Polymorphisms in Dopamine System Genes Are Associated With Individual Differences in Attention in Infancy

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Knowledge about the functional status of the frontal cortex in infancy is limited. This study investigated the effects of polymorphisms in four dopamine system genes on performance in a task developed to assess such functioning, the Freeze-Frame task, at 9 months of age. Polymorphisms in the catechol-*O*-methyltransferase (*COMT*) and the dopamine D4 receptor (*DRD4*) genes are likely to impact directly on the functioning of the frontal cortex, whereas polymorphisms in the dopamine D2 receptor (*DRD2*) and dopamine transporter (*DAT1*) genes might influence frontal cortex functioning indirectly via strong frontostriatal connections. A significant effect of the *COMT* valine^{158}methionine (Val^{158}Met) polymorphism was found. Infants with the Met/Met genotype were significantly less distractible than infants with the Val/Val genotype in Freeze-Frame trials presenting an engaging central stimulus. In addition, there was an interaction with the *DAT1* 3′ variable number of tandem repeats polymorphism; the *COMT* effect was present only in infants who did not have two copies of the *DAT1* 10-repeat allele. These findings indicate that dopaminergic polymorphisms affect selective aspects of attention as early as infancy and further validate the Freeze-Frame task as a frontal cortex task.

Keywords: frontal cortex, infancy, dopamine genes, attention, frontal-subcortical circuits

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The frontal cortex is associated with important cognitive functions such as working memory and various aspects of cognitive control (for a review, see Fuster, 1997; Gazzaley & D'Esposito, 2007). Despite years of intensive study of this area in adults and nonhuman primates, relatively little is known about the functional status of the frontal cortex in infancy.

The frontal cortex has a more protracted development than other areas of the brain, with synaptogenesis continuing well into middle childhood (Glantz, Gilmore, Hamer, Lieberman, & Jarskog, 2007; Huttenlocher, 1990). Glucose metabolism and regional cerebral blood flow also peak later in the frontal cortex (Chugani & Phelps, 1986; Chugani, Phelps, & Mazziotta, 1987; Franceschini et al., 2007). Despite this protracted developmental course, infant neuroimaging studies have shown activation in the frontal cortex during language processing, processing of novel stimuli, and working memory (Baird et al., 2002; Bell, 2001; Bell & Fox, 1992, 1997; Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Homae, Watanabe, Nakano, & Taga, 2007; Nakano, Watanabe, Homae, & Taga, 2009). Furthermore, Diamond and colleagues have shown that performance on a task that has been directly associated

with the frontal cortex, the A-not-B task (Piaget, 1954), improves drastically during the second half of the first year of life (Diamond, 1985; Diamond & Goldman-Rakic, 1989; Diamond, Zola-Morgan, & Squire, 1989).

A previous report sought to validate a new infant frontal cortex task, the Freeze-Frame task, by investigating the relationship between this task and other infant and toddler frontal cortex tasks (Holmboe, Fearon, Csibra, Tucker, & Johnson, 2008). The Freeze-Frame task was developed to assess various aspects of inhibitory control in infancy using eye movements as the dependent measure. In this task, infants are encouraged to stay fixated on an animated cartoon in the center of a computer screen. On every trial, a peripheral distractor (a white square) is presented. If the infant looks to this distractor, the animation is frozen for a brief period of time. Furthermore, the task involves two alternating trial types. In the "interesting" trials, a dynamic and changeable animation is presented, whereas the "boring" trials present the same simple animation (a rotating orange star) every time.

In the study by Holmboe et al. (2008), 9-month-old infants stopped looking to the distractors during the course of the test session. Infants also looked less to the distractors in the interesting trials right from the beginning of the session. No evidence of an interaction between trial type and phase of the test session was found. Individual performance indices suggested that infants who looked less to the distractors in the interesting trials than the boring trials early in the Freeze-Frame session performed better on the A-not-B task at 9 months of age. Another Freeze-Frame index, which assessed infants' ability to selectively learn to inhibit looks to the distractors, was associated with significantly better performance on a frontal cortex task (the Spatial Conflict task; Gerardi-Caulton, 2000; Rothbart, Ellis, Rueda, & Posner, 2003) at 24 months of age, suggesting that Freeze-Frame performance at 9 months is predictive of later frontal cortex functioning (Holmboe et al., 2008).

Even though these results indicate that performance on the Freeze-Frame task shares a significant proportion of its variance with performance on other infant and toddler frontal cortex tasks, this is nonetheless relatively indirect evidence that the task depends on the frontal cortex. More definitive evidence that the task is indeed associated with the functioning of the frontal cortex would involve establishing a direct relationship between performance on the task and biological markers of frontal cortex functioning. One way to address this issue is to investigate the potential effect of genetic variation. In the present study, we therefore investigated the relationship between performance on the Freeze-Frame task and well-characterized candidate polymorphisms in dopamine system genes.

The neurotransmitter dopamine plays a major role in the frontal cortex. For example, depletion of dopamine, but not noradrenaline or serotonin, in the dorsolateral prefrontal cortex causes delayed-response deficits similar to those seen after ablation of that area (Brozoski, Brown, Rosvold, & Goldman, 1979; Collins, Roberts, Dias, Everitt, & Robbins, 1998; Roberts et al., 1994). Furthermore, recordings from prefrontal dopamine-sensitive neurons in primates have shown these neurons to be active during the delay period in working memory tasks (Goldman-Rakic, Muly, & Williams, 2000; Sawaguchi & Goldman-Rakic, 1991; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). Finally, Diamond and colleagues investigated children treated early and continuously for phenylketonuria (PKU) and found that estimated dopamine levels in the frontal cortex affected children's performance on frontal cortex tasks throughout infancy and early childhood (Diamond, Prevor, Callender, & Druin, 1997).

We investigated two dopamine system genes that have been demonstrated to impact on frontal cortex function in several studies: the catechol-*O*-methyltransferase gene (*COMT*) and the dopamine D4 receptor gene (*DRD4*). However, the dopamine system is not restricted to the frontal cortex. It also plays an important role in subcortical areas such as the striatum. We therefore included two dopaminergic polymorphisms believed to affect neurotransmission primarily in the striatum: the dopamine D2 receptor gene (*DRD2*) TaqIA polymorphism and the 40-bp 3′ variable number of tandem repeats (VNTR) polymorphism in the dopamine transporter gene (*DAT1, SLC6A3*). These polymorphisms could potentially affect performance in the Freeze-Frame task via frontal-subcortical circuits linking the frontal cortex to distinct areas of the striatum (Alexander, DeLong, & Strick, 1986; Cummings, 1993; Cummings & Miller, 2007; Di Martino et al., 2008; Nieoullon, 2002).

The striatum used to be regarded as a subcortical relay of information from diverse cortical areas, especially in relation to movement control (reviewed in Alexander et al., 1986). However, Alexander et al. proposed a model whereby distinct basal ganglia-thalamocortical circuits process information relevant to different functional domains. Two of these circuits involve parts of the prefrontal cortex (the dorsolateral prefrontal and the lateral orbitofrontal circuits), and one involves the anterior cingulate. In support of this model, work on experimental animals as well as neuropsychological studies of human patients have shown deficits in the functions associated with specific frontal areas (e.g., working memory function associated with the dorsolateral prefrontal cortex) after lesion of other nodes in the relevant frontal-subcortical circuit (Cummings, 1993; Divac, Rosvold, & Szwarcbart, 1967; Stuss et al., 1998; Yehene, Meiran, & Soroker, 2008). Furthermore, the existence of strong functional connections between the striatum and different parts of the frontal cortex has been confirmed in an analysis of human functional magnetic resonance imaging (fMRI) data (Di Martino et al., 2008). Given this extensive evidence for frontal-subcortical networks, it seemed important to investigate not just dopamine genes likely to affect processing in the frontal cortex but also dopamine genes acting primarily at the subcortical level.

Looking at the individual genes in more detail, the *COMT* gene codes for the COMT enzyme, which metabolizes catecholamines, such as dopamine and noradrenaline (Chen et al., 2004; Männistö & Kaakkola, 1999; Tunbridge, Harrison, & Weinberger, 2006). The role of COMT in catabolizing dopamine in the frontal cortex is particularly important because of the relative lack of dopamine transporters and the positioning of these transporters at a distance from synaptic release sites (Sesack, Hawrylak, Matus, Guido, & Levey, 1998). Thus, COMT accounts for approximately 50–60% of the metabolic degradation of dopamine in the frontal cortex (Karoum, Chrapusta, & Egan, 1994; Yavich, Forsberg, Karayiorgou, Gogos, & Männistö, 2007). In contrast, COMT catabolism plays only a minor role in the striatum where the dopamine transporter is abundant and better situated for dopamine reuptake (Karoum et al., 1994; Yavich et al., 2007; for a review, see Tunbridge et al., 2006). Consistent with this, studies of COMT-

deficient mice have demonstrated increased dopamine availability in the frontal cortex but not the striatum (Gogos et al., 1998; Yavich et al., 2007). The important role of COMT in the cortex compared with the striatum has also recently been shown in vivo in the human brain using positron emission tomography (PET; Slifstein et al., 2008).

The Val[158]Met polymorphism (rs4680) in the *COMT* gene affects the activity level of the COMT enzyme. The polymorphism is an evolutionarily recent G (guanine) to A (adenine) missense mutation at codon 158, resulting in a substitution of methionine (Met) for valine (Val) in the COMT enzyme (Chen et al., 2004; Lachman et al., 1996; Tunbridge et al., 2006, 2007). The Val and Met alleles are almost equally frequent in populations of European descent (Met-allele frequency = .47; heterozygosity = .48), whereas the Val allele is more common in other parts of the world (Met-allele frequency = .16–.34; heterozygosity = .27–.45; Palmatier, Kang, & Kidd, 1999).

The Met variant of the enzyme is less stable at body temperature (Chen et al., 2004; Lotta et al., 1995), resulting in three to four times less COMT enzyme activity in the human liver and red blood cells (Männistö & Kaakkola, 1999). In the human brain this difference is smaller, but still considerable, with Met/Met homozygotes having approximately 40% less COMT activity than Val/Val homozygotes in the prefrontal cortex (Chen et al., 2004). The alleles are codominant, resulting in Val/Met heterozygotes having an intermediate level of COMT activity (Egan et al., 2001; Männistö & Kaakkola, 1999; Tunbridge et al., 2006). This evidence strongly suggests that Met/Met homozygotes have the highest baseline level of dopamine available in the prefrontal cortex (because less dopamine is catabolized) with Val/Met heterozygotes having an intermediate level and Val/Val homozygotes having the lowest level of prefrontal dopamine (Tunbridge et al., 2006, 2007).

Several studies have demonstrated a relationship between the *COMT* Val[158]Met polymorphism and performance on tasks associated with the frontal cortex. For example, in an initial study, Egan et al. (2001) found that the *COMT* Val[158]Met polymorphism affected performance on the Wisconsin Card Sorting Test. Val/Val homozygotes performed significantly worse than Met/Met homozygotes and heterozygotes. Furthermore, the number of Met alleles (0–2) that an individual had significantly predicted neural efficiency in the frontal cortex during an *N*-back task, as measured by fMRI. In this task, all genotype groups performed at the same level, but Val/Val homozygotes showed significantly greater activation (indicating lower neural efficiency) in the frontal cortex than heterozygotes, and heterozygotes showed significantly greater activation than Met/Met homozygotes (Egan et al., 2001). Even though there are also negative findings in the literature (Barnett, Scoriels, & Munafò, 2008; Dennis et al., in press), the evidence for an effect of the *COMT* Val[158]Met polymorphism on neural efficiency as well as on a range of frontal cortex tasks has been replicated in several studies (Barnett, Jones, Robbins, & Müller, 2007; Bertolino et al., 2006; Blasi et al., 2005; Caldú et al., 2007; Diaz-Asper et al., 2008; Krämer et al., 2007; Mattay et al., 2003; Meyer-Lindenberg et al., 2006; Sheldrick et al., 2008; Stefanis et al., 2005). This evidence has been extended to a mouse model by Papaleo et al. (2008). The effect of the *COMT* Val[158]Met polymorphism on prefrontal efficiency has also recently been confirmed by meta-analysis (Mier, Kirsch, & Meyer-Lindenberg, in press).

Finally, a study by Diamond, Briand, Fossella, and Gehlbach (2004) demonstrated an effect of the *COMT* Val[158]Met polymorphism on school-age children's performance on a task hypothesized to depend on dopamine in the prefrontal cortex. This finding demonstrates the potential effect of variation in COMT activity at younger ages and opens up the possibility that the *COMT* Val[158]Met polymorphism might already have an effect on frontal cortex functioning in infancy.

The second candidate gene in our study was the *DRD4* gene. Knowledge about the distribution of the D[4] receptor in the human brain is limited because of the lack of appropriate radioligands (Hurd & Hall, 2005; Oak, Oldenhof, & Van Tol, 2000). However, existing evidence suggests that D[4] receptors are most abundant in the retina, followed by the prefrontal cortex (Oak et al., 2000). Hurd and Hall (2005) suggested that transmission via D[4] receptors is predominantly inhibitory in nature, resulting in disinhibition of excitatory transmission when these receptors are blocked. Thus, a lack of, or less efficient, D[4] receptors may lead to deficits in frontal cortex functioning.

The most widely studied polymorphism of the *DRD4* gene is located in the third exon and contains a 48–base pair variable number of tandem repeats (48-bp VNTR). Nine alleles of the *DRD4* 48-bp VNTR have been identified worldwide, with the number of repeats ranging between 2 and 10. The 4- and 7-repeat alleles are the most common globally, though the 2-repeat allele is prevalent in South and East Asian populations. In a population of mixed European ancestry, allele frequencies are .57, .21, and .12 for the 4-, 7-, and 2-repeat alleles, respectively (Chang, Kidd, Livak, Pakstis, & Kidd, 1996).

The number of 48-bp repeats has been hypothesized to affect the transmitted signal in the postsynaptic neuron. However, findings from in vitro studies have shown that the *DRD4* 48-bp VNTR does not significantly alter D[4] receptor activity (Oak et al., 2000). A more recent study suggests that the different repeat sequences may affect gene expression differentially, that is, the density of D[4] receptors in the brain. This study found that the 7-repeat allele had reduced expression compared with the 2-repeat and 4-repeat alleles (Schoots & Van Tol, 2003).

The *DRD4* 48-bp VNTR has been extensively studied in relation to attention deficit hyperactivity disorder (ADHD; Li, Sham, Owen, & He, 2006). ADHD has been linked to performance deficits on tasks assessing frontal cortex functions, such as response inhibition, selective attention, and set shifting (for a review, see Cornish et al., 2005). The 7-repeat allele has been consistently associated with ADHD in meta-analyses (Faraone et al., 2005; Li et al., 2006). Furthermore, the *DRD4* 48-bp VNTR has been shown to affect prefrontal gray matter volume in a sample of boys diagnosed with ADHD, their siblings, and controls (Durston et al., 2005). Recently, the 7-repeat allele has also been found to be associated with impulsivity and lower levels of response inhibition in healthy adults, both on its own (Congdon, Lesch, & Canli, 2008) and in combination with other polymorphisms in dopamine system genes (Congdon et al., 2008; Eisenberg et al., 2007). Finally, the 7-repeat allele has been linked to faster habituation in infancy and increased novelty seeking in adolescence (Laucht, Becker, & Schmidt, 2006) and to sensation seeking in toddlers when combined with poor parenting (Sheese, Voelker, Rothbart, & Posner, 2007). Therefore, the *DRD4* 48-bp VNTR can be considered a candidate polymorphism for frontal cortex functioning in infancy.

Turning to the genes most likely to act at the subcortical level, we note that the D_2 receptor is considerably less prevalent in the cerebral cortex than in the striatum (Ito, Okubo, Halldin, & Farde, 1999; Lidow, Goldman-Rakic, Rakic, & Innis, 1989). The *DRD2* TaqIA polymorphism was identified during the chromosomal localization of the gene. However, this polymorphism is located in the 3′ untranslated region, 10 kb downstream from the *DRD2* gene, actually in the adjacent gene *ANKK1* (Neville, Johnstone, & Walton, 2004); therefore, newer nomenclature refers to this polymorphism as the *DRD2/ANKK1* TaqIA polymorphism. The A1 allele is the minor allele, and the A1-present (A1+) genotype group (A1/A1 and A1/A2 genotypes) has a prevalence of approximately 31% in Caucasian individuals (Noble, 2000). The presence of this allele has been associated with lower D_2 receptor density in the human brain, as measured with PET, especially in the striatum (Jönsson et al., 1999; Pohjalainen et al., 1998; Ritchie & Noble, 2003; Thompson et al., 1997). Therefore, this polymorphism might serve as a good genetic marker for D_2 receptor density in the brain.

In contrast to the *DRD4* 48-bp VNTR, the *DRD2* TaqIA polymorphism is not associated with ADHD (Faraone et al., 2005). However, the A1 allele has been associated with various addictions (Munafò, Matheson, & Flint, 2007; Young, Lawford, Nutting, & Noble, 2004) and a more impulsive response style in a monetary reward task in healthy adults (Eisenberg et al., 2007). Little evidence exists for a role of the *DRD2* TaqIA polymorphism in frontal cortex functioning. However, Reuter et al. (2005) showed a significant interaction between the *DRD2* TaqIA polymorphism and the *COMT* Val[158]Met polymorphism on a Stroop-like task where participants had to respond as quickly as possible to the written form of color words written in incongruent colors. The interaction effect accounted for 13% of the variance in performance on this task. This result opens up the possibility that the *DRD2* gene (and perhaps other subcortical dopaminergic genes) impacts indirectly on frontal cortex functioning via interactions with genes affecting dopaminergic neurotransmission directly in the frontal cortex (e.g., *COMT* and *DRD4*).

Finally, we investigated the potential effect of a well-known polymorphism of the dopamine transporter gene (*DAT1*). The dopamine transporter is primarily expressed in the mesencephalon (a subcortical area with strong dopaminergic projections to the striatum and frontal cortex), with the highest density in the basal ganglia (Hurd & Hall, 2005). The *DAT1* gene contains a 40-bp VNTR in the 3′ untranslated region. Alleles range from 3 to 13 repeats, but the most common are the 9-repeat and 10-repeat alleles (Cornish et al., 2005). In populations of European ancestry, the frequencies of the 9- and 10-repeat alleles vary, but most studies report frequencies of approximately .30 for the 9-repeat allele and .70 for the 10-repeat allele (Kang, Palmatier, & Kidd, 1999). Although analyses of mRNA levels in brain regions resulted in contradictory findings (Mill, Asherson, Browes, D'Souza, & Craig, 2002; Wonodi et al., 2009), two independent large-scale in vivo single photon emission computed tomography (SPECT) studies have shown that healthy individuals with at least one copy of the 9-repeat allele (9/9 and 9/10 genotypes) have higher transporter density, and therefore presumably more effective dopamine removal at the synapse, than individuals with the 10/10 genotype (van de Giessen et al., 2008; van Dyck et al., 2005).

In terms of phenotypes, the *DAT1* gene has been studied extensively in relation to ADHD because stimulant medication used in its treatment acts by blocking the dopamine transporter. Evidence

suggests that 10/10 homozygosity is associated with a slightly increased risk of ADHD (Faraone et al., 2005; Yang et al., 2007). Furthermore, Cornish et al. (2005) reported an association between the 10/10 genotype and ADHD symptoms in a general population sample. This group also found an independent association between the 10/10 genotype and poorer performance on measures of selective attention and response inhibition in their selected high- and low-risk sample. A similar trend was found by Congdon et al. (2008) in a sample of healthy adults. Despite these findings, recent neuroimaging studies in adults have indicated a more efficient neural response in the prefrontal cortex of 10/10 homozygotes during a working memory task (Bertolino et al., 2006; Caldú et al., 2007), a pattern similar to that seen in participants with the *COMT* Met/Met genotype. One recent study also found higher levels of impulsivity in healthy adults with at least one 9-repeat allele (Forbes et al., 2009), contradicting other behavioral results. The behavioral effects of *DAT1* 3′ VNTR polymorphism may depend on the population studied.

In summary, the present study investigated whether performance on the Freeze-Frame task at 9 months of age was associated with genetic polymorphisms affecting important aspects of dopamine function in the brain. Because dopamine plays an important role in both the frontal cortex and the striatum, direct effects of the *COMT* Val[158]Met and *DRD4* 48-bp VNTR were hypothesized, with potential interacting or indirect effects of the *DRD2* TaqIA and *DAT1* 3′ VNTR polymorphisms.

Method

Sample

Infants were recruited from the greater London area. Data from two independent cohorts of infants were combined in the present study. Cohort 1 consisted of a small group of infants ($N = 24$). Behavioral results from this cohort have been reported previously (Holmboe et al., 2008). Cohort 2 consisted of a considerably larger group of infants ($N = 104$) who took part in a longitudinal study of frontal cortex functioning during the first year of life. Ninety-four infants from the original cohort of 104 infants (recruited at 4 months) participated in the study at 9 months. Data from this cohort have not been reported previously.

Data on parental education and household income were only collected in Cohort 2 but generally represent families recruited for studies at our laboratory. Parents were in their mid-thirties (mothers: $M = 34.43$, $SD = 4.90$; fathers: $M = 36.45$, $SD = 6.61$) and were primarily, but not exclusively, of middle or upper-middle-class socioeconomic status (maternal years of education: $M = 17.80$, $SD = 3.55$; household income in U.K. pounds: $M = 65,076$, $SD = 61,854$).[1] Seventy-nine percent of the infants tested (Cohorts 1 and 2 combined) had a White/Caucasian ethnic background (approximately three fourths of these infants were of British or Irish descent), and 21% had other or mixed ethnic background. Of the infants with other than Caucasian ethnic background ($N = 26$),

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[1] Approximate equivalent in U.S. dollars: $M = 120,511$, $SD = 114,544$, based on the average U.K. pound per U.S. dollar exchange rate of 0.54 in 2006 (NationMaster.com, 2009), when the majority of the data were collected.

8% had an Asian ethnic background, 15% had a Black ethnic background, and 77% had a mixed ethnic background (e.g., mother Asian and father Caucasian). Ethical permission for the study was obtained from the School of Psychology ethics board at Birkbeck, University of London.

The Freeze-Frame Task

A detailed description of the Freeze-Frame task can be found in Holmboe et al. (2008). In short, infants were presented with animations in the center of a 19-in (48.3-cm) color monitor. Infants were seated in their parent's lap at a 60-cm distance from the monitor. On every trial, a white square was flashed on the right or the left side of the screen (the distractor). If the infant looked to the distractor, the animation was stopped for 3,000 ms. If the infant did not look to the distractor, the animation continued after distractor presentation for the duration of the trial. Distractor duration was calibrated individually for each infant by increasing it by 40 ms on every trial where the infant did not look to the distractor. When the infant had looked to the distractor on two consecutive trials, distractor duration was fixed at the current duration for the rest of the test session. The even-numbered trials presented dynamic and colorful animations changing every 2 s (interesting trials), whereas the odd-numbered trials always presented the same uninteresting rotating orange star (boring trials). Infants were encouraged to complete 60 trials.

A few minor adjustments were made to the task used in Cohort 2. Most importantly, the animations were slightly smaller and a different set of animations was used for the interesting trials. The procedure used in Cohort 2 was the same as the procedure used in Cohort 1; however, in the new version, distractor duration did not increase beyond 1,200 ms. Infants were encouraged to complete 80 trials. The data were analyzed as described in Holmboe et al. (2008). That is, the session was divided into phases (from two trials before the calibration trial), invalid trials were excluded, and the proportion of looks to the distractors was calculated separately for boring and interesting trials in each phase. However, the additional data collection allowed an extra phase in the analyses. Thus, there were four phases of the experiment, each containing 16 trials (8 boring and 8 interesting).

Video recordings of each infant's behavior were coded offline. The coding procedure in Cohort 2 was similar to the procedure reported in Holmboe et al. (2008). The trial was considered invalid if the infant was not looking at the central stimulus at distractor onset or looked away during the distractor. The trial was also considered invalid if the infant blinked, that is, if the pupils were fully covered, during distractor presentation (unless the infant made a clear saccade to the distractor at the same time). In addition, the trial was considered invalid if these behaviors occurred during the 1,000 ms following distractor presentation. This criterion was added because in trials where the infant looks away immediately following distractor presentation, it is impossible to know whether the infant would have looked to the distractor had he or she not looked away from the screen. On rare occasions, a trial was excluded because the infant's eyes were out of view (e.g., if the infant's hand was in front of his or her eyes); such trials were considered invalid if the eyes were out of view for more than two frames (80 ms) during distractor presentation or within the 1,000

ms following distractor presentation. Finally, trials in which a saccade toward the distractor was initiated earlier than three frames (120 ms) after distractor onset were also considered invalid; such saccades were most likely anticipatory or random. Intercoder reliability in Cohort 2 was satisfactory for both looking behavior ($\kappa = .94$) and trial validity ($\kappa = .86$) based on data from 10 participants. (Intercoder reliability in Cohort 1 was similar; see Holmboe et al., 2008.)

Collection of Buccal Swabs and DNA Extraction

Buccal (cheek) swabs were collected when infants were 3.5 years of age in Cohort 1 as part of a follow-up study and when infants were 4 months old in Cohort 2. The buccal swab was collected by the parent in the lab (by rubbing a cotton bud on the inside of the child's cheeks for approximately 5–10 s) and then put in a sample tube by the experimenter. Two swabs per DNA sample tube were collected, and two independent samples per infant were shipped and isolated separately with a DNA-purification kit obtained from Gentra (Minneapolis, US), yielding a total of 2–10 μg DNA per sample.

Genotyping

Genotyping procedures were carried out using published protocols (*DRD2* TaqIA: Grandy, Zhang, & Civelli, 1993; *DRD4* 48-bp VNTR: Ronai et al., 2000; *COMT* Val[158]Met: Tarnok et al., 2007; *DAT1* 3′ VNTR: Vandenbergh et al., 1992). The two DNA samples from each infant were genotyped separately for all of the investigated polymorphisms. In order to ensure successful genotyping, we took the following precautions: In case of unsuccessful amplification of the *DRD4* 48-bp and *DAT1* 3′ VNTR polymorphisms (~10%) the polymerase chain reaction (PCR) was repeated. In addition, we carried out independent amplification reactions for 50% of the samples at the *DRD4* 48-bp VNTR because of the problematic amplification of the longer alleles (Ronai et al., 2000); this quality control step yielded the same genotypes as the ones originally obtained. For the *DRD2* TaqIA polymorphism, genotyping was repeated in case of unsuccessful amplification (~5%) or nonidentical results for the two samples at the restriction enzyme digestion (~8%). The *COMT* Val[158]Met polymorphism (rs4680) was also genotyped by an alternative method with a predesigned TaqMan kit (C_25746809_50, Applied Biosystems, Foster City, CA) on a 7300 Real-Time PCR System; the genotypes were in accordance with the original ones. Unsuccessful genotyping of the *COMT* Val[158]Met polymorphism occurred in 1–3% of samples (1% with the real-time PCR method, 3% with the allele-specific amplification method by Tarnok et al., 2007). Genotyping of these samples was repeated. After regenotyping, the genotyping success rate was 100% for all four polymorphisms.

Data Analyses

Data were analyzed with SPSS for Windows, Version 15. We analyzed behavioral data using repeated measures analysis of variance (ANOVA) and genotype data using the Linear Mixed Model (LMM) procedure in SPSS, assuming a diagonal covariance structure, and with a random intercept term. Participant ID was entered as the subject variable (treated as a random effect). Phase

and trial type were entered as repeated measures, and proportion of looks to the distractors was entered as the dependent variable. Genotype was entered as a between-subjects factor. All main effects and interaction terms were entered into the model as fixed effects (full factorial design).

The advantage of LMM is that data from participants with missing data points, in this case missing data from one or more phases of the experiment, can be included in the analysis (Garson, 2008). Missing data points are inevitable in infant studies and, given the fact that the genotype effects in which we were interested were likely to be modest in magnitude, we wished to include as much of the data in the analyses as possible.

Because of the risk of population stratification in ethnically mixed samples (Hutchison, Stallings, McGeary, & Bryan, 2004), genotype analyses were carried out on both the entire sample and on the subsample of infants of Caucasian ethnic origin. Significant main effects and interactions were followed up by post hoc tests and checked against a false discovery rate (FDR) adjusted p value based on the total number of post hoc tests carried out across all genotype analyses in both the total sample and the Caucasian subsample (33 post hoc tests in total). The FDR was controlled at $p < .05$ with the method described by Benjamini, Drai, Elmer, Kafkafi, and Golani, (2001). Only post hoc comparisons that remained significant after controlling the FDR are reported.

The Hardy–Weinberg equilibrium test was calculated with Knud Christensen's program (Christensen, 1999); for the *DAT1* 3′ VNTR, the three common genotypes from two frequent alleles (9- and 10-repeat) were included in the analysis, and for the *DRD4* 48-bp VNTR, genotypes from four common alleles (2-, 3-, 4-, and 7-repeat) were analyzed. For the *COMT* Val[158]Met and *DRD2* TaqIA polymorphisms, there were only three genotypes and therefore, all infants could be included in the Hardy–Weinberg test.

In the analyses investigating potential genotype effects on Freeze-Frame performance, we compared the most frequent 10/10 genotype of the *DAT1* 3′ VNTR with all other genotypes (9/9, 9/10, and other types of heterozygotes, i.e., 3/10, 7/10, 10/11). The latter group is referred to as the non-10/10 group. Genotype grouping for the *DRD4* 48-bp VNTR polymorphism was based on the presence or absence of the 7-repeat allele (the 7+ group and the 7− group, respectively). One infant with the genotype 4/8 was included in the 7+ group.

Results

Genotype and Allele Distribution

Genotype data were available for 19 of the 24 infants in Cohort 1. Seventeen of these infants were of Caucasian ethnic origin. In Cohort 2, genotype data were available for all 94 infants (71 Caucasian) tested at 9 months of age. When the two cohorts were pooled, genotype data were available for 113 infants (88 Caucasian). One hundred and two of these infants (79 Caucasian) calibrated in the task (see below) and could be included in the analyses. Genotype frequencies for each of the four polymorphisms are presented in Table 1, and allele frequencies are presented in a supplemental table online. Alleles and genotypes were in Hardy–Weinberg equilibrium for all polymorphisms, with the exception of the *DRD4* 48-bp VNTR polymorphism in the total sample (see note to Table 1). When the Hardy–Weinberg analysis

Table 1

Genotype Frequencies in the Total Sample and the Caucasian Subsample for the Four Dopamine System Gene Polymorphisms

Genotype	Total	Caucasian	Grouping
DRD4 48-bp VNTR			
2/3	2 (2.0)	2 (2.5)	7−
2/4	10 (9.8)	9 (11.4)	7−
2/7	8 (7.8)	4 (5.1)	7+
3/4	8 (7.8)	6 (7.6)	7−
3/7	2 (2.0)	2 (2.5)	7+
4/4	48 (47.1)	36 (45.6)	7−
4/5	2 (2.0)	0 (0.0)	7−
4/7	21 (20.6)	19 (24.1)	7+
4/8	1 (1.0)	1 (1.3)	7+
7+	32 (31.4)	26 (32.9)	
COMT Val[158]Met			
Met/Met	28 (27.5)	19 (24.1)	Met/Met
Val/Met	47 (46.1)	37 (46.8)	Val/Met
Val/Val	27 (26.5)	23 (29.1)	Val/Val
DRD2 TaqIA			
A1/A1	4 (3.9)	4 (5.1)	A1+
A1/A2	29 (28.4)	20 (25.3)	A1+
A2/A2	69 (67.6)	55 (69.6)	A1−
A1+	33 (32.4)	24 (30.4)	
DAT1 3' VNTR			
3/10	1 (1.0)	0 (0.0)	Non-10/10
7/10	1 (1.0)	0 (0.0)	Non-10/10
9/9	4 (3.9)	3 (3.8)	Non-10/10
9/10	35 (34.3)	30 (38.0)	Non-10/10
10/10	60 (58.8)	45 (57.0)	10/10
10/11	1 (1.0)	1 (1.3)	Non-10/10
Non-10/10	42 (41.2)	34 (43.0)	
	102[a]	79[a]	

Note. Percentages are presented in brackets. Only data from infants who calibrated in the Freeze-Frame task are included in the table (data from infants who did not calibrate could not be used in the analyses). All polymorphisms except the dopamine D4 receptor (*DRD4*) 48–base pair (48-bp) variable number of tandem repeats (VNTR) polymorphism conformed to Hardy–Weinberg equilibrium: *DRD4* 48-bp VNTR: $\chi^2(6) = 12.95$, $p = .044$ (all participants); $\chi^2(6) = 5.80$, $p = .45$ (Caucasian participants only). Catechol-*O*-methyltransferase (*COMT*) valine[158]methionine (Val[158]Met): $\chi^2(1) = 0.63$, $p = .43$ (all participants); $\chi^2(1) = 0.29$, $p = .59$ (Caucasian participants only). Dopamine D2 receptor (*DRD2*) Taq1A: $\chi^2(1) = 0.18$, $p = .67$ (all participants); $\chi^2(1) = 1.37$, $p = .24$ (Caucasian participants only). *DAT1* 3' VNTR: $\chi^2(1) = 0.16$, $p = .69$ (all participants); $\chi^2(1) = 0.54$, $p = .46$ (Caucasian participants only).
[a] Total *N*.

of the *DRD4* 48-bp VNTR was restricted to the Caucasian subsample, the p value increased to .45. In order to ensure a genetically homogenous population, we carried out every genotype analysis in the Caucasian subsample as well. Allele and genotype frequencies were generally in agreement with the frequencies reported for a mixed European population (see introduction) and were similar in the total sample and the Caucasian subsample.

Freeze-Frame Behavioral Results

One hundred and two infants of the 113 infants with genotype data available calibrated in the Freeze-Frame task (79 in the

Caucasian subsample), that is, they looked to the distractor on two consecutive trials (6 infants did not calibrate, and 5 infants were incorrectly calibrated by the experimenter; these infants could not be included in the analyses). Distractor duration, on average, was calibrated in 5.53 trials ($SD = 8.13$; range = 2 to 64), and the mean calibrated distractor duration was 324 ms ($SD = 181$; range = 200 to 1,200). The average proportion of valid trials was 0.82 ($SD = 0.10$). Infants in Cohort 2 had a slightly lower proportion of valid trials than did infants in Cohort 1 (0.81 vs. 0.90), probably because of the session being a few minutes longer in Cohort 2, but the groups did not differ significantly in terms of calibration data (data not shown).

The proportion of looks to the distractors in each phase and trial type is presented in Table 2. Freeze-Frame results from Cohort 1 have been reported previously (Holmboe et al., 2008). In the previous study, a repeated measures ANOVA indicated that there were significant main effects of phase and trial type but no interaction. Results were unchanged in the sample of infants from Cohort 1 for whom genotype data were available (data not shown). These results were also replicated in Cohort 2—for trial type, $F(1, 68) = 79.29$, $p < .001$, $\eta_p^2 = .54$; for phase, $F(2, 136) = 99.63$, $p < .001$, $\eta_p^2 = .59$; for phase × trial type, $F(2, 136) = 0.63$, $p = .53$—and in the total sample: for trial type, $F(1, 81) = 105.99$, $p < .001$, $\eta_p^2 = .57$; for phase, $F(2, 162) = 117.42$, $p < .001$, $\eta_p^2 = .59$; for phase × trial type, $F(2, 162) = 0.59$, $p = .55$. The same significant effects were found when four phases were included in an ANOVA using data from Cohort 2 (data not shown). These results indicate that there is a clear main effect of trial type on looks to the distractors such that infants looked less to the distractors in the interesting trials than in the boring trials. Infants also showed a decrease in looks to the distractors during the test session, and this decrease was similar in the two trial types, that is, there was no interaction (Table 2).

For the genotype analyses, we wished to combine the data from the two cohorts to increase power. In order to combine all of the available data, it was important to establish that infants in the two cohorts performed the task in the same way. A few minor parameters of the Freeze-Frame task differed between the two cohorts (see Method). Therefore, the repeated measures ANOVA was repeated with cohort as a between-subjects variable. This analysis clearly replicated the main effects and lack of interaction (data not shown). It is important to note that there was no significant main effect of, or interactions involving, cohort (all $ps > .30$). Given this lack of significant differences between the two cohorts, we deemed it appropriate to pool the data for the genotype analyses.

In all of the genotype analyses reported below, the main effects of phase and trial type remained significant, with no interaction between phase and trial type (data not shown). Furthermore, none of the polymorphisms was associated with basic task parameters such as the calibrated distractor duration or proportion of valid trials after controlling the FDR.

The *COMT* Val[158]Met Polymorphism and Freeze-Frame Performance

All four phases of the Freeze-Frame task were included in the LMM, as this analysis incorporates all available data. The LMM analysis indicated that there was a significant main effect of *COMT* Val[158]Met genotype on the proportion of looks to the distractors, $F(2,564.08) = 3.01$, $p < .050$. No interactions involving *COMT* Val[158]Met genotype reached significance in the total sample (all $ps > .15$). When the analysis was restricted to Caucasian infants, this picture changed. The main effect of *COMT* Val[158]Met genotype was no longer significant, $F(2,418.32) = 2.20$, $p = .112$, but the *COMT* Val[158]Met genotype × trial type interaction was significant, $F(2,418.32) = 4.38$, $p = .013$, indicating that *COMT* Val[158]Met genotype affected performance in the two trial types differentially. No other interactions approached significance (all $ps > .70$).

Post hoc analyses of the main effect of *COMT* Val[158]Met genotype in the total sample indicated that none of the differences between genotype groups survived the FDR correction. Post hoc analyses of the *COMT* Val[158]Met genotype × trial type interaction observed in the Caucasian subsample indicated a significant difference in looks to the distractors in interesting trials both between the Met/Met and Val/Val groups ($p < .0001$) and between the Met/Met and Val/Met groups ($p < .01$). No other post hoc comparisons reached significance after controlling the FDR. The *COMT* Val[158]Met genotype differences in the Caucasian subsample are illustrated in Figure 1a.

The *DRD4* 48-bp VNTR Polymorphism and Freeze-Frame Performance

The LMM analysis of the effect of the *DRD4* 48-bp VNTR on performance in the Freeze-Frame task showed no significant effects involving genotype in either the total or the Caucasian subsample (all $ps > .15$). This indicates that, in the current sample, the 7+ group did not differ from the 7− group in terms of Freeze-Frame performance at 9 months of age.

The *DRD2* TaqIA Polymorphism and Freeze-Frame Performance

The LMM showed no significant effects involving *DRD2* TaqIA genotype (all $ps > .70$). This result was unchanged when the analysis was restricted to Caucasian infants (all $ps > .20$). The *DRD2* TaqIA polymorphism did not therefore have any significant effect on Freeze-Frame performance in the present sample.

Table 2

Descriptive Statistics for the Proportion of Looks to the Distractors Across Phases and Trial Types in the Freeze-Frame Task

Trial type and phase	M	SD
Boring trials		
Phase 1	.69	.22
Phase 2	.42	.28
Phase 3	.40	.24
Phase 4[a]	.39	.25
Total	.48	.17
Interesting trials		
Phase 1	.45	.25
Phase 2	.19	.19
Phase 3	.13	.16
Phase 4[a]	.11	.15
Total	.22	.14

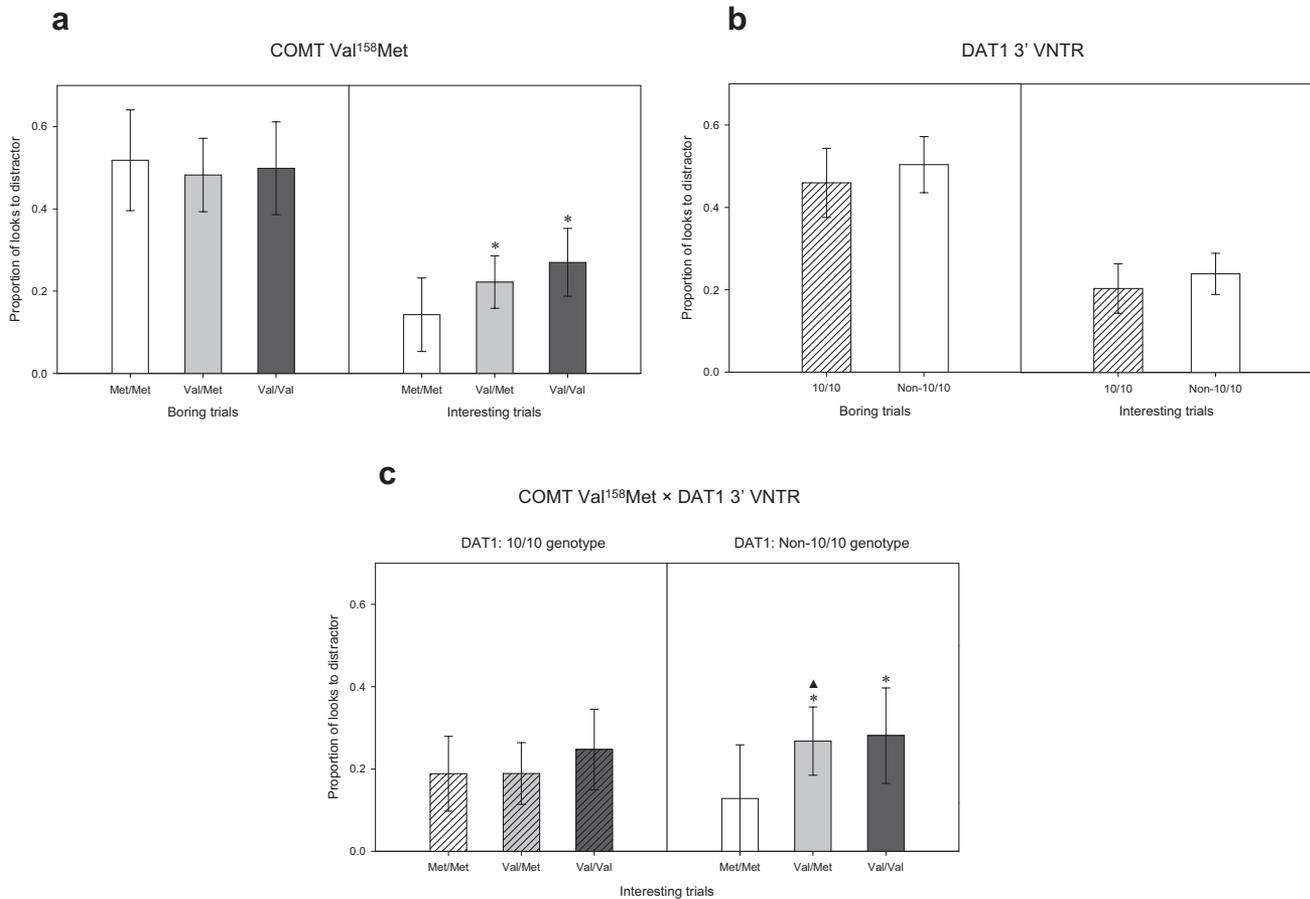[a] Only infants in Cohort 2 completed four phases.

Figure 1. The effect of the catechol-*O*-methyltransferase (*COMT*) valine[158]methionine (Val[158]Met) and dopamine transporter (*DAT1*) 3′ variable number of tandem repeats (VNTR) polymorphisms on Freeze-Frame performance. Error bars indicate the 95% confidence interval of the mean. (a) The mean proportion of looks to the distractors in the boring and interesting Freeze-Frame trials in the three *COMT* Val[158]Met genotype groups in the Caucasian subsample (Met/Met, $n = 19$; Val/Met, $n = 37$; Val/Val, $n = 23$). An asterisk indicates a significant difference from the Met/Met group at $p < .01$. (b) The mean proportion of looks to the distractors in the boring and interesting Freeze-Frame trials in the *DAT1* 3′ VNTR 10/10 and non-10/10 genotype groups (10/10, $n = 60$; non-10/10, $n = 42$); the overall difference between the two genotype groups (across trial types) was significant at $p < .05$. (c) The effect of the *COMT* Val[158]Met polymorphism on the mean proportion of looks to the distractors in the interesting Freeze-Frame trials in the two *DAT1* genotype groups (10/10 + Met/Met, $n = 19$; 10/10 + Val/Met, $n = 26$; 10/10 + Val/Val, $n = 15$; non-10/10 + Met/Met, $n = 9$; non-10/10 + Val/Met, $n = 21$; non-10/10 + Val/Val, $n = 12$). An asterisk indicates a significant difference from the Met/Met group at $p < .01$ within the non-10/10 group, and a triangle indicates a significant difference at $p < .01$ between the Val/Met group in the non-10/10 group compared with the Val/Met group in the 10/10 group.

The *DAT1* 3′ VNTR Polymorphism and Freeze-Frame Performance

The LMM analysis of the *DAT1* 3′ VNTR showed a significant main effect of genotype in the total sample, $F(1,569.52) = 3.98$, $p = .047$. No interactions reached significance (all $ps > .15$). When the analysis was restricted to Caucasian infants, the main effect of *DAT1* 3′ VNTR genotype was only significant at trend level, $F(1,427.74) = 2.92$, $p = .088$. There was also a marginally significant *DAT1* 3′ VNTR genotype × phase interaction, $F(3,191.66) = 2.34$, $p = .075$. The main effect of *DAT1* 3′ VNTR genotype in the total sample was due to the 10/10 group looking less to the distractors overall than the non-10/10 group. This

difference is illustrated in Figure 1b. No post hoc analyses were carried out, as only the main effect of *DAT1* 3′ VNTR genotype was significant.

Analysis of the Combined Effect of the *COMT* Val[158]Met and *DAT1* 3′ VNTR Polymorphisms on Freeze-Frame Performance

The genotype distribution of the *COMT* Val[158]Met and *DAT1* 3′ VNTR, which had genotype × genotype group sizes between 9 and 26 participants (see legend to Figure 1), allowed us to investigate the potential interaction between these two polymorphisms.

(Genotype frequencies for the other polymorphisms in the study resulted in group sizes that were too small to allow investigation of interactions, with the size of minor genotype × genotype groups being less than 5.) An LMM where both *DAT1* 3′ VNTR genotype and *COMT* Val[158]Met genotype were entered as independent variables showed a significant main effect of *COMT* Val[158]Met genotype, $F_{(2,528.98)} = 3.41$, $p = .034$, and a trend significant effect of *DAT1* 3′ VNTR genotype, $F_{(1,529.47)} = 3.30$, $p = .070$. In addition to these main effects, there was a significant *COMT* Val[158]Met genotype × trial type interaction, $F_{(2,528.98)} = 3.19$, $p = .042$, and a significant *DAT1* 3′ VNTR genotype × *COMT* Val[158]Met genotype × trial type interaction, $F_{(2,528.98)} = 4.09$, $p = .017$. The *DAT1* 3′ VNTR genotype × phase interaction approached significance, $F_{(3,240.18)} = 2.24$, $p = .084$, as did the *DAT1* 3′ VNTR genotype × *COMT* Val[158]Met genotype × phase interaction, $F_{(6,241.10)} = 1.91$, $p = .079$. No other interactions approached significance in the total sample (all $ps > .35$).

In the Caucasian subsample alone, the results were slightly different. The main effect of *COMT* Val[158]Met genotype approached significance, $F_{(2,373.00)} = 2.82$, $p = .061$. The same was the case for the *DAT1* 3′ VNTR genotype, $F_{(1,374.07)} = 3.82$, $p = .051$. Again, the *COMT* Val[158]Met genotype × trial type interaction was significant, $F_{(2,373.00)} = 4.13$, $p = .017$. Finally, the *DAT1* 3′ VNTR genotype × phase interaction was significant in the Caucasian subsample, $F_{(3,170.63)} = 2.98$, $p = .033$. No other interactions reached significance in the Caucasian subsample (all $ps > .20$).

Post hoc analyses were restricted to the novel interaction effects involving *COMT* Val[158]Met and *DAT1* 3′ VNTR because all significant and near-significant main effects were qualified by a significant interaction and because other interactions, such as the *COMT* Val[158]Met genotype × trial type interaction, essentially indicated the same genotype effects as the analyses of the two polymorphisms separately. Post hoc analyses of the *DAT1* 3′ VNTR genotype × *COMT* Val[158]Met genotype × trial type interaction in the total sample indicated that within the *DAT1* non-10/10 group there was a significant difference in looks to the distractors in the interesting trials between the Met/Met and Val/Val groups ($p < .001$) and between the Met/Met and Val/Met groups ($p = .001$). In contrast, no *COMT* genotype differences reached significance in the *DAT1* 10/10 group after controlling the FDR. This pattern of results is illustrated in Figure 1c. With regard to performance in each *COMT* genotype group across *DAT1* genotypes, infants with the Val/Met genotype who also had the *DAT1* 10/10 genotype looked significantly less to the distractors in the interesting trials than did infants with the Val/Met genotype in the *DAT1* non-10/10 group ($p < .01$). The other *COMT* genotype groups did not differ significantly across *DAT1* genotype groups in the interesting trials (Figure 1c). None of the post hoc tests of the *DAT1* 3′ VNTR genotype × *COMT* Val[158]Met genotype × trial type interaction showed significant effects in the boring trials after controlling the FDR.

Post hoc analyses indicated that the *DAT1* 3′ VNTR genotype × phase interaction found in the Caucasian subsample was due to a highly significant difference in proportion of looks to the distractors between the 10/10 group and the non-10/10 group in phase 3 of the Freeze-Frame session ($p < .001$).

Discussion

In the present study, we investigated whether performance in a novel task developed to assess frontal cortex functioning in infancy, the Freeze-Frame task (Holmboe et al., 2008), was associated with common polymorphisms in four dopamine system genes. Previous research has clearly shown that dopamine plays an important role in the frontal cortex (Brozoski et al., 1979; Collins et al., 1998; Diamond et al., 1997; Goldman-Rakic et al., 2000; Roberts et al., 1994; Sawaguchi & Goldman-Rakic, 1991; Vijayraghavan et al., 2007).

Behaviorally, we replicated previous findings on the Freeze-Frame task (Holmboe et al., 2008). In relation to the polymorphisms likely to impact directly on frontal cortex function, we found a significant association between Freeze-Frame performance and the *COMT* Val[158]Met polymorphism. Given the extensive evidence for an association between the *COMT* Val[158]Met polymorphism and performance on a range of frontal cortex tasks (Diamond et al., 2004; Diaz-Asper et al., 2008; Egan et al., 2001; Mattay et al., 2003; Sheldrick et al., 2008; Stefanis et al., 2005; see also Papaleo et al., 2008), as well as effects on neural efficiency in the frontal cortex during performance of these tasks (Bertolino et al., 2006; Blasi et al., 2005; Caldú et al., 2007; Egan et al., 2001; Krämer et al., 2007; Mattay et al., 2003; Meyer-Lindenberg et al., 2006; Mier et al., in press), it seems likely that *COMT* Val[158]Met genotype affects dopamine levels in the frontal cortex and thereby Freeze-Frame performance in our infant sample.

Furthermore, it is worth noting that this effect was specific to the interesting trials, at least in the Caucasian subsample (Figure 1a). This suggests that the *COMT* Val[158]Met effect is not a general effect impacting on infants' distractibility level in any given situation. Rather, it seems to be the case that infants with the low-enzyme activity Met/Met genotype became particularly focused on the central stimulus compared with the high-enzyme activity Val/Val genotype when this stimulus was engaging. However, it should be noted that the interaction with trial type was significant in the Caucasian subsample only and therefore might not generalize to other populations.

We found little evidence that the *DRD4* 48-bp VNTR polymorphism affects performance on the Freeze-Frame task at 9 months of age, though the sample was too small to detect subtle effects. In terms of the polymorphisms that are likely to act in the striatum, we did not observe any effect of the *DRD2* TaqIA either. We did, however, observe an effect of the *DAT1* 3′ VNTR polymorphism. In contrast to the effect of the *COMT* Val[158]Met polymorphism, this effect did not appear to be specific to a particular trial type. Instead, we found evidence of an overall difference in the proportion of looks to the distractors, with the 10/10 group looking less to the distractors than did the non-10/10 group (Figure 1b). The results therefore suggest that the *DAT1* 3′ VNTR polymorphism modulates overall distractibility in the Freeze-Frame task, though there was a tendency for this genotype effect to be stronger at the end of the test session. Given the fact that the dopamine transporter plays an important role in the striatum (Hurd & Hall, 2005; Karoum et al., 1994), this effect could be due to modulation of general attentional mechanisms mediated by the subcortical dopamine system or frontal-subcortical connections (Alexander et al., 1986; Cummings, 1993).

Finally, we investigated the potential interaction between the *COMT* Val[158]Met and *DAT1* 3′ VNTR polymorphisms on Freeze-Frame performance. The results of these analyses broadly replicated the main effects and interactions found in the analysis of each polymorphism separately. However, the analysis also revealed a significant *DAT1* 3′ VNTR genotype × *COMT* Val[158]Met genotype × trial type interaction, suggesting that the *DAT1* 3′ VNTR polymorphism modulated the effect of the *COMT* Val[158]Met polymorphism on Freeze-Frame performance. Basically, the effect of the *COMT* Val[158]Met polymorphism on the proportion of looks to the distractors in the interesting trials was strong in the *DAT1* non-10/10 group, with particularly large differences between the Met/Met group and the two other genotype groups (Figure 1c, right panel). In contrast, the equivalent effect in the *DAT1* 10/10 group virtually disappeared (Figure 1c, left panel).

Presuming that a lower level of distractibility in the interesting trials is an expression of a higher degree of selective inhibition, these results suggest that infants with higher COMT enzyme activity (Val/Val and Val/Met) actually benefit from having the *DAT1* 10/10 genotype, whereas this is not the case for infants with low COMT enzyme activity (Met/Met). This was confirmed at least for the Val/Met genotype; this genotype showed a significant reduction in looks to the distractors in the interesting trials when combined with the 10/10 genotype rather than with the non-10/10 genotype (Figure 1c). Though preliminary given the sample size, these findings are particularly interesting because they suggest that the interaction between a predominantly frontal dopaminergic polymorphism (*COMT* Val[158]Met) and a predominantly striatal dopaminergic polymorphism (*DAT1* 3′ VNTR) results in large performance differences on the Freeze-Frame task as early as 9 months of age.

Despite the likely effect of both frontal and subcortical mechanisms in the reported results, it is not possible to establish the exact neural substrate of this interaction from the current data. Previous studies have found additive genetic effects of the *DAT1* 3′ VNTR and *COMT* Val[158]Met polymorphisms on neural efficiency in the frontal cortex but no epistasis (Bertolino et al., 2006; Caldú et al., 2007). Further research involving neuroimaging data will help elucidate the potential role of the frontal cortex and the striatum in the genotype effects found in the present study.

It should be mentioned that it would have been ideal to investigate all possible interactions among the four polymorphisms in the study. However, only the *COMT* Val[158]Met and the *DAT1* 3′ VNTR polymorphisms had genotype frequencies providing enough power to investigate interaction effects (see Results). For the *DRD4* 48-bp VNTR and the *DRD2* TaqIA polymorphisms, the genotype frequencies involving the minor allele were too low to test meaningful interactions. A clear limitation of the study is therefore the relatively small sample size (though large for an infant study). Future studies should address the question of interactions between all four (and additional) polymorphisms in dopamine system genes in a larger infant cohort. Furthermore, assessment of additional genetic ancestry-informative markers would prevent the sample reduction caused by analyzing the Caucasian-only sample.

The current study constitutes a snapshot in time at 9 months of age. Future studies over a wider age range may help elucidate which patterns of Freeze-Frame performance are adaptive throughout infancy and early childhood and how these patterns relate to polymorphisms in dopamine system genes. Some progress has already been made toward this at the behavioral level in the work by Holmboe et al. (2008), where performance indices on early frontal cortex tasks showed both positive and negative associations with later performance. Nevertheless, an important conclusion to be drawn from the results of the present study is that polymorphisms in dopamine system genes play an important role as early as infancy. Previous studies have found effects of the *DRD4* 48-bp VNTR on temperament and relatively broad aspects of attention in infancy (Auerbach et al., 1999; Auerbach, Benjamin, Faroy, Geller, & Ebstein, 2001; Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001; Ebstein et al., 1998; Laucht et al., 2006; Sheese et al., 2007). The current study adds to this evidence by showing that the *COMT* Val[158]Met polymorphism, which is thought to play an important role specifically in the frontal cortex, affects performance on a simple saccadic inhibition task in infancy.

In conclusion, the results of the present study further validate the Freeze-Frame task and demonstrate that variation in dopaminergic neurotransmission in the frontal cortex and associated subcortical structures can have an impact on infant attention as early as 9 months of age. The exact neural substrate and developmental course of these genotypic differences is a fruitful area for future research. This research holds the promise of deepening our understanding of the genetic underpinnings of individual differences in the important functions mediated by the frontal cortex from an early age.

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