of ADHD ($\eta p^2 = .052$). *DAT1* intron8 was associated with parent-rated hyperactivity ($\eta p^2 = .045$) and both *DAT1* 9/10 VNTR ($\eta p^2 = .105$) and *DRD2* rs2283265 ($\eta p^2 = .069$) were associated with teacher-rated inattention. These findings suggest that dopaminergic gene polymorphisms *may* modulate EMD and ADHD symptoms in children with ASD but require replication with larger independent samples.

1. Introduction

Children with autism spectrum disorder (ASD) experience a wide range of psychiatric symptoms consistent with emotion dysregulation (EMD), such as depression, anxiety, anger, and irritability, as well as attention-deficit hyperactivity disorder (ADHD; Gadow, DeVincent, & Pomeroy, 2006; Gadow, DeVincent, Pomeroy, & Azizian, 2005). These symptoms are associated with high rates of social and academic impairment (Kaat, Gadow, & Lecavalier, 2013), but little is known about pathogenic

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variables that may contribute to their co-occurrence with ASD. EMD and ADHD in children with ASD are phenomenologically similar in many ways to comparable symptoms and disorders in non-ASD youth (Gadow, DeVincent, & Drabick, 2008; Gadow et al., 2006; Gadow, Guttmann-Steinmetz, Rieffe, & DeVincent, 2012; Guttmann-Steinmetz, Gadow, & DeVincent, 2009; Guttmann-Steinmetz, Gadow, DeVincent, & Crowell, 2010), and this suggests that research about the latter may inform the former (e.g., Cohen et al., 2011; Gadow et al., 2013; Guerini et al., 2011).

Dopamine, brain regions rich in dopamine receptors, and genes involved in dopamine metabolism and signaling are all shown to be involved in emotion regulation and dysregulation (Alcaro, Huber, & Panksepp, 2007; Badgaiyan, Fischman, & Alpert, 2009; Beiderbeck et al., 2012; Garcia-Garcia, Clemente, Domínguez-Borràs, & Escera, 2010; Levita, Dalley, & Robbins, 2002; Opmeer, Kortekaas, & Aleman, 2010; Salgado-Pineda, Delaveau, Blin, & Nieoullon, 2005), including depression (Klimek, Schenck, Han, Stockmeier, & Ordway, 2002; Meyer et al., 2001; Roy, Karoum, & Pollack, 1992), as well as ADHD (Levy, 1991; Wender, 1971). For example, the 9/10 variable number tandem repeat (VNTR) in the 3′-untranslated region (UTR) of the dopamine transporter (DAT) gene (*DAT1/SLC6A3*) was found to be associated with depression (Felten, Montag, Markett, Walter, & Reuter, 2011), anxiety (Gadow, Roohi, DeVincent, & Hatchwell, 2008), and processing negative emotional stimuli (Garcia-Garcia et al., 2010). It also evidences modest association with ADHD (Gizer, Ficks, & Waldman, 2009) as do other *DAT1* variants including a VNTR on intron8 and the single nucleotide polymorphism (SNP) rs27072, but effect sizes across studies are generally heterogeneous. Researchers have recently established regulatory functions for the *DAT1* intron8 5/6 repeat VNTR and rs27072 variants (Pinsonneault et al., 2011) as well as SNP (rs2283265) in the dopamine D2 receptor gene (*DRD2*) (Zhang et al., 2007), which enables a focused approach to gene-behavior associations founded on strong evidence for genetic influence in dopaminergic signaling.

Although research findings suggest that (a) dysregulation of dopamine metabolism or signaling is likely implicated in the etiology of EMD and ADHD, and (b) specific functional dopaminergic gene variants may modulate symptom severity, little is known of their relation with comparable symptoms in children with ASD. The primary objective of the present study was to explore potential relations of the aforementioned dopamine gene variants with severity of EMD and ADHD symptoms in children with ASD. This seemed reasonable because both spectra are common in children with ASD and often co-occur in ASD samples (suggesting shared pathogenic mechanisms). We also considered whether *DAT1* intron8 and *DRD2* rs2283265 jointly led to a non-additive association with symptom severity because prior work has documented a functional epistatic interaction (Sullivan et al., 2013).

2. Materials and methods

2.1. Participants

Participants were recruited from referrals to a university hospital developmental disabilities specialty clinic located on Long Island, New York. All youth ($N = 110$) between 4 and 14 years old with the prerequisite measures and a diagnosis of ASD were included in the present study. Demographic characteristics were as follows: age ($M = 7.5 \pm 2.6$), gender (86% male), ethnicity (91% Caucasian), socioeconomic status assessed with Hollingshead's (1975) index of occupational and educational social status ($M = 42.0 \pm 11.2$), single-parent household (10%), and current psychotropic medication use (25%). Most children (73%) had IQs ≥ 70 based primarily on WISC or Standford–Binet test scores obtained from the school. A subsample of youth ($n = 67$) participated in prior studies of other gene variants (e.g., Gadow, Roohi, et al., 2008; Roohi, DeVincent, Hatchwell, & Gadow, 2009) as did the entire sample (Gadow et al., 2013; Gadow, Smith, & Pinsonneault, 2014). Both referred (Gadow et al., 2005) and epidemiologic (Simonoff et al., 2008) samples of children with ASD indicate high levels of co-occurring psychopathology. In the present study, the percentage of youth with *T* scores >65 for parent/teacher ratings (Gadow & Sprafkin, 1997, 2002, 2008) were as follows: ADHD (63%/46%), oppositional defiant disorder (22%/29%), generalized anxiety disorder (21%/25%), major depressive episode (36%/39%) and separation anxiety disorder (7%, parents' ratings only).This study was approved by a university Institutional Review Board; informed consent was obtained; and appropriate measures were taken to protect patient (and rater) confidentiality.

2.2. Procedure

Prior to scheduling their initial clinic evaluation, the parents of potential participants were mailed a packet of materials including behavior rating scales, background information questionnaire, and permission for release of school evaluation records. Ratings of child behavior were obtained from parents (primarily the mother) and teachers for 105 and 97 children, respectively. Diagnoses of ASD were confirmed by an expert diagnostician and based on five sources of information about ASD symptoms to verify *DSM-IV* criteria: (a) comprehensive developmental history, (b) clinician interview with child and caregiver(s), (c) prior evaluations, (d) informal observations of the child in the clinic setting, and (d) review of validated ASD rating scales including the Child Symptom Inventory-4 (CSI-4) (Gadow & Sprafkin, 2002), which evidenced high sensitivity and specificity in identifying 5–12-year-old children with ASD in two independent studies (DeVincent & Gadow, 2009; Gadow, Schwartz, DeVincent, Strong, & Cuva, 2008). Most youth (81%) were also evaluated with the Autism Diagnostic Observation Schedule (Lord et al., 2000) and/or Autism Diagnostic Interview-Revised (Rutter, LeCouteur, & Lord, 2003). Exceptions were children who had previously received an ASD diagnosis from a qualified clinician.