

*Polymorphisms in dopamine system genes  
are associated with individual differences  
in attention in infancy*

Article

Accepted Version

Holmboe, K., Nemoda, Z., Fearon, R. M. P., Csibra, G.,  
Sasvari-Szekely, M. and Johnson, M. H. (2010)  
Polymorphisms in dopamine system genes are associated with  
individual differences in attention in infancy. *Developmental  
Psychology*, 46 (2). pp. 404-416. ISSN 0012-1649 doi:  
10.1037/a0018180 Available at  
<https://centaur.reading.ac.uk/17514/>

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Published version at: <http://dx.doi.org/10.1037/a0018180>

To link to this article DOI: <http://dx.doi.org/10.1037/a0018180>

Publisher: American Psychological Association

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1 Polymorphisms in Dopamine System Genes are Associated with Individual Differences in  
2 Attention in Infancy

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## 1 Abstract

2 Knowledge about the functional status of the frontal cortex in infancy is limited. This study  
3 investigated the effects of polymorphisms in four dopamine system genes on performance in  
4 a task developed to assess such functioning, the Freeze-Frame task, at 9 months of age.

5 Polymorphisms in the catechol-*O*-methyltransferase (*COMT*) and the dopamine D4 receptor  
6 (*DRD4*) genes are likely to impact directly on the functioning of the frontal cortex, while  
7 polymorphisms in the dopamine D2 receptor (*DRD2*) and dopamine transporter (*DAT1*)

8 genes might influence frontal cortex functioning indirectly via strong fronto-striatal  
9 connections. A significant effect of the *COMT* Val<sup>158</sup>Met polymorphism was found. Infants

10 with the Met/Met genotype were significantly less distractible than infants with the Val/Val  
11 genotype in Freeze-Frame trials presenting an engaging central stimulus. In addition, there

12 was an interaction with the *DAT1* 3' VNTR polymorphism; the *COMT* effect was only

13 present in infants who did not have two copies of the *DAT1* 10-repeat allele. These findings  
14 indicate that dopaminergic polymorphisms already affect selective aspects of attention in  
15 infancy, and further validate the Freeze-Frame task as a frontal cortex task.

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17 Key words: Frontal cortex, Infancy, Dopamine genes, Attention, Frontal-subcortical circuits

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1 Polymorphisms in Dopamine System Genes are Associated with Individual Differences in  
2 Attention in Infancy

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4 Introduction

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

9 The frontal cortex has a more protracted development than other areas of the brain, with  
10 synaptogenesis continuing well into middle childhood (Glantz, Gilmore, Hamer, Lieberman,  
11 & Jarskog, 2007; Huttenlocher, 1990). Glucose metabolism and regional cerebral blood flow  
12 also peak later in the frontal cortex (Chugani & Phelps, 1986; Chugani, Phelps, & Mazziotta,  
13 1987; Franceschini et al., 2007). Despite this protracted developmental course, infant  
14 neuroimaging studies have shown activation in the frontal cortex during language processing,  
15 processing of novel stimuli, and working memory (Baird et al., 2002; Bell, 2001; Bell & Fox,  
16 1992, 1997; Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Homae, Watanabe,  
17 Nakano, & Taga, 2007; Nakano, Watanabe, Homae, & Taga, 2008). Furthermore, Diamond  
18 and colleagues have shown that performance on a task which has been directly associated  
19 with the frontal cortex, the A-not-B task (Piaget, 1954), improves drastically during the  
20 second half of the first year of life (Diamond, 1985; Diamond & Goldman-Rakic, 1989;  
21 Diamond, Zola-Morgan, & Squire, 1989).

22 A previous report sought to validate a new infant frontal cortex task, the Freeze-Frame  
23 task, by investigating the relationship between this task and other infant and toddler frontal  
24 cortex tasks (Holmboe, Fearon, Csibra, Tucker, & Johnson, 2008). The Freeze-Frame task  
25 was developed to assess various aspects of inhibitory control in infancy using eye movements

1 as the dependent measure. In the task, infants are encouraged to stay fixated on an animated  
2 cartoon in the centre of a computer screen. On every trial a peripheral distractor (a white  
3 square) is presented. If the infant looks to this distractor, the animation is frozen for a brief  
4 period of time. Furthermore, the task involves two alternating trial types. In the *interesting*  
5 trials a dynamic and changeable animation is presented, whereas the *boring* trials present the  
6 same simple animation (a rotating orange star) every time.

7 In the study by Holmboe and colleagues (2008) it was found that 9-month-old infants  
8 stopped looking to the distractors during the course of the test session. Infants also looked  
9 less to the distractors in the interesting trials right from the beginning of the session. No  
10 evidence of an interaction between trial type and phase of the test session was found.  
11 Individual performance indices suggested that infants who looked less to the distractors in the  
12 interesting trials than the boring trials early in the Freeze-Frame session performed better on  
13 the A-not-B task at 9 months of age. Another index, which assessed infants' ability to  
14 selectively learn to inhibit looks to the distractors, was associated with significantly better  
15 performance on a frontal cortex task at 24 months of age, the Spatial Conflict task (Gerardi-  
16 Caulton, 2000; Rothbart, Ellis, Rueda, & Posner, 2003), suggesting that Freeze-Frame  
17 performance at 9 months is predictive of later frontal cortex functioning (Holmboe et al.,  
18 2008).

19 Even though these results indicate that performance on the Freeze-Frame task shares a  
20 significant proportion of its variance with performance on other infant and toddler frontal  
21 cortex tasks, this is still relatively indirect evidence that the task depends on the frontal  
22 cortex. More definitive evidence that the task is indeed associated with the functioning of the  
23 frontal cortex would involve establishing a direct relationship between performance on the  
24 task and biological markers of frontal cortex functioning. One way to address this issue is to  
25 investigate the potential effect of genetic variation. In the present study we therefore

1 investigated the relationship between performance on the Freeze-Frame task and well-  
2 established candidate polymorphisms in dopamine system genes.

3 The neurotransmitter dopamine plays a major role in the frontal cortex. For example,  
4 depletion of dopamine, but not noradrenaline or serotonin, in the dorsolateral prefrontal  
5 cortex causes delayed-response deficits similar to those seen after ablation of that area  
6 (Brozoski, Brown, Rosvold, & Goldman, 1979; Collins, Roberts, Dias, Everitt, & Robbins,  
7 1998; Roberts et al., 1994). Furthermore, recordings from prefrontal dopamine-sensitive  
8 neurons in primates have shown these neurons to be active during the delay period in  
9 working memory tasks (Goldman-Rakic, Muly, & Williams, 2000; Sawaguchi & Goldman-  
10 Rakic, 1991; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). Finally,  
11 Diamond and colleagues investigated children treated early and continuously for  
12 phenylketonuria (PKU) and found that estimated dopamine levels in the frontal cortex  
13 affected children's performance on frontal cortex tasks throughout infancy and early  
14 childhood (Diamond, Prevor, Callender, & Druin, 1997).

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

1       The striatum used to be regarded as a subcortical relay of information from diverse  
2 cortical areas, especially in relation to movement control (reviewed in Alexander et al.,  
3 1986). However, Alexander and colleagues (1986) proposed a model whereby distinct basal  
4 ganglia-thalamo-cortical circuits process information relevant to different functional  
5 domains. Two of these circuits involve parts of the prefrontal cortex (the dorsolateral  
6 prefrontal and the lateral orbitofrontal circuits), and one involves the anterior cingulate. In  
7 support of this model, work on experimental animals as well as neuropsychological studies of  
8 human patients have shown deficits in the functions associated with specific frontal areas  
9 (e.g., working memory function associated with the dorsolateral prefrontal cortex) after lesion  
10 of other nodes in the relevant frontal-subcortical circuit (Cummings, 1993; Divac, Rosvold,  
11 & Szwarcbart, 1967; Stuss et al., 1998; Yehene, Meiran, & Soroker, 2008). Furthermore, the  
12 existence of strong functional connections between the striatum and different parts of the  
13 frontal cortex has been confirmed in an analysis of human functional magnetic resonance  
14 imaging (fMRI) data (Di Martino et al., 2008). Given this extensive evidence for frontal-  
15 subcortical networks, it seemed important to investigate not just dopamine genes likely to  
16 affect processing in the frontal cortex, but also dopamine genes acting at the subcortical level.

17       Looking at the individual genes in more detail, the COMT enzyme metabolizes  
18 catecholamines such as dopamine and noradrenaline (Chen et al., 2004; Männistö &  
19 Kaakkola, 1999; Tunbridge, Harrison, & Weinberger, 2006). The role of COMT in  
20 catabolizing dopamine in the frontal cortex is particularly important due to the relative lack of  
21 dopamine transporters and the positioning of these transporters at a distance from synaptic  
22 release sites (Sesack, Hawrylak, Matus, Guido, & Levey, 1998). Thus, COMT accounts for  
23 approximately 50-60% of the metabolic degradation of dopamine in the frontal cortex  
24 (Karoum, Chrapusta, & Egan, 1994; Yavich, Forsberg, Karayiorgou, Gogos, & Männistö,  
25 2007). In contrast, COMT catabolism only plays a minor role in the striatum where the



1 dopamine transporter is abundant and better situated for dopamine reuptake (Karoum et al.,  
2 1994; Yavich et al., 2007; for review, see Tunbridge et al., 2006). Consistent with this,  
3 studies of COMT-deficient mice have demonstrated increased dopamine availability in the  
4 frontal cortex, but not the striatum (Gogos et al., 1998; Yavich et al., 2007). The important  
5 role of COMT in the cortex compared to the striatum has also recently been shown *in vivo* in  
6 the human brain using positron emission tomography (PET) (Slifstein et al., 2008).

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

15 The Met variant of the enzyme is less stable at body temperature (Chen et al., 2004; Lotta  
16 et al., 1995), resulting in 3 to 4 times less COMT enzyme activity in the human liver and red  
17 blood cells (Männistö & Kaakkola, 1999). In the human brain this difference is smaller, but  
18 still considerable, with Met/Met homozygotes having approximately 40% less COMT  
19 activity than Val/Val homozygotes in the prefrontal cortex (Chen et al., 2004). The alleles are  
20 codominant, resulting in Val/Met heterozygotes having an intermediate level of COMT  
21 activity (Egan et al., 2001; Männistö & Kaakkola, 1999; Tunbridge et al., 2006). This  
22 evidence strongly suggests that Met/Met homozygotes have the *highest* baseline level of  
23 dopamine available in the prefrontal cortex (because less dopamine is catabolized) with  
24 Val/Met heterozygotes having an intermediate level, and Val/Val homozygotes having the  
25 lowest level of prefrontal dopamine (Tunbridge et al., 2006; Tunbridge et al., 2007).

1 Several studies have demonstrated a relationship between the *COMT* Val<sup>158</sup>Met  
2 polymorphism and performance on tasks associated with the frontal cortex. For example,  
3 Egan et al. (2001) found that the *COMT* Val<sup>158</sup>Met polymorphism affected performance on  
4 the Wisconsin Card Sorting Test (WCST). Val/Val homozygotes performed significantly  
5 worse than Met/Met homozygotes and heterozygotes. Furthermore, the number of Met-alleles  
6 (0-2) that an individual had significantly predicted neural efficiency in the frontal cortex  
7 during an fMRI task, the N-back task (Egan et al., 2001). In this task all genotype groups  
8 performed at the same level, but Val/Val homozygotes showed significantly greater  
9 activation (indicating lower neural efficiency) in the frontal cortex than heterozygotes, and  
10 heterozygotes showed significantly greater activation than Met/Met homozygotes. Recent  
11 meta-analyses have been inconsistent in terms of the relationship between performance on the  
12 WCST and the *COMT* Val<sup>158</sup>Met polymorphism (Barnett, Jones, Robbins, & Müller, 2007;  
13 Barnett, Scoriels, & Munafò, 2008). However, the evidence for an effect on neural efficiency  
14 as well as on a range of frontal cortex tasks has been replicated in several studies (Bertolino  
15 et al., 2006; Blasi et al., 2005; Caldú et al., 2007; Diaz-Asper et al., 2008; Krämer et al.,  
16 2007; Mattay et al., 2003; Meyer-Lindenberg et al., 2006; Sheldrick et al., 2008; Stefanis et  
17 al., 2005), and has recently been extended to a mouse model of the Val<sup>158</sup>Met polymorphism  
18 (Papaleo et al., 2008). Finally, a study by Diamond and colleagues (2004) demonstrated an  
19 effect of the *COMT* Val<sup>158</sup>Met polymorphism on school-age children's performance on a task  
20 hypothesized to depend on dopamine in the prefrontal cortex. This finding demonstrates the  
21 potential effect of variation in COMT activity at younger ages, and opens up the possibility  
22 that the *COMT* Val<sup>158</sup>Met polymorphism might have an effect on frontal cortex functioning  
23 already in infancy.

24 The second candidate gene in our study was the *DRD4* gene. Knowledge about the  
25 distribution of the D<sub>4</sub> receptor in the human brain is limited due to the lack of appropriate

1 radioligands (Hurd & Hall, 2005; Oak, Oldenhof, & Van Tol, 2000). However, existing  
2 evidence suggests that D<sub>4</sub> receptors are most abundant in the retina, followed by the  
3 prefrontal cortex (Oak et al., 2000). Hurd and Hall (2005) suggest that transmission via D<sub>4</sub>  
4 receptors is predominantly inhibitory in nature, resulting in disinhibition of excitatory  
5 transmission when these receptors are blocked (Hurd & Hall, 2005). Thus, a lack of or less  
6 efficient D<sub>4</sub> receptors may lead to deficits in frontal cortex functioning.

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

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

20 The *DRD4* 48-bp VNTR has been extensively studied in relation to Attention Deficit  
21 Hyperactivity Disorder (ADHD) (Li, Sham, Owen, & He, 2006). ADHD has been linked to  
22 performance deficits on tasks assessing frontal cortex functions such as response inhibition,  
23 selective attention and set shifting (for review, see Cornish et al., 2005). The 7-repeat allele  
24 has been consistently associated with ADHD in recent meta-analyses (Faraone et al., 2005; Li  
25 et al., 2006). Furthermore, the *DRD4* 48-bp VNTR has been shown to affect prefrontal grey

1 matter volume in a sample of boys diagnosed with ADHD, their siblings and controls  
2 (Durstun et al., 2005). Recently, the 7-repeat allele has also been found to be associated with  
3 impulsivity and lower levels of response inhibition in healthy adults, both on its own  
4 (Congdon, Lesch, & Canli, 2008) and in combination with other polymorphisms in dopamine  
5 system genes (Congdon et al., 2008; Eisenberg et al., 2007). Finally, the 7-repeat allele has  
6 been linked to faster habituation in infancy and increased novelty seeking in adolescence  
7 (Laucht, Becker, & Schmidt, 2006), and to sensation seeking in toddlers when combined with  
8 poor parenting (Sheese, Voelker, Rothbart, & Posner, 2007). Therefore, the *DRD4* 48-bp  
9 VNTR can be considered a candidate polymorphism for frontal cortex functioning in infancy.

10 Turning to the genes most likely to act at the subcortical level, the  $D_2$  receptor is  
11 considerably less prevalent in the cerebral cortex than in the striatum (Ito, Okubo, Halldin, &  
12 Farde, 1999; Lidow, Goldman-Rakic, Rakic, & Innis, 1989). The *DRD2* TaqIA  
13 polymorphism is located in the 3' untranslated region, 10 kb downstream from the *DRD2*  
14 gene, actually in the adjacent gene *ANKK1* (Neville, Johnstone, & Walton, 2004). A1 is the  
15 minor allele. The A1-present (A1+) genotype has a prevalence of approximately 31% in  
16 Caucasian individuals (Noble, 2000). The presence of this allele has been associated with  
17 lower  $D_2$  receptor density in the human brain using PET, especially in the striatum (Jönsson  
18 et al., 1999; Pohjalainen et al., 1998; Ritchie & Noble, 2003; Thompson et al., 1997).

19 In contrast to the *DRD4* 48-bp VNTR, the *DRD2* TaqIA polymorphism is not associated  
20 with ADHD (Faraone et al., 2005). However, the A1 allele has been associated with various  
21 addictions (Munafò, Matheson, & Flint, 2007; Young, Lawford, Nutting, & Noble, 2004) and  
22 a more impulsive response style in a monetary reward task in healthy adults (Eisenberg et al.,  
23 2007). Little evidence exists for a role of the *DRD2* TaqIA polymorphism in frontal cortex  
24 functioning. However, Reuter and colleagues (2005) showed a significant interaction between  
25 the *DRD2* TaqIA polymorphism and the *COMT* Val<sup>158</sup>Met polymorphism on a Stroop-like

1 task where participants had to respond to the written form of color words written in  
2 incongruent colors as quickly as possible. The interaction effect accounted for 13% of the  
3 variance in performance on this task. This result opens up the possibility that the *DRD2* gene  
4 (and perhaps other subcortical dopaminergic genes) impacts indirectly on frontal cortex  
5 functioning via interactions with genes affecting dopaminergic neurotransmission directly in  
6 the frontal cortex (e.g., *COMT* and *DRD4*).

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

22 In terms of phenotypes, the *DAT1* gene has been studied extensively in relation to ADHD  
23 because stimulant medication used in its treatment acts by blocking the dopamine transporter.  
24 Evidence suggests that 10/10 homozygosity is associated with a slightly increased risk of  
25 ADHD (Faraone et al., 2005). Furthermore, Cornish and colleagues (2005) reported an

1 association between the 10/10 genotype and ADHD symptoms in a general population  
2 sample. This group also found an independent association between the 10/10 genotype and  
3 poorer performance on measures of selective attention and response inhibition in their  
4 selected high- and low-risk sample. A similar trend was found by Congdon and colleagues  
5 (2008) in a sample of healthy adults. Despite these findings, recent neuroimaging studies in  
6 adults have indicated a more efficient neural response in the prefrontal cortex of 10/10  
7 homozygotes during a working memory task (Bertolino et al., 2006; Caldú et al., 2007), a  
8 pattern similar to that which is seen in subjects with the *COMT* Met/Met genotype. One  
9 recent study also found higher levels of impulsivity in healthy adults with at least one 9-  
10 repeat allele (Forbes et al., 2007), contradicting other behavioral results. The behavioral  
11 effects of the *DATI* 3' VNTR polymorphism may depend on the population studied.

12 In summary, the present study investigated whether performance on the Freeze-Frame  
13 task at 9 months of age was associated with genetic polymorphisms affecting important  
14 aspects of dopamine function in the brain. Since dopamine plays an important role in both the  
15 frontal cortex and the striatum, direct effects of the *COMT* Val<sup>158</sup>Met and *DRD4* 48-bp  
16 VNTR were hypothesized, with potential interacting or indirect effects of the *DRD2* TaqIA  
17 and the *DATI* 3' VNTR polymorphisms.

## 18 Methods

### 19 *Sample*

20 Infants were recruited from the greater London area. Data from two independent cohorts  
21 of infants were combined in the present study. Cohort 1 consisted of a small group of infants  
22 ( $N = 24$ ). Behavioral results from this cohort have been reported previously (Holmboe et al.,  
23 2008). Cohort 2 consisted of a considerably larger group of infants ( $N = 104$ ) who took part  
24 in a longitudinal study of frontal cortex functioning during the first year of life. Ninety-four

1 infants from the original cohort of 104 infants (recruited at 4 months) participated in the  
2 study at 9 months. Data from this cohort have not been reported previously.

3 Data on parental education and household income were only collected in Cohort 2, but  
4 generally represent families recruited for studies at our laboratory. Parents were in their mid-  
5 thirties (mothers:  $M = 34.43$ ,  $SD = 4.90$ ; fathers:  $M = 36.45$ ,  $SD = 6.61$ ) and primarily, but not  
6 exclusively, of middle or upper-middle class socio-economic status (maternal years of  
7 education:  $M = 17.80$ ,  $SD = 3.55$ ; household income in £:  $M = 65,076$ ,  $SD = 61,854$ <sup>1</sup>).

8 Seventy-nine percent of the infants tested (Cohorts 1 and 2 combined) had a White/Caucasian  
9 ethnic background (approx.  $\frac{3}{4}$  of these infants were of British or Irish descent), and 21% had  
10 other or mixed ethnic background. Of the infants with other than Caucasian ethnic  
11 background ( $N = 26$ ), 8% of infants had an Asian ethnic background, 15% had a Black ethnic  
12 background, and 77% had a mixed ethnic background (e.g., mother Asian and father  
13 Caucasian). Ethical permission for the study was obtained from the School of Psychology  
14 ethics board at Birkbeck, University of London.

### 15 *The Freeze-Frame task*

16 A detailed description of the Freeze-Frame task can be found in Holmboe et al. (2008). In  
17 short, infants were presented with animations in the centre of a 19-inch color monitor. Infants  
18 were seated in their parent's lap at a 60-cm distance from the monitor. On every trial a white  
19 square was flashed on the right or left side of the screen (the distractor). If the infant looked  
20 to the distractor, the animation was stopped for 3000 ms. If the infant did not look to the  
21 distractor, the animation continued after distractor presentation for the duration of the trial.  
22 Distractor duration was calibrated individually for each infant by increasing it by 40 ms on

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<sup>1</sup> Approximate US\$ equivalent:  $M = 120,511$ ,  $SD = 114,544$ , based on the average GB£ per US\$ exchange rate of 0.54 in 2006 (NationMaster.com, 2009) when the majority of the data was collected.

1 every trial where the infant did not look to the distractor. When the infant had looked to the  
2 distractor on two consecutive trials, distractor duration was fixed at the current duration for  
3 the rest of the test session. The even-numbered trials presented dynamic and colorful  
4 animations changing every 2 s (interesting trials), whereas the odd-numbered trials always  
5 presented the same uninteresting rotating orange star (boring trials). Infants were encouraged  
6 to complete 60 trials.

7 A few minor adjustments were made to the task used in Cohort 2. Most importantly, the  
8 animations were slightly smaller and a different set of animations was used for the interesting  
9 trials. The procedure used in Cohort 2 was the same as the procedure used in Cohort 1. In the  
10 new version distractor duration did not increase beyond 1200 ms. Infants were encouraged to  
11 complete 80 trials. The data were analyzed as described in Holmboe et al. (2008). That is, the  
12 session was divided into phases (from two trials before the calibration trial), invalid trials  
13 were excluded, and the proportion of looks to the distractors was calculated separately for  
14 boring and interesting trials in each phase. However, the additional data collection allowed an  
15 extra phase in the analyses. Thus, there were 4 phases of the experiment, each containing 16  
16 trials (8 boring and 8 interesting).

17 Video recordings of each infant's behavior were coded offline. The coding procedure in  
18 Cohort 2 was similar to the procedure reported in Holmboe et al. (2008). The trial was  
19 considered invalid if the infant was not looking at the central stimulus at distractor onset. The  
20 trial was also considered invalid if the infant blinked (i.e., the pupils were fully covered)  
21 during distractor presentation. In addition, the trial was considered invalid if these behaviors  
22 occurred during the 1000 ms following distractor presentation. This criterion was added  
23 because in trials where the infant looks away immediately following distractor presentation, it  
24 is impossible to know whether the infant *would have* looked to the distractor if they had not  
25 looked away from the screen. On rare occasions, a trial was excluded because the infant's



1 eyes were out of view (e.g., if the infant's hand was in front of his or her eyes); such trials  
2 were considered invalid if the eyes were out of view for more than 2 frames (80 ms) during  
3 distractor presentation or within the 1000 ms following distractor presentation. Finally, trials  
4 where a saccade to the distractor was initiated earlier than 3 frames (120 ms) after distractor  
5 onset were also considered invalid; such saccades were most likely anticipatory or random.  
6 Inter-coder reliability in Cohort 2 was satisfactory for both looking behavior ( $\kappa = .94$ ) and  
7 trial validity ( $\kappa = .86$ ), based on data from 10 participants. (Inter-coder reliability in Cohort 1  
8 was similar; see Holmboe et al., 2008.)

### 9 *Collection of buccal swabs and DNA extraction*

10 Buccal (cheek) swabs were collected at 3.5 years of age in Cohort 1 as part of a follow-  
11 up study, and at 4 months in Cohort 2. The buccal swab was collected by the parent in the lab  
12 (by rubbing the cotton bud on the inside of the child's cheeks for approximately 5-10  
13 seconds), and then put in a sample tube by the experimenter. Two swabs per DNA sample  
14 tube were collected, and two independent samples per infant were shipped and isolated  
15 separately using a DNA-purification kit obtained from Gentra (Minneapolis, US), yielding  
16 total of 2-10  $\mu\text{g}$  DNA per sample.

### 17 *Genotyping*

18 Genotyping procedures were carried out using published protocols (*DRD2* TaqIA:  
19 Grandy, Zhang, & Civelli, 1993; *DRD4* 48-bp VNTR: Ronai et al., 2000; *COMT* Val<sup>158</sup>Met:  
20 Tarnok et al., 2007; *DAT1* 3' VNTR: Vandenberg et al., 1992). Both DNA samples from  
21 each infant were genotyped for all the investigated polymorphisms. In order to ensure  
22 successful genotyping, the following precautions were taken: In case of unsuccessful  
23 amplification (~10%) at the *DRD4* and *DAT1* VNTR genotyping, the PCR reaction was  
24 repeated, hence the genotyping success rate was 100%. In addition, independent

1 amplification reactions were carried out for 50% of the samples at the DRD4 VNTR, because  
2 of the problematic amplification of the longer alleles (Ronai et al., 2000), this quality  
3 checkup yielded the same genotypes as the ones originally obtained. At the DRD2 TaqI  
4 restriction enzyme digestion genotyping was repeated in case of unsuccessful amplification  
5 (~5%) or non-identical results for the two samples (~8%). The *COMT* Val<sup>158</sup>Met SNP  
6 (rs4680) was also genotyped by an alternative method using a pre-designed TaqMan kit  
7 (C\_25746809\_50, Applied BioSystem, Foster City, USA) on a 7300 Real-Time PCR System;  
8 the genotypes were in accordance with the original ones.

### 9 *Data analyses*

10 Behavioral data were analyzed using repeated measures analysis of variance (ANOVA).  
11 For the genotype analyses, data were analyzed using a Linear Mixed Model analysis (LMM)  
12 assuming a diagonal covariance structure. Phase and Trial Type were entered as repeated  
13 measures and proportion of looks to the distractors was entered as the dependent measure.  
14 The advantage of LMM is that data from participants with missing data points, in this case  
15 missing data from one or more phases of the experiment, can be included in the analysis  
16 (Garson, 2008). Missing data points are inevitable in infant studies, and, given the fact that  
17 the genotype effects we were interested in were likely to be modest in magnitude, we wished  
18 to include as much of the data in the analyses as possible.

19 Due to the risk of population stratification in ethnically mixed samples (Hutchison,  
20 Stallings, McGeary, & Bryan, 2004), genotype analyses were carried out on both the entire  
21 sample and on the subsample of infants of Caucasian ethnic origin. Significant main effects  
22 and interactions were followed up by posthoc tests and checked against a False Discovery  
23 Rate (FDR) adjusted *p*-value based on the total number of posthoc tests carried out across all  
24 genotype analyses in both the total sample and the Caucasian subsample (33 posthoc tests in  
25 total). The FDR was controlled at  $p < .05$  using the method described by Benjamini et al.

1 (2001). Only posthoc comparisons that remained significant after controlling the FDR are  
2 reported.

3 The Hardy-Weinberg (HW) equilibrium test was calculated using Knud Christensen's  
4 program (Christensen, 1999); for the *DATI* 3' VNTR the three common genotypes from two  
5 frequent alleles (9- and 10-repeat) were included in the analysis, and for the *DRD4* 48-bp  
6 VNTR, genotypes from 4 common alleles (2-, 3-, 4-, 7-repeat) were analyzed. For the *COMT*  
7 Val<sup>158</sup>Met and *DRD2* TaqIA polymorphisms there were only 3 genotypes, and therefore all  
8 infants could be included in the HW test.

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

## 15 Results

### 16 *Genotype and allele distribution*

17 Genotype data were available for 19 out of the 24 infants in Cohort 1. Seventeen of these  
18 infants were of Caucasian ethnic origin. In Cohort 2 genotype data were available for all 94  
19 infants (71 Caucasian) tested at 9 months of age. When the two cohorts were pooled,  
20 genotype data were available for 113 infants (88 Caucasian). One hundred and two of these  
21 infants calibrated in the task (see below) and could be included in the analyses. Genotype  
22 frequencies for each of the four polymorphisms are presented in Table 1, and allele  
23 frequencies are presented in the Supplementary Table. Alleles and genotypes were in Hardy-  
24 Weinberg equilibrium for all polymorphisms, with the exception of the *DRD4* 48-bp VNTR

1 polymorphism in the total sample (see note to Table 1). When the Hardy-Weinberg analysis  
2 of the *DRD4* 48-bp VNTR was restricted to the Caucasian subsample, the *p*-value increased  
3 to .45. In order to ensure a genetically homogenous population, every genetic analysis was  
4 carried out in the Caucasian subsample as well. Allele and genotype frequencies were  
5 generally in agreement with the frequencies reported for a mixed European population (see  
6 Introduction), and were very similar in the total sample and the Caucasian subsample.

### 7 *Freeze-Frame behavioral results*

8 One hundred and two infants out of the 113 infants with genotype data available  
9 calibrated in the Freeze-Frame task (79 in the Caucasian subsample), i.e. they looked to the  
10 distractor on two consecutive trials (6 infants did not calibrate, and 5 infants were incorrectly  
11 calibrated by the experimenter; these infants could not be included in the analyses). Distractor  
12 duration was on average calibrated in 5.53 trials ( $SD = 8.13$ , ranging from 2 to 64), and the  
13 mean calibrated distractor duration was 324 ms ( $SD = 181$ , ranging from 200 to 1200). The  
14 average proportion of valid trials was .82 ( $SD = .10$ ). Infants in Cohort 2 had a slightly lower  
15 proportion of valid trials than infants in Cohort 1 (.81 vs. .90), probably due to the session  
16 being a few minutes longer in the former cohort, but the groups did not differ significantly in  
17 terms of calibration data (data not shown).

18 The proportion of looks to the distractors in each phase and trial type is presented in  
19 Table 2. Freeze-Frame results from Cohort 1 have been reported previously (Holmboe et al.,  
20 2008). In the previous study a repeated measures ANOVA indicated that there were  
21 significant main effects of Phase and Trial Type, but no interaction. Results were unchanged  
22 in the sample of infants from Cohort 1 for whom genotype data were available (data not  
23 shown). These results were also replicated in Cohort 2 (Trial Type:  $F(1,68) = 79.29, p < .001$ ,  
24  $\eta_p^2 = .54$ ; Phase:  $F(2,136) = 99.63, p < .001, \eta_p^2 = .59$ ; Phase  $\times$  Trial Type:  $F(2,136) = 0.63, p$

1 = .53), and in the total sample (Trial Type:  $F(1,81) = 105.99, p < .001, \eta_p^2 = .57$ ; Phase:  
2  $F(2,162) = 117.42, p < .001, \eta_p^2 = .59$ ; Phase  $\times$  Trial Type:  $F(2,162) = 0.59, p = .55$ ). The  
3 same significant effects were found when 4 phases were included in the ANOVA of data  
4 from Cohort 2 (data not shown). These results indicate that there is a clear main effect of  
5 Trial Type on looks to the distractors such that infants look less to the distractors in the  
6 interesting trials than in the boring trials. Infants also show a decrease in looks to the  
7 distractors during the test session, and this decrease is similar in the two trial types, i.e., no  
8 interaction (Table 2).

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

18 In all of the genotype analyses reported below the main effects of Phase and Trial Type  
19 remained highly significant with no interaction between Phase and Trial Type (data not  
20 shown). Furthermore, none of the polymorphisms was associated with basic task parameters  
21 such as the calibrated distractor duration or proportion of valid trials after controlling the  
22 FDR.

23 *The COMT Val<sup>158</sup>Met polymorphism and Freeze-Frame performance*

1 All 4 phases of the Freeze-Frame task were included in the LMM since this analysis  
2 incorporates all available data. The LMM analysis indicated that there was a significant main  
3 effect of *COMT* Val<sup>158</sup>Met Genotype on the proportion of looks to the distractors,  
4  $F(2,564.08) = 3.01, p < .050$ . No interactions involving *COMT* Val<sup>158</sup>Met Genotype reached  
5 significance in the total sample (all  $ps > .15$ ). When the analysis was restricted to Caucasian  
6 infants this picture changed. The main effect of *COMT* Val<sup>158</sup>Met Genotype was no longer  
7 significant,  $F(2,418.32) = 2.20, p = .112$ , but the *COMT* Val<sup>158</sup>Met Genotype  $\times$  Trial Type  
8 interaction was,  $F(2,418.32) = 4.38, p = .013$ , indicating that *COMT* Val<sup>158</sup>Met Genotype  
9 affected performance in the two trial types differentially. No other interactions approached  
10 significance (all  $ps > .70$ ).

11 Post hoc analyses on the main effect of *COMT* Val<sup>158</sup>Met Genotype in the total sample  
12 indicated that none of the differences between genotype groups survived the FDR correction.  
13 Post hoc analyses of the *COMT* Val<sup>158</sup>Met Genotype  $\times$  Trial Type interaction observed in the  
14 Caucasian subsample indicated a significant difference in looks to the distractors in  
15 interesting trials both between the Met/Met and Val/Val group ( $p < .0001$ ) and between the  
16 Met/Met and Val/Met group ( $p < .01$ ). No other posthoc comparisons reached significance  
17 after controlling the FDR. The *COMT* Val<sup>158</sup>Met genotype differences in the Caucasian  
18 subsample are illustrated in Figure 1a.

#### 19 *The DRD4 48-bp VNTR polymorphism and Freeze-Frame performance*

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

#### 24 *The DRD2 TaqIA polymorphism and Freeze-Frame performance*

1 The LMM showed no significant effects involving *DRD2* TaqIA Genotype (all  $ps > .70$ ).  
 2 This result was unchanged when the analysis was restricted to Caucasian infants (all  $ps >$   
 3  $.20$ ). The *DRD2* TaqIA polymorphism did not therefore have any significant effect on  
 4 Freeze-Frame performance in the present sample.

#### 5 *The DAT1 3' VNTR polymorphism and Freeze-Frame performance*

6 The LMM analysis of the *DAT1* 3' VNTR showed a significant main effect of Genotype  
 7 in the total sample,  $F(1,569.52) = 3.98, p = .047$ . No interactions reached significance (all  $ps$   
 8  $> .15$ ). When the analysis was restricted to Caucasian infants, the main effect of *DAT1* 3'  
 9 VNTR Genotype was only marginally significant,  $F(1,427.74) = 2.92, p = .088$ . There was  
 10 also a marginally significant *DAT1* 3' VNTR Genotype  $\times$  Phase interaction,  $F(3,191.66) =$   
 11  $2.34, p = .075$ . The main effect of *DAT1* 3' VNTR Genotype in the total sample was due to  
 12 the 10/10 group looking less to the distractors overall than the non-10/10 group. This  
 13 difference is illustrated in Figure 1b. No posthoc analyses were carried out since only the  
 14 main effect of *DAT1* 3' VNTR Genotype was significant.

#### 15 *Analysis of the combined effect of the COMT Val<sup>158</sup>Met and DAT1 3' VNTR polymorphisms* 16 *on Freeze-Frame performance*

17 The genotype distribution of the *COMT* Val<sup>158</sup>Met and *DAT1* 3' VNTR, with genotype  $\times$   
 18 genotype group sizes between 9 and 26 participants (see legend to Figure 1), allowed us to  
 19 investigate the potential interaction between these two polymorphisms. (Genotype  
 20 frequencies for the other polymorphisms investigated in the study resulted in group sizes that  
 21 were too small to investigate interactions, with  $n$  for minor genotype  $\times$  genotype groups being  
 22 less than 5.) An LMM where both *DAT1* 3' VNTR Genotype and *COMT* Val<sup>158</sup>Met  
 23 Genotype were entered as independent variables showed a significant main effect of *COMT*  
 24 Val<sup>158</sup>Met Genotype,  $F(2,528.98) = 3.41, p = .034$ , and a marginally significant effect of

1 *DATI* 3' VNTR Genotype,  $F(1,529.47) = 3.30, p = .070$ . In addition to these main effects,  
 2 there was a significant *COMT* Val<sup>158</sup>Met Genotype  $\times$  Trial Type interaction,  $F(2,528.98) =$   
 3 3.19,  $p = .042$ , and a significant *DATI* 3' VNTR Genotype  $\times$  *COMT* Val<sup>158</sup>Met Genotype  $\times$   
 4 Trial Type interaction,  $F(2,528.98) = 4.09, p = .017$ . The *DATI* 3' VNTR Genotype  $\times$  Phase  
 5 interaction approached significance,  $F(3,240.18) = 2.24, p = .084$ , as did the *DATI* 3' VNTR  
 6 Genotype  $\times$  *COMT* Val<sup>158</sup>Met Genotype  $\times$  Phase interaction,  $F(6,241.10) = 1.91, p = .079$ .  
 7 No other interactions approached significance in the total sample (all  $ps > .35$ ).

8 In the Caucasian subsample alone the results were slightly different. The main effect of  
 9 *COMT* Val<sup>158</sup>Met Genotype was marginally significant,  $F(2,373.00) = 2.82, p = .061$ . The  
 10 same was the case for the *DATI* 3' VNTR Genotype,  $F(1,374.07) = 3.82, p = .051$ . Again, the  
 11 *COMT* Val<sup>158</sup>Met Genotype  $\times$  Trial Type interaction was significant,  $F(2,373.00) = 4.13, p =$   
 12  $.017$ . Finally, the *DATI* 3' VNTR Genotype  $\times$  Phase interaction was significant in the  
 13 Caucasian subsample,  $F(3,170.63) = 2.98, p = .033$ . No other interactions reached  
 14 significance in the Caucasian subsample (all  $ps > .20$ ).

15 Post hoc analyses were restricted to the novel interaction effects involving *COMT*  
 16 Val<sup>158</sup>Met and *DATI* 3' VNTR because all significant and near-significant main effects were  
 17 qualified by a significant interaction, and because other interactions, such as the *COMT*  
 18 Val<sup>158</sup>Met Genotype  $\times$  Trial Type interaction, essentially indicated the same genotype effects  
 19 as the analyses of the two polymorphisms separately. Posthoc analyses of the *DATI* 3' VNTR  
 20 Genotype  $\times$  *COMT* Val<sup>158</sup>Met Genotype  $\times$  Trial Type interaction in the total sample indicated  
 21 that within the *DATI* non-10/10 group there was a significant difference in looks to the  
 22 distractors in the interesting trials between the Met/Met and Val/Val groups ( $p < .001$ ) and  
 23 between the Met/Met and Val/Met groups ( $p = .001$ ). In contrast, no *COMT* genotype  
 24 differences reached significance in the *DATI* 10/10 group after controlling the FDR. This  
 25 pattern of results is illustrated in Figure 1c. Regarding performance in each *COMT* genotype



1 group across *DATI* genotypes, infants with the Val/Met genotype who also had the *DATI*  
2 10/10 genotype looked significantly less to the distractors in the interesting trials than infants  
3 with the Val/Met genotype in the *DATI* non-10/10 group ( $p < .01$ ). The other *COMT*  
4 genotype groups did not differ significantly across *DATI* genotype groups in the interesting  
5 trials (Figure 1c). None of the posthoc tests of the *DATI* 3' VNTR Genotype  $\times$  *COMT*  
6 Val<sup>158</sup>Met Genotype  $\times$  Trial Type interaction showed significant effects in the boring trials  
7 after controlling the FDR.

8 Posthoc analyses indicated that the *DATI* 3' VNTR Genotype  $\times$  Phase interaction found  
9 in the Caucasian subsample was due to a highly significant difference in proportion of looks  
10 to the distractors between the 10/10 group and the non-10/10 group in Phase 3 of the Freeze-  
11 Frame session ( $p < .001$ ).

## 12 Discussion

13 The present study investigated whether performance in a novel task developed to assess  
14 frontal cortex functioning in infancy, the Freeze-Frame task (Holmboe et al., 2008), was  
15 associated with common polymorphisms in four dopamine system genes. Previous research  
16 has clearly shown that dopamine plays an important role in the frontal cortex (Brozoski et al.,  
17 1979; Collins et al., 1998; Diamond et al., 1997; Goldman-Rakic et al., 2000; Roberts et al.,  
18 1994; Sawaguchi & Goldman-Rakic, 1991; Vijayraghavan et al., 2007).

19 Behaviorally, we replicated previous findings on the Freeze-Frame task (Holmboe et al.,  
20 2008). In relation to the polymorphisms likely to impact directly on frontal cortex function,  
21 we found a significant association between Freeze-Frame performance and the *COMT*  
22 Val<sup>158</sup>Met polymorphism. Given the extensive evidence for an association between the  
23 *COMT* Val<sup>158</sup>Met polymorphism and performance on a range of frontal cortex tasks  
24 (Diamond et al., 2004; Diaz-Asper et al., 2008; Egan et al., 2001; Mattay et al., 2003;  
25 Sheldrick et al., 2008; Stefanis et al., 2005; see also Papaleo et al., 2008), as well as effects

1 on neural efficiency in the frontal cortex during performance of these tasks (Bertolino et al.,  
2 2006; Blasi et al., 2005; Caldú et al., 2007; Egan et al., 2001; Krämer et al., 2007; Mattay et  
3 al., 2003; Meyer-Lindenberg et al., 2006), it seems likely that *COMT* Val<sup>158</sup>Met genotype  
4 affects dopamine levels in the frontal cortex and thereby Freeze-Frame task performance in  
5 our infant sample.

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

14 We found little evidence that the *DRD4* 48-bp VNTR polymorphism affects performance  
15 on the Freeze-Frame task at 9 months of age, though the sample was too small to detect  
16 subtle effects. In terms of the polymorphisms which are likely to act in the striatum, we did  
17 not observe any effect of the *DRD2* TaqIA either. We did however observe an effect of the  
18 *DATI* 3' VNTR polymorphism. In contrast to the effect of the *COMT* Val<sup>158</sup>Met  
19 polymorphism, this effect did not appear to be specific to a particular trial type. Instead, we  
20 found evidence of an overall difference in the proportion of looks to the distractors with the  
21 10/10 group looking less to the distractors than the non-10/10 group (Figure 1b). The results  
22 therefore suggest that the *DATI* 3' VNTR polymorphism modulates overall distractibility in  
23 the Freeze-Frame task, though there was a tendency for this genotype effect to be stronger at  
24 the end of the test session. Given the fact that the dopamine transporter plays an important  
25 role in the striatum (Hurd & Hall, 2005; Karoum et al., 1994), this effect could be due to

1 modulation of general attentional mechanisms mediated by the subcortical dopamine system  
2 or frontal-subcortical connections (Alexander et al., 1986; Cummings, 1993).

3 Finally, we investigated the potential interaction between the *COMT* Val<sup>158</sup>Met and  
4 *DATI* 3' VNTR polymorphisms on Freeze-Frame performance. The results of these analyses  
5 broadly replicated the main effects and interactions found in the analysis of each  
6 polymorphism separately. However, the analyses also revealed a significant *DATI* 3' VNTR  
7 Genotype × *COMT* Val<sup>158</sup>Met Genotype × Trial Type interaction, suggesting that the *DATI*  
8 3' VNTR polymorphism modulated the effect of the *COMT* Val<sup>158</sup>Met polymorphism on  
9 Freeze-Frame performance. Basically, the effect of the *COMT* Val<sup>158</sup>Met polymorphism on  
10 the proportion of looks to the distractors in the interesting trials was strong in the *DATI* non-  
11 10/10 group, with particularly large differences between the Met/Met group and the two other  
12 genotype groups (Figure 1c, right panel). In contrast, the equivalent effect in the *DATI* 10/10  
13 group virtually disappeared (Figure 1c, left panel).

14 Presuming that a lower level of distractibility in the interesting trials is an expression of a  
15 higher degree of selective inhibition, these results suggest that infants with the higher *COMT*  
16 enzyme activity alleles (Val/Val and Val/Met) actually benefit from having the *DATI* 10/10  
17 genotype, whereas this is not the case for infants with the low-activity enzyme (Met/Met).  
18 This was confirmed at least for the Val/Met genotype; this genotype showed a significant  
19 reduction in looks to the distractors in the interesting trials when combined with the 10/10  
20 genotype rather than with the non-10/10 genotype (Figure 1c). Though preliminary given the  
21 sample size, these findings are particularly interesting because they suggest that the  
22 interaction between a predominantly frontal dopaminergic polymorphism (*COMT* Val<sup>158</sup>Met)  
23 and a predominantly striatal dopaminergic polymorphism (*DATI* 3' VNTR) results in large  
24 performance differences on the Freeze-Frame task already at 9 months.

1 It should be mentioned that it would have been ideal to investigate all possible  
2 interactions between the four polymorphisms in the study. However, only the *COMT*  
3 Val<sup>158</sup>Met and the *DATI* 3' VNTR polymorphisms had genotype frequencies providing  
4 enough power to investigate interaction effects (see Methods). For the *DRD4* 48-bp VNTR  
5 and the *DRD2* TaqIA polymorphisms the genotype frequencies involving the minor allele  
6 were too low to test meaningful interactions. Future studies should address the question of  
7 interactions between all four (and additional) polymorphisms in dopamine system genes in a  
8 larger infant cohort.

9 Despite the likely effect of both frontal and subcortical mechanisms in the reported  
10 results, it is not possible to establish the exact neural substrate of this interaction from the  
11 current data. Previous studies have found additive genetic effects of the *DATI* 3' VNTR and  
12 *COMT* Val<sup>158</sup>Met polymorphisms on neural efficiency in the frontal cortex (Bertolino et al.,  
13 2006; Caldú et al., 2007). However, an interaction between the two polymorphisms has not  
14 previously been reported (though see Prata et al., 2009, for a recent study which found an  
15 epistatic effect in the parietal cortex). Further research using neuroimaging data will help  
16 elucidate the potential role of the frontal cortex and the striatum in these genotype effects.

17 The current study constitutes a snapshot in time at 9 months of age. Future studies over a  
18 wider age range may help elucidate which patterns of Freeze-Frame performance are adaptive  
19 throughout infancy and early childhood, and how these patterns relate to polymorphisms in  
20 dopamine system genes. Some progress has already been made towards this at the behavioral  
21 level in the work by Holmboe and colleagues (2008) where performance indices on early  
22 frontal cortex tasks showed both positive and negative associations with later performance.  
23 Nevertheless, an important conclusion to be drawn from the results of the present study is that  
24 polymorphisms in dopamine system genes play an important role already in infancy. Previous  
25 studies have found effects of the *DRD4* 48-bp VNTR on temperament and relatively broad

1 aspects of attention in infancy (Auerbach et al., 1999; Auerbach, Benjamin, Faroy, Geller, &  
2 Ebstein, 2001; Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001; Ebstein et al., 1998;  
3 Laucht et al., 2006; Sheese et al., 2007). The current study adds to this evidence by showing  
4 that the *COMT* Val<sup>158</sup>Met polymorphism, which is thought to play an important role  
5 specifically in the frontal cortex, affects performance on a simple saccadic inhibition task in  
6 infancy.

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

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1 Table 1.  
 2 *Genotype frequencies in the total sample and the Caucasian subsample (percentages in*  
 3 *brackets).*

<i>Polymorphism</i>	<i>Genotype</i>	<i>Total</i>	<i>Caucasian</i>	<i>Grouping</i>
<i>DRD4</i> 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)	
<i>COMT</i> Val <sup>158</sup> 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
<i>DRD2</i> Taq1A	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)	
<i>DATI</i> 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
<hr/>				
	Non-10/10	42 (41.2)	34 (43.0)	
<hr/>				
Total <i>N</i>		102	79	
<hr/>				

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*Note.* Only data from infants who calibrated in the Freeze-Frame task are included in the

3

table (data from infants who did not calibrate could not be used in the analyses). All

4

polymorphisms except the *DRD4* 48-bp VNTR polymorphism conformed to Hardy-

5

Weinberg equilibrium: *DRD4* 48-bp VNTR:  $\chi^2 = 12.95$ ,  $df = 6$ ,  $p = .044$  (all participants);  $\chi^2$

6

$= 5.80$ ,  $df = 6$ ,  $p = .45$  (Caucasians only). *COMT* Val<sup>158</sup>Met:  $\chi^2 = 0.63$ ,  $df = 1$ ,  $p = .43$  (all

7

participants);  $\chi^2 = 0.29$ ,  $df = 1$ ,  $p = .59$  (Caucasians only). *DRD2* Taq1A:  $\chi^2 = 0.18$ ,  $df = 1$ ,  $p =$

8

.67 (all participants);  $\chi^2 = 1.37$ ,  $df = 1$ ,  $p = .24$  (Caucasians only). *DAT1* 3' VNTR:  $\chi^2 = 0.16$ ,

9

$df = 1$ ,  $p = .69$  (all participants);  $\chi^2 = 0.54$ ,  $df = 1$ ,  $p = .46$  (Caucasians only).

10

1 Table 2.  
 2 *Descriptive statistics for the proportion of looks to the distractors across phases and trial*  
 3 *types in the Freeze-Frame task.*

	<i>Mean</i>	<i>SD</i>
Boring, Phase 1	.69	.22
Boring, Phase 2	.42	.28
Boring, Phase 3	.40	.24
Boring, Phase 4*	.39	.25
Boring, Total	.48	.17
Interesting, Phase 1	.45	.25
Interesting, Phase 2	.19	.19
Interesting, Phase 3	.13	.16
Interesting, Phase 4*	.11	.15
Interesting, Total	.22	.14

4 *Note.* \*Only infants in Cohort 2 completed 4 phases.

5

## Figure Caption

1  
2 *Figure 1.* The effect of the *COMT* Val<sup>158</sup>Met and *DATI* 3' VNTR polymorphisms on Freeze-  
3 Frame performance. Error bars indicate the 95% confidence interval of the mean.  
4 *a,* The mean proportion of looks to the distractors in the boring and interesting Freeze-Frame  
5 trials in the three *COMT* Val<sup>158</sup>Met genotype groups in the Caucasian subsample (Met/Met, *n*  
6 = 19; Val/Met, *n* = 37; Val/Val, *n* = 23); the asterisk (\*) indicates a significant difference  
7 from the Met/Met group at  $p < .01$ .  
8 *b,* The mean proportion of looks to the distractors in the boring and interesting Freeze-Frame  
9 trials in the *DATI* 10/10 and non-10/10 genotype groups (10/10, *n* = 60; non-10/10, *n* = 42);  
10 the overall difference between the two genotype groups (across trial types) was significant at  
11  $p < .05$ .  
12 *c,* The effect of the *COMT* Val<sup>158</sup>Met polymorphism on the mean proportion of looks to the  
13 distractors in the interesting Freeze-Frame trials in the two *DATI* genotype groups (10/10 +  
14 Met/Met, *n* = 19; 10/10 + Val/Met, *n* = 26; 10/10 + Val/Val, *n* = 15; non-10/10 + Met/Met, *n*  
15 = 9; non-10/10 + Val/Met, *n* = 21; non-10/10 + Val/Val, *n* = 12); the asterisk (\*) indicates a  
16 significant difference from the Met/Met group at  $p < .01$  within the non-10/10 group, and the  
17 triangle (▲) indicates a significant difference at  $p < .01$  between the Val/Met group in the  
18 non-10/10 group compared to the Val/Met group in the 10/10 group.