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Additive effects of the dopamine D2 receptor and dopamine transporter genes on the error-related negativity in young children

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The error-related negativity (ERN) is a negative deflection in the event-related potential that occurs approximately 50ms following the commission of an error at fronto-central electrode sites. Previous models suggest dopamine plays a role in the generation of the ERN. We recorded event-related potentials (ERPs) while 279 children aged 5–7 years completed a simple Go/No-Go task; the ERN was examined in relation to the dopamine D2 receptor (*DRD2*) and dopamine transporter (*DAT1*) genes. Results suggest an additive effect of the *DRD2* and *DAT1* genotype on ERN magnitude such that children with at least one *DRD2* A1 allele and children with at least one *DAT1* 9 allele have an increased (i.e. more negative) ERN. These results provide further support for the involvement of dopamine in the generation of the ERN.

Keywords: *DRD2*, *DAT1*, error-related ERPs, error-related negativity, performance monitoring

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The error-related negativity (ERN) is a neural measure of action monitoring that has been proposed as a possible endophenotype for anxiety and depressive disorders (Olvet & Hajcak 2008). The ERN is a negative deflection at fronto-central electrodes in the response-locked event-related brain potential, occurring 50 milliseconds after the commission of errors compared to correct responses in speeded reaction time tasks (Falkenstein *et al*. 1991; Gehring *et al*. 1993; Hajcak *et al*. 2005). It is thought to reflect activation of a generic error detection system that is evident across a variety of stimulus and response modalities (Gehring *et al*. 1993; van Veen & Carter 2002) and to be generated in the Anterior Cingulate Cortex (ACC) (Dehaene *et al*. 1994; Holroyd *et al*. 1998; Mathalon *et al*. 2003; van Veen & Carter 2002).

The ERN appears to be related to variation in trait anxiety (Amodio *et al*. 2008; Boksem *et al*. 2006; Endrass *et al*. 2008; Hajcak *et al*. 2003a; Weinberg *et al*. 2010), but not associated with state-related changes (Hajcak *et al*. 2008; Moser *et al*. 2005). Increased ERN amplitudes have been observed in unaffected first-degree relatives of obsessive compulsive disorder (OCD) patients (Riesel *et al*. 2011). Additionally, a twin study has shown ERN amplitudes to be significantly heritable (40–60%) (Anokhin *et al*. 2008). Taken together, these studies suggest that the ERN may meet all of the criteria for an endophenotype related to anxiety disorders (Gottesman & Gould 2003; Olvet & Hajcak 2008).

According to the reinforcement learning theory of the ERN, the ERN results from the disinhibition of the ACC by dopamine neurons when the basal ganglia evaluate ongoing actions as worse than expected (Holroyd & Coles 2002). Supporting the involvement of dopamine in the generation of the ERN, administration of a dopamine agonist (D-amphetamine) leads to an increased ERN amplitude (De Bruijn *et al*. 2004) and the administration of a dopamine antagonist (i.e. haloperidol) leads to a decreased ERN (De Bruijn *et al*. 2006; Zirnheld *et al*. 2004). Additionally, several studies have found that individuals with Parkinson's disease, which is characterized by dopamine depletion, have a diminished ERN (Jocham & Ullsperger 2009; Ito & Kitagawa 2006; Stemmer *et al*. 2004; Willemssen *et al*. 2008). Suggesting some specificity between dopamine and the ERN, one study found that the selective serotonin reuptake inhibitor paroxetine had no effect on ERN amplitude (De Bruijn *et al*. 2006).

In light of these data, it may be fruitful to examine associations between the ERN and genetic polymorphisms related to variation in dopamine. This study examined two dopamine genes: D2 dopamine receptor (*DRD2*) gene and dopamine transporter gene (*DAT1* or *SCL6A3*).

The *DRD2* gene located on chromosome 11q, encodes the D2 subtype of the dopamine receptor. The Taq1 A1 polymorphism (rs1870497) of the *DRD2* gene has been related to reduced D2 dopamine receptor binding affinity (Noble 2003), and more specifically to lower dopamine receptor density in the striatum (Jonsson *et al*. 1999). An *in vivo* positron emission tomography (PET) study suggested that individuals with the A1 allele are characterized by a significant decrease in *DRD2* receptor availability in the striatum relative to individuals homozygous for the A2 allele (Pohjalainen *et al*. 1998a) and a post-mortem study found fewer D2 receptors in the brains of individuals with the A1 allele. Importantly, evidence suggests that carriers of the A1 allele have upregulated synthesis of dopamine in

the brain due to decreased autoreceptor function (Laakso *et al*. 2005). Based upon the pharmacological findings previously discussed, carriers of the A1 allele may exhibit an increased ERN due to increased availability of dopamine. In general, adults have fewer D2 receptors than children (Seeman *et al*. 1987) and women may have fewer D2 receptors in the striatum than men (Pohjalainen *et al*. 1998b). Studies of animals and humans have linked the *DRD2* polymorphism to impaired social functioning and anxious and depressive symptoms (Hayden *et al*. 2010; Lawford *et al*. 2006; Schneier *et al*. 2000; Shively *et al*. 1997).

The second dopamine gene examined was *DAT1*, which is located on chromosome 5p15.3 and codes for a dopamine transporter protein that terminates synaptic transmission by the reuptake of dopamine into the presynaptic neuron (Amara & Kuhar 1993; Giros & Caron 1993; Fuke *et al*. 2001; Vandenbergh *et al*. 1992). The two most prevalent variants are the 9-repeat and 10-repeat alleles; individuals with the 9-repeat, in normative samples, have been shown to have more DAT protein availability in the striatum (Jacobsen *et al*. 2000; Van de Giessen *et al*. 2009; van Dyck *et al*. 2005). One study found an association between the 10-repeat allele and hypoactivation in the left anterior cingulate cortex compared to 9-repeat carriers, suggesting that the 10-repeat allele may be associated with a smaller ERN (Brown *et al*. 2010). The *DAT1* has been examined in association with attention deficit hyperactivity disorder (ADHD) (Faraone *et al*. 2005), hyperactivity (Diamond 2007), novelty seeking (Sabol *et al*. 1999), delay aversion and motor functions (Heinz *et al*. 2000), alcohol withdrawal symptoms (Sander *et al*. 1997), PTSD (Segman *et al*. 2002), and generalized anxiety, social phobia, OCD and Tourette's in children (Rowe *et al*. 1998).

In adults, two previous studies have investigated the role of the *DRD2* (Mueller *et al*. 2011) and *DAT1* (Biehl *et al*. 2011) polymorphisms in the generation of the ERN, both finding no association. The ERN has recently begun to be examined in children, suggesting that although it may be slightly more posterior, it is both spatially and temporally similar to the ERN in adults (Brooker *et al*. 2011; Ladouceur *et al*. 2007; Meyer *et al*. 2012; Torpey *et al*. 2009) and has been shown to increase in magnitude with age (Davies *et al*. 2004; Torpey *et al*. 2011). Thus, both the ERN (Davies *et al*. 2004; Torpey *et al*. 2011) and dopamine systems (Fareri *et al*. 2008) are known to change across the lifespan, and therefore may relate to one another differently among children than in adults. In children, two previous studies of the same sample reported no independent association of *DRD2* and *DAT1* genotypes with the ERN (Althaus *et al*. 2009, 2010). However, the sample was comprised of 65 children, most of them with a diagnosis of either Pervasive Developmental Disorder or ADHD. No study to date has examined the relationship between these two dopamine genotypes and ERN in a large normative sample of children.

In this study, ERPs were recorded while 279 children aged 5–7 years completed a simple Go/No-Go task. Information about each child's dopamine genotypes (*DRD2* and *DAT1*) was collected to investigate potential relationships between the ERN and dopamine-related gene polymorphisms. Given that the *DRD2* A1 allele has been associated with an upregulation of dopamine and the *DAT1 9* allele has been associated with increased activation of the ACC, we expected that children with the *DRD2* A1 allele and children with the *DAT1* 9 allele would have larger (i. e., more negative) ERN amplitudes.

Method

Participants

The sample included 279 children (124 female) from a suburban community. The original sample included 412 children. In this analysis 57 were excluded due to non-consent for genetic information and 3 were excluded because they carried a rare variant of the *DAT1* gene. Because Olvet and Hajcak (2008) found that six or more error trials are needed for a stable ERN, data from 73 of 352 (20.74%) children in total were excluded from further analyses.

The mean age of the children was 6.10 years, SD = 0.43, range = 5.15–7.57 years at the time of the laboratory visit. The children were part of a larger study that involved an initial assessment approximately 3 years prior. Originally, potential participants were identified through a commercial mailing list. Eligible families were contacted by the Stony Brook University Center for Survey Research and had a child between 3 and 4 years of age, with no developmental disability or significant medical conditions, and at least one English-speaking biological parent. In the overall sample, 87.4% of the children were Caucasian, 69.3% had at least one parent who was a college graduate and 95.4% came from two-parent homes.

Genetic analysis

When participants came to the laboratory for the initial assessment, buccal cells were collected for genetic analysis by rubbing the inside of each child participant's cheek with two swabs. The Qiagen DNA Micro Kit (Qiagen, Valencia, CA, USA) was used to extract genomic DNA from buccal swab samples according to the manufacturer's instructions. Extracts were kept at 4°C when being analyzed, and were held at −80°C for long-term storage. Polymerase chain reaction (PCR) was carried out using the Applied Biosystems thermal cycler Gene Amp 9700 (Applied Biosystems, Foster City, CA, USA), and PCR products were separated on 6% polyacrylamide gels, stained with ethidium bromide, and visualized and documented by a UV imaging system (BioRad Labs, Mississauga, Ontario, Canada).

For the detection of the *DRD2* Taq1A polymorphism, oligonucleotide primers 5′-CACGGCTGGCCAAGTTGTCTA-3′ (forward) and 5′-CACCTTCCTGAGTGTCATCAA-3′ (reverse) were used to amplify a 300-bp region flanking the *Taq1A* site (Grandy *et al*. 1993). The PCR conditions used were initial denaturation for 5 min at 95°C followed by 30 cycles of 30 seconds denaturation at 94°C, 30 seconds annealing at 58°C, and 30 seconds extension at 72°C, followed by a 5 min final extension at 72°C. The amplicons were digested overnight with 1U of Taq$^{\alpha}$1 restriction enzyme (New England BioLabs, Ipswich, MA, USA). The A1 allele is uncut by the restriction enzyme, whereas the A2 allele generates 125 and 175 bp fragments. Of the 279 children who provided a DNA sample, 11children had the A1A1 homozygous genotype, 80 were heterozygous (A1A2) and 188 had the A2A2 homozygous genotype. These genotype frequencies are in Hardy–Weinberg equilibrium $\chi^2(1) = 0.56$, $P = 0.45$. All genotyping was performed by research technicians blind to other study data. Consistent with most published research, and considering the rarity of the A1A1 genotype, groups for data analysis were formed based on whether children had ($N = 91$) or did not have ($N = 188$) an A1 allele.

A 40 nucleotide VNTR polymorphism has been identified within the 3′ non-coding region of the *DAT1* gene. Alleles of this VNTR sequence range from 3 to 13 repeats, but the 9-repeat and 10-repeat alleles are the most common (Palmatier *et al*. 1999). For this study, the primers used were 5′-TGTGGTGTAGGGAACGGCCTGAG-3′ (forward) and 5′-CTTCCTGGAGGTCACGG CTCAAGG-3′ (reverse). PCR conditions were as follows: 5 min initial denaturation at 95°C and 30 cycles of 30 seconds initial denaturation at 94°C, 45 seconds annealing at 67.5°C, 45 seconds extension at 72°C, followed by 5 min of final extension at 72°C. The 9-repeat and 10-repeat

products yield a 440- and 480-bp fragment, respectively. Of those 279 children we were successfully able to genotype for the *DAT1* allele, 138 of them were homozygous for the *DAT1* 10R allele, 24 of them were homozygous for the 9R allele, and 117 were 9R/10R heterozygous. These genotype frequencies are in Hardy–Weinberg equilibrium $\chi^2(1) = 0.01$, $P = 0.92$. Three of the children had an unusual variant (the 11R) and have been excluded from the analysis. Consistent with previous studies (Althaus *et al*. 2010), two groups were formed based on whether children were homozygous for the 10R allele (138 children) or carried at least one 9R allele (141 children). Additionally, the results of a chi-square test of independence suggest that the variants of the two genotypes (*DRD2* and *DAT1*) are independent, $\chi^2(1, N = 279) = 0.26$, $P = 0.61$.

Task and materials

A Go/No-Go paradigm, described previously in Torpey *et al*. (2011), was administered using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA). The stimuli were green equilateral triangles in four different orientations. There were a total of 240 trials, 60% of the triangles were vertically aligned and pointed up, 20% were vertically aligned and pointed down, 10% were tilted slightly to the left, and 10% were titled slightly to the right. Children were instructed to respond to upward-pointing triangles by pressing a button, and to withhold responses to all other stimuli.

Procedure

A series of practice blocks were administered to ensure that the participant understood the various aspects of the task. After completing the practice blocks, children were instructed that for each block, they would earn one point for correct responses on Go trials and for withholding responses on No-Go trials. They were told that if they earned enough points, they could win up to $5.00. Speed of response was again emphasized to the children. Between each block, the experimenter told the participants how many points they earned and reminded the children of the task instructions, emphasizing response speed.

Psychophysiological recording

Data were acquired using the Active Two system (Biosemi, Amsterdam, The Netherlands). 32 Ag/AgCl-tipped electrodes arranged according to the American Electroencephalographic Society labeling system (1994) were used with a small amount of electrolyte (Signa Gel; Bio-Medical Instruments Inc., Warren, MI, USA) applied to the child's scalp at each electrode position. For more information on data acquisition, see Torpey *et al*. (2011).

Offline, all data processing was performed with Brain Vision Analyzer (Brain Products, Gilching, Germany). Electroencephalogram data was re-referenced to the nose, and high- and low-pass filtered at 1 and 30 Hz, respectively. From the continuous EEG, 1500 milliseconds segments were extracted beginning 500 milliseconds prior to correct and erroneous responses. ERP data were corrected for blinks and eye-movements using the method developed by Gratton, Coles, and Donchin (1983). Additional artifacts were rejected when any of the following criteria are met: a voltage step of more than 50 μV between data points, a voltage difference of 300 μV within a single trial or a voltage difference of less than 0.5 μV within 100 milliseconds intervals. Data were also visually inspected for any remaining artifacts. ERP averages were then created separately for each trial type (correct and error) and were baseline corrected by subtracting from each data point the average activity the −500 to −300 milliseconds window prior to the response. Trials were not included in ERP averages if the reaction time occurred outside of a 200–1300 milliseconds window.

The ERP and behavioral results in the full sample have been reported previously (Torpey *et al*. 2011). In this study, we focus on the impact of *DRD2* and *DAT1* genotype on the error-related negativity (ERN) and correct-related negativity (CRN), which were scored at Cz as the average voltage in the window from 0 to 100 milliseconds after the response, where error-related brain response was maximal (Torpey *et al*. 2011). The ERN can be calculated by averaging the error-trial waveform or by subtracting the correct-trial waveform from the error-trial waveform (i.e. ΔERN) (Pailing *et al*. 2002). The ERN on error trials alone likely includes processes common to both error and correct responses. By subtracting correct from error trials (ΔERN), processes common to both correct and error responses are removed, resulting in a measure of neural activity specific to errors. Thus, all analyses examined the CRN, ERN and ΔERN.

Behavioral measures included both the number of errors of commission and omission for each subject. Average reaction times (RTs) on error and correct trials were also calculated separately, as were RTs on correct trials that followed errors trials to evaluate post-error RT slowing. Trials were removed from all analyses if reaction times were faster than 200 milliseconds or slower than 1300 milliseconds.

Statistical analyses were conducted using SPSS (Version 17.0) General Linear Model software, with Greenhouse-Geisser correction applied to *P* values associated with multiple-df, repeated-measures comparisons when necessitated by violation of the assumption of sphericity. Analyses were structured with the goal of finding main effects as well as interactive or additive effects of child *DRD2* and *DAT1* genotypes on the ERN, CRN and ΔERN. Repeated measures analysis of variances (ANOVAs) were conducted, with response type (i.e. CRN and ERN) as a within-subject variable and *DRD2* and *DAT1* genotypes as between-subjects variables. Follow-up one-way ANOVAs were conducted to determine how each genotype specifically related to CRN, ERN and ΔERN. Additionally, hierarchical multiple regression analyses were performed to confirm that the effects of *DRD2* and *DAT1* were additive on ERN. A follow-up repeated measures ANOVA was conducted with age, reaction time, and accuracy as covariates, followed by a mediation analysis. Finally, *post hoc* ANOVAs were conducted to investigate the potential role of gender in the relationship between the dopamine genotypes and ERN.

Results

Because of technical error, the behavioral data from six participants were lost; however, the ERP data for these subjects were included in the analyses. This left a total of 273 subjects that could be included in the behavioral analyses and 279 subjects included in the ERP and genetic analyses.

Behavioral data

Performance measures in the overall sample, and as a function of *DRD2* and *DAT1* genotype, are presented in Table 1. Consistent with previous work, children were significantly faster on error trials than on correct go trials, $t(1, 272) = 32.42$, $P < 0.001$. Compared to the overall mean of correct trial reaction time, participants were slower to generate a correct response on trials that occurred after an error, $t(1, 272) = 5.90$, $P < 0.001$. However, there were no overall reaction time differences as a function of either *DRD2* or *DAT1* genotype, $F_{1,269} = 0.02$, $P = 0.89$, $F_{1,269} = 2.90$, $P = 0.09$, respectively; neither *DRD2*, $F_{1,269} = 0.71$, $P = 0.40$, nor *DAT1*, $F_{1,269} = 0.46$, $P = 0.50$, interacted with trial type to impact reaction time. However, there was a three-way interaction between trial type, *DRD2*, and *DAT1*, $F_{1,269} = 4.56$, $P < 0.05$.

As depicted in Fig. 3, *post-hoc t*-tests suggested that within the *DRD2* A1 group, children who were homozygous for *DAT1* 10/10, were slower on correct trials than children with a *DAT1* 9 allele, $t(1, 88) = -2.65$, $P < 0.01$. Within the *DRD2* A1 group, reaction time on error trials did not differ significantly between the two *DAT1* genotypes,

Table 1: Means (SD) of behavioral measures (milliseconds), ERN, CRN and (ERN–CRN) amplitude (μV) at Cz for the entire sample and the genotypes

	All children ($N = 279$)	*DRD2* A1 ($N = 91$)	*DRD2* A2/A2 ($N = 188$)	*DAT1* 10/10 ($N = 138$)	*DAT1* 9 ($N = 141$)
Errors of commission	16.01 (7.62)	15.57 (6.51)	16.37 (8.10)	17.05 (8.13)	1520 (7.01)
Errors of omission	10.12 (11.05)	8.68 (9.58)	10.83 (11.66)	11.60 (12.06)	8.71 (9.83)
RT errors	509 (88)	511 (94)	507 (85.26)	514 (92)	503 (84)
RT correct	626 (72)	624 (77)	627 (70)	632 (71)	621 (72)
Post-error RT	655 (119)	647 (116)	660 (121)	655 (112)	656 (126)
Post-error slowing	28 (79)	22 (81)	32 (81)	23 (73)	35 (89)
ERN	0.09 (10.06)	−2.03 (7.37)	1.12 (10.99)	0.79 (11.34)	−0.59 (8.61)
CRN	9.18 (5.94)	9.32 (5.55)	9.11 (6.13)	8.56 (6.13)	9.78 (5.70)
ΔERN	−9.09 (10.26)	−11.35 (8.28)	−7.99 (10.95)	−7.78 (11.99)	−10.37 (8.07)

Table 2: Overall and Incremental results from hierarchical regression analysis of genotype predicting ERPs at Cz

	ERN		CRN		ΔERN	
	R^2	F	R^2	F	R^2	F
Overall results						
Step 1: *DRD2*	0.022	6.11**	0.00	0.072	0.024	6.67**
Step 2: *DAT1*	0.025	3.64*	0.01	1.49	0.038	5.52**
Incremental results						
Step 1: *DRD2*	0.02	6.11**	0.00	0.072	0.024	6.67**
Step 2: *DAT1*	0.004	1.17	0.01	2.91	0.015	4.28*

$t(1, 88) = -1.01$, $P = 0.32$. Within the *DRD2* A2/A2 group, neither correct, $t(1, 181) = 0.36$, $P = 0.72$, nor error reaction times, $t(1, 181) = -.59$, $P = 0.56$, differed significantly between the *DAT1* groups.

Additionally, post-error slowing did not differ by *DRD2* genotype, $F_{1,272} = 0.64$, $P = 0.42$, or by *DAT1* genotype, $F_{1,272} = 0.004$, $P = 0.95$, and there were no significant two- or three-way interactions involving genotypes and post-error slowing (all *ps* > 0.1).

Overall, participants committed an average of 16.10, SD = 7.62, errors of commission and an average of 10.12, SD = 11.05, errors of omission, out of a total of 240 trials. Children with at least one *DAT1* 9 allele made significantly fewer errors of commission and fewer errors of omission than children who were homozygous for the *DAT1* 10 allele, $F_{1,272} = 4.08$, $P < 0.05$ and $F_{1,272} = 4.75$, $P < 0.05$, respectively. All other effects and interactions did not reach significance (all *ps* > 0.1).

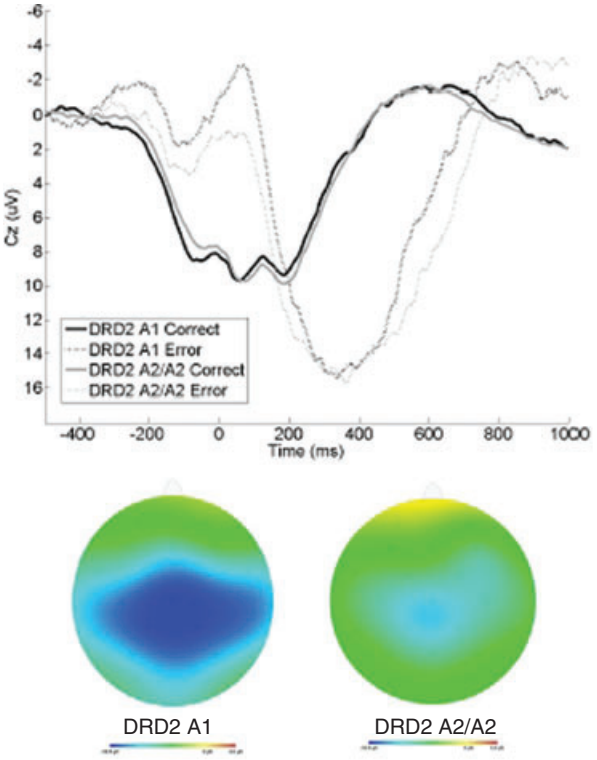

Figure 1: Response-locked waveforms at Cz for ERN and CRN for *DRD2* genotype.

ERPs

Means and standard deviations of ERN, CRN and ΔERN as a function of genotype are included in Table 2, response-locked waveforms at Cz for ERN and CRN for each genotype are included in Figs 1 and 2. The ERP response was more negative following errors than correct responses, $F_{1,275} = 222.25$, $P < 0.001$. There was no overall difference in brain activity as a function of the *DRD2* or *DAT1* genotypes, $F_{1,275} = 2.98$, $P < 0.09$, and $F_{1,275} = 0.51$, $P = 0.48$, respectively. However, the effect of trial type was qualified by a significant interaction with *DRD2* genotype, $F_{1,275} = 6.37$, $P < 0.01$. Children with at least one *DRD2* A1 allele had a larger (i.e. more negative) ΔERN than children who were homozygous for the *DRD2* A2 allele, $F_{1,277} = 6.67$, $P < .01$. This effect was driven by the effect of *DRD2* genotype on the ERN, $F_{1,277} = 6.11$, $P < 0.01$ such that children carrying at least one *DRD2* A1 allele had a significantly larger (i.e. more negative) ERN than children carrying the *DRD2* A2 allele (homozygous for A2). Children did not differ in CRN between the two *DRD2* genotypes, $F_{1,277} = 0.072$, $P = 0.79$.

In addition, the difference between ERN and CRN also varied as a function of *DAT1* genotype, $F_{1,275} = 3.88$, $P < 0.05$. Although neither the ERN nor the CRN differed

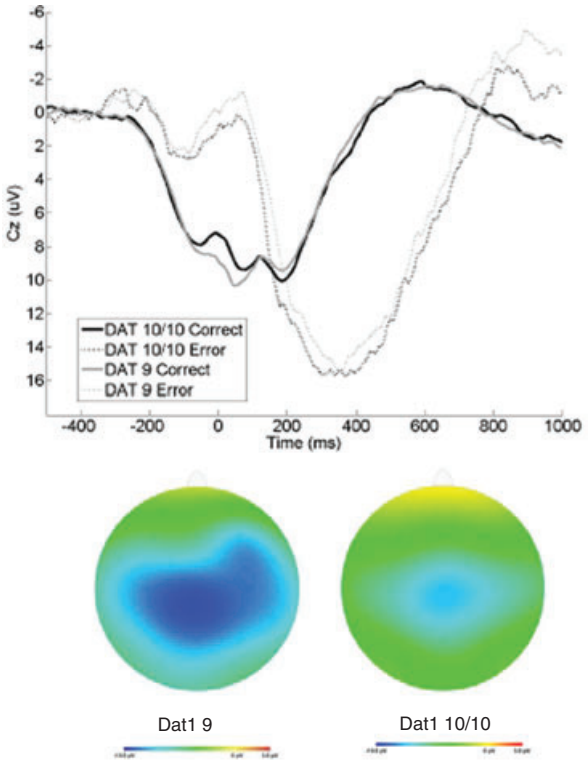

Figure 2: Response-locked waveforms at Cz for ERN and CRN for *DAT1* genotype.

between the two genotypes alone, $F_{1,277} = 1.32$, $P = 0.25$ and $F_{1,277} = 2.95$, $P = 0.09$, respectively, children with the *DAT1* 10 allele (homozygous for *DAT1* 10) had a significantly smaller (i.e. less negative) ΔERN than children with the *DAT1* 9 allele (with at least one *DAT1* 9 allele), $F_{1,277} = 4.53$, $P < 0.05$.

Neither the *DAT1* by *DRD2* two-way interaction, $F_{1,275} = 3.62$, $P = 0.06$, nor the three-way interaction between trial type, *DAT1* genotype, and *DRD2* genotype reached significance, $F_{1,275} = 0.01$, $P = 0.92$, suggesting two independent effects on error-related brain response related to the *DAT1* and *DRD2* genes. To investigate the possibility that the genotypes related differently to frontal/posterior electrode sites, a repeated-measures ANOVA was conducted that suggested that the effect of trial type at Pz was also qualified by a significant interaction with the *DRD2*, $F(1, 275) = 6.053$, $P < 0.01$, and the *DAT1* genotype, $F(1, 275) = 6.46$, $P < 0.01$. An additional repeated-measures ANOVA suggested that the effect of trial type at Fz was qualified by a significant interaction with the *DRD2* genotype, $F(1,275) = 5.74$, $P < .05$, but not the *DAT1* genotype, $F(1,275) = 2.51$, $P = 0.12$.).

Hierarchical multiple regression analyses

To test for unique contribution of each genotype on the ERN, CRN and ΔERN we conducted separate hierarchical multiple regression analyses in which each of the ERPs were the dependent variables and potential predictor variable were the *DRD2* and *DAT1* genotypes. Results are shown in Table 2. As can be seen from the table, the additional variance accounted for in the ERPs by adding *DAT1* as a predictor was significant in the case of ΔERN, $R^2 = 0.015$, $P < 0.05$, although not in any of the other ERP measures. The variance in the difference score ΔERN accounted for by *DRD2* alone was 2.4% and after *DAT1* was added, the variance accounted for increased to a total of 3.8%, a significant increment. Thus, *DAT1* significantly predicts the difference score ΔERN even after controlling for *DRD2*. This suggests an additive effect of the two genotypes. Overall and incremental results from the hierarchical regression analyses are included in Table 2.

Mediation analysis

A follow-up repeated measure ANOVA suggested that when overall accuracy, reaction time (on error and correct trials), and age are added as covariates, the interaction between trial type and *DRD2* remained significant, $F_{1,265} = 6.07$, $P < 0.01$, however, the effect of trial type was no longer qualified by the interaction with *DAT1*, $F_{1,265} = 1.94$, $P = 0.17$. Statistical analyses were conducted to test the potential mediation of accuracy on the relationship between *DAT1* and ΔERN. The original beta for the relationship between *DAT1* and ERN was 2.60, $t(278) = 2.13$, $P < 0.05$ and the beta for the relationship between *DAT1* and accuracy was −4.75, $t(272) = -2.73$, $P < 0.01$. In the second regression analysis, the beta for accuracy predicting ERN was -.12, $t(272) = -2.51$, $P < 0.01$ and the beta for *DAT1* predicting ERN was reduced to 2.03, $t(272) = 1.63$, $P = 0.12$. This reduction was significant; Sobel's test $Z = 1.85$, $P < 0.05$ (Fig. 3).

Gender

A follow-up repeated measure ANOVA suggested that when gender was added as a covariate, it did not result in a significant interaction with ERN, $F_{1,274} = 0.16$, $P = 0.69$, and the interaction of *DRD2* and ERN, $F_{1,274} = 6.35$, $P < 0.01$, and *DAT1* and ERN, $F_{1,274} = 3.99$, $P < 0.05$, remained significant. However, a previous study has suggested that

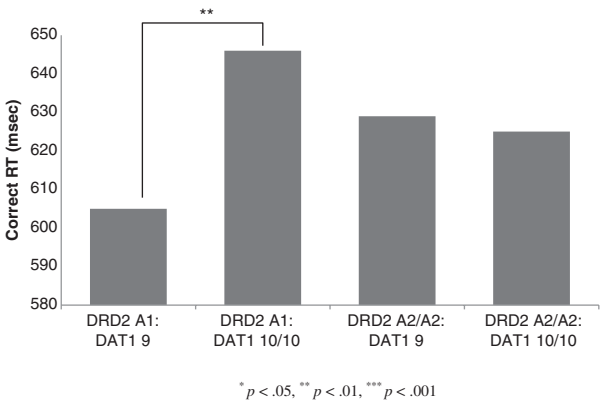

Figure 3: Correct reaction time (milliseconds) for the combined genotype groups and significance for *post hoc t*-tests.

males and females differ in *DRD2* binding in the striatum (Pohjalainen *et al*. 1998b) so further *post hoc* analyses were completed by dividing the sample into males and females. In males, the effect of trial type was not significantly qualified by an interaction with *DRD2* genotype, $F_{1,155} = 0.88$, $P = 0.35$. However, in females there was a significant interaction of trial type with *DRD2* genotype, $F_{1,123} = 7.20$, $P < 0.01$, such that females with the *DRD2* A1 allele had a significantly more negative ERN, M = −3.67, SD = 7.53, than females without the *DRD2* A1 allele, M = 1.01, SD = 11.04.

Discussion

The results of this study suggest that there is an additive effect of the *DRD2* and *DAT1* genotype on ERN magnitude such that children with at least one *DRD2* A1 allele and children with at least one *DAT1* 9 allele have an increased (i.e. more negative) ERN. This finding fits with the notion that the ERN is related to a reduction in dopaminergic activity seen on error trials when an expected reward is not delivered (Holroyd & Coles 2002).

Studies have suggested that the generation of the CRN may be due to error processing during correct trials (Coles *et al*. 2001); for instance, there is an increase in CRN amplitude as a function of subjectively rated inaccuracy on correct trials (Scheffers & Coles 2000). Although the children with the *DAT1* 9 allele did display a larger (i.e. more negative) ERN on error trials, they were also characterized by a smaller (i.e. less negative) CRN on correct trials – and better performance overall. It could be that these children were more accurate in judging when they had actually made an error and thus had a smaller CRN and larger ERN. This increased performance could be due to enhanced perceptual or attentional abilities. In fact, the *DAT1* 10/10 allele has previously been associated with attention deficit hyperactivity disorder (Faraone *et al*. 2005; Thapar *et al*. 2005), and decreased selective attention and response inhibition (Cornish *et al*. 2005).

Additionally, children with the *DAT1* 9 allele committed fewer errors of commission and omission, and within the *DRD2* A1 group, children with the *DAT1* 9 allele were faster on correct trials. In this sample, the magnitude of ΔERN was previously related to better performance, indicated by greater accuracy, more correct No-Go trials and fewer errors of commission and omission (Torpey *et al*. 2011). And, previous studies have consistently found that ERN amplitude is increased when people make fewer errors (Amodio *et al*. 2008; Hajcak *et al*. 2003b). Additional statistical analyses were consistent with the hypothesis that increased accuracy may have driven the relationship observed between the *DAT1* 9 allele and increased ΔERN.

Overall, these findings fit with a previous study suggesting that children with the short variant of the 5-*HTTLPR* gene and also with a *DRD2* A1 allele had a larger ERN (Althaus *et al*. 2009). While previous investigations of the relationship between the *DAT1* genotype and ERN did not find a significant independent effect, this may have been due to a small sample size or in the study examining adults, age-related changes in dopamine transporter density (Althaus *et al*. 2010; Biehl *et al*. 2011). In fact, a previous study suggests that dopamine transporter density declines with age in a linear manner (Innis *et al*. 2002). It is important to note that one study found an association in adults with the *DRD2* A1 allele and a reduced negative feedback-related fMRI signal in the rostral cingulate zone (Klein *et al*. 2007). However, this study included only male participants and it has been suggested that females may have a lower *DRD2* binding affinity (Pohjalainen *et al*. 1998b). Follow-up analyses in our sample suggested that the relationship between the *DRD2* A1 allele and ERN was only apparent in females. It may be that females have fewer D2 receptors and that females with the *DRD2* A1 allele have even fewer receptors, contributing to a larger ERN. Future studies should investigate the possibility that the relationship between the *DRD2* genotype and ERN may vary depending on gender.

In a previous paper, we reported a significant relationship between the *DRD2* A1 allele and anxious symptoms emerging around age 3 (Hayden *et al*. 2010). A tentative possibility is that one mechanism through which the *DRD2* A1 allele relates to enhanced anxiety in young children is by increased error monitoring related to fewer D2 receptors in the striatum. However, more research in this area is needed to substantiate this. Traditionally, the *DRD2* A1 allele has been studied in adults in relationship to substance abuse (Dick & Foroud 2003) and a recent study suggests that an increased ERN is found in alcohol-dependent patients, especially those with comorbid anxiety disorders (Schellekens *et al*. 2010). Additionally, some evidence suggests anxiety may be a risk factor for the development of substance abuse problems (Cimander *et al*. 2001; Grant *et al*. 2004; Sartor *et al*. 2007). It is possible that the *DRD2* A1 allele is related to an underlying liability to anxiety in childhood that transitions into a substance abuse trajectory by adulthood.

It is also important to note that the relationships observed between the two dopamine genes and ERN were found in a sample of young children. Indeed, the amplitude of the ERN increases with age (Davies *et al*. 2004; Torpey *et al*. 2011), D2 receptor expression in the striatum increases in childhood until age 5 and then decreases into adulthood (Seeman *et al*. 1987), and dopamine transporter density declines with age (Innis *et al*. 2002). Taken together, it is possible that the relationships observed between dopamine genotypes and ERN may vary as a function of age. Additionally, it is possible that genetic variants may have different functional consequences across development (Wahlstrom *et al*. 2007). Limited research has been done on this topic for the *DRD2* and *DAT1* genotypes, therefore generalizing research in children to adults and vice versa must be done cautiously. Prospective studies on the relationship of dopamine genes and ERN across development are needed to clarify this and also shed light on the hypothesized causal relationship between the genotypes and ERN. We are currently investigating this issue in ongoing and longitudinal studies.

This study is the first to find independent effects of two dopamine genes on ERN. This finding supports the reinforcement learning theory that suggests the ERN is

related to a reduction in dopaminergic activity seen on error trials when an expected reward signal is not delivered (Holroyd & Coles 2002). Additionally, the association between candidate genes and the ERN may provide a potential mechanism through which the *DRD2* and *DAT1* genotypes relate to clinical phenotypes. Future research in adolescents and adults is needed to investigate the association of other dopamine genes (specifically: Dopamine receptor D4 and Catechol-*O*-methyltransferase) and error-related neural activity, and how dopamine-mediated error-related brain activity relates to clinical disorders across development.

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