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Genetic Associations with Reflexive Visual Attention in Infancy and Childhood

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Abstract

This study elucidates genetic influences on reflexive (as opposed to sustained) attention in children (aged 9–16 years; $N = 332$) who previously participated as infants in visual attention studies using orienting to a moving bar (Dannemiller, 2004). We investigated genetic associations with reflexive attention measures in infancy and childhood in the same group of children. The genetic markers (single nucleotide polymorphisms and variable number tandem repeats on the genes *APOE*, *BDNF*, *CHRNA4*, *COMT*, *DRD4*, *HTR4*, *IGF2*, *MAOA*, *SLC5A7*, *SLC6A3*, and *SNAP25*) are related to brain development and/or to the availability of neurotransmitters such as acetylcholine, dopamine, or serotonin. This study shows that typically developing children have differences in reflexive attention associated with their genes, as we found in adults (Lundwall, Guo, & Dannemiller, 2012). This effort to extend our previous findings to outcomes in infancy and childhood was necessary because genetic influence may differ over the course of development. Although two of the genes that were tested in our adult study (Lundwall et al., 2012) were significant in either our infant study (*SLC6A3*) or child study (*DRD4*), the specific markers tested differed. Performance on the infant task was associated with *SLC6A3*. In addition, several genetic associations with an analogous child task occurred with markers on *CHRNA4*, *COMT*, and *DRD4*. Interestingly, the child version of the task involved an interaction such that which genotype group performed poorer on the child task depended on whether we were examining the higher or lower infant scoring group. These findings are discussed in terms of genetic influences on reflexive attention in infancy and childhood.

Keywords

visual orienting of attention; candidate gene study

Attention is one aspect of cognition that is vital to success in a variety of life activities such as avoiding dangers (e.g., predators or traffic), obtaining food, succeeding in school and

work, and engaging with others. Children can show relative deficits in attention from early in life (Dannemiller, 2004; Holmboe et al., 2010; Jones & Klin, 2013; Scafidi & Field, 1997). These deficits may be connected with disorders of attention. Attention-deficit disorder (ADHD) is relatively common; the prevalence of clinically significant ADHD symptoms in children is 4.19% for males and 1.77% for females (Cuffe, Moore, & McKeown, 2005). Several other psychological disorders also have a component of attention deficit (e.g., anxiety, autism spectrum disorder, and depression). Many of these disorders are influenced by multiple genes along with environmental factors (Bobb et al., 2005; Funke et al., 2005; McCauley et al., 2004) and some of the symptoms of these disorders exist within the general population. This suggests that typically developing children carry risk alleles for these disorders and may show subtle differences in attention task performance, such as those observable in adults (Lundwall et al., 2012). Our use of the term “risk allele” indicates that such polymorphisms influence individual differences in behavior, even when there is no clinical disorder. We are interested in genetic influences on attention between infancy and childhood.

According to several researchers, there is a general need for studies on the developmental profile of attention in infancy and childhood (Dye & Bavelier, 2010; Holmboe et al., 2010; Konrad et al., 2005). This is especially true for reflexive attention. Reflexive attention is one aspect of attention that may have genetic influence. Reflexive attention is orienting to either a moving or suddenly appearing stimulus. Lack of research on age-related differences in reflexive attention may be because some researchers have assumed that reflexive attention emerges within the first year of life and remains stable afterwards (Enns, 1990; Enns & Trick, 2006; Plude, Enns, & Brodeur, 1994). In addition, Beane and Marrocco (2004) state that many researchers have assumed that reflexive attention is not related to attentional deficits. However, our previous studies with adults indicate that there are differences in reflexive attention associated with genetic differences (Lundwall et al., 2012) and such studies seem worthwhile to undertake with infants and children.

Investigating genetic influences at different ages is important because, even though the genotype of an individual does not change over the course of his or her life, gene expression does change (Bird, 2002; Fowden, 2003; Li, Cui, Hart, Klaassen, & Zhong, 2009; Prampara et al., 2011; Trueba et al., 2005). This means different levels of neurotransmitter availability and receptor efficiency might create different associations with behavior.

While there are very few genetic association studies examining reflexive attention, there is some evidence that specific genes or neurotransmitters are associated with reflexive attention. For example, Bellgrove et al. (2007) studied the *SLC6A3 (DAT1)* gene and found that two VNTRs bias spatial attention in healthy children on a reflexive attention task. Markant, Cicchetti, Hetzel, and Thomas (2014) relate *COMT* to spatial attention in infancy and suggest that variations in dopamine signaling in prefrontal cortex contribute to individual differences in reflexive attention during early development. Finally, Craft, Gourovitch, Dowton, Swanson, and Bonforte (1992) found lateralized deficits in reflexive attention in males with early treated phenylketonuria (which is associated with dopamine depletion). We could find no other genetic association studies on reflexive attention in infants and children. Studies of genetic influence on reflexive attention in infancy and

childhood in the same subjects are especially uncommon. Addressing this lack is part of what motivates our study.

Our study investigates genetic influences on the attention in the same subjects in infancy and childhood. In this paper, we ask whether specific candidate genes are associated with reflexive attention measures collected at these two time points. Genetic studies with a developmental component could make an important contribution to our understanding of attention, potentially suggesting improved interventions if several potential pathways between the brain and behavior were better understood.

Potential Genetic Influences on Attention

Neurotransmitters, such as acetylcholine, dopamine, norepinephrine, and serotonin are a good place to look for the pathways of potential influence on attention. Neurotransmitters can influence the efficiency of neural transmission (Berridge et al., 2006; MacDonald, Nyberg, & Backman, 2006). Furthermore, medications that enhance the availability of certain neurotransmitters can help with cognitive performance (Arnsten & Dudley, 2005; Johnson et al., 2008; Lijffijt et al., 2006). Many studies find genetic associations with sustained attention and/or ADHD (Greenwood, Sunderland, Friz, & Parasuraman, 2000; Parasuraman, Greenwood, & Sunderland, 2002; Walitza et al., 2005; Winterer et al., 2007), and these same neurotransmitters are also sometimes found to be associated with reflexive attention. For example, there is some evidence for the involvement of cholinergic (Beane & Marrocco, 2004; Oberlin, Alford, & Marrocco, 2005), dopaminergic (Bellgrove et al., 2007; Holmboe et al., 2010; Oberlin et al., 2005), and serotonergic genes (Oades et al., 2008) with reflexive attention. Even though these studies are rare, it is plausible that genetic variation leads to changes in neurotransmitter function that influence differential development of reflexive attention. For example, both dopamine and serotonin are neuromodulators that guide axon growth. Variation in their early influence could lead to lasting changes in neural tracts. The impact of these changes will not necessarily be the same as for sustained attention.

We included genes associated with the neuromodulator and neurotransmitter dopamine, which has been particularly identified as involved in attention. As a neuromodulator, dopamine has powerful effects on the development of neural pathways during certain phases of development (Leo et al., 2003; Rothmond, Weickert, & Webster, 2012). In addition, dopamine is a neurotransmitter that is involved in the transmission of neural messages across synapses in temporoparietal and frontal regions (Bédard et al., 2010; Chudasama & Robbins, 2006; Störmer, Passow, Biesenack, & Li, 2012). The relative efficiency with which a neural message is transmitted can influence cognitive aspects of mood, motivation, and attention (Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011; Diehl & Gershon, 1992). Some literature specifically links reflexive attention to dopaminergic genes (Bellgrove et al., 2007; Holmboe et al., 2010; Oberlin et al., 2005). In addition, it is plausible that genetic variation (since it leads to changes in the proteins produced) influences behavior via neuronal and synaptic changes. The dopamine system includes tonic (baseline) and phasic (responsive) aspects that are regulated in the basal ganglia and frontal lobe (Bilder, Volavka, Lachman, & Grace, 2004; Grace, 1991) and has widespread connections throughout the

brain. Genes that we examine that influence dopamine availability are: *COMT*, *DRD4*, *IGF2*, *MAOA*, *SLC6A3*, and *SNAP25*. The *COMT* gene codes for an enzyme which degrades catecholamine transmitters, including dopamine (Volavka, Bilder, & Nolan, 2004). It has been associated with many cognitive functions, including sustained attention (Bellgrove, Hawi, et al., 2005). *DRD4* codes for a dopamine receptor and has been associated with inattentive symptoms and novelty seeking (Lasky-Su, Anney, et al., 2008; Munafò, Yalcin, Willis-Owen, & Flint, 2008). *IGF2* is an insulin-like growth factor that has been associated with dopamine neuron homeostasis (Sutherland et al., 2008). *MAOA* encodes a mitochondrial enzyme that catalyzes the oxidative deamination of dopamine and serotonin (Caspi et al., 2002) and has been associated with ADHD and impulsivity (Lawson et al., 2003; Manuck, Flory, Ferrell, Mann, & Muldoon, 2000). *SLC6A3* is responsible for dopamine clearance from the synapse of midbrain neurons (Kang, Palmatier, & Kidd, 1999) and has been associated with ADHD (Cornish, Wilding, & Hollis, 2008). Finally, *SNAP25* encodes a protein important to vesicle docking and neurotransmitter release generally (including dopamine) (Benagiano et al., 2011; Bergquist, Niazi, & Nissbrandt, 2002; Chen, Scales, Patel, Doung, & Scheller, 1999; Grumelli et al., 2008; Mehta & Battenberg, 1996; Söllner et al., 1993; Tafoya et al., 2006). *SNAP25* has been associated with ADHD (Feng et al., 2005). All of these genes have been associated with attention or cognition generally.

Acetylcholine is another neurotransmitter that has been found to be related to attention and ADHD (Fisher et al., 2002; Greenwood et al., 2000; Parasuraman et al., 2002; Walitza et al., 2005; Winterer et al., 2007). The cholinergic system has projections throughout the cortex as well as to subcortical areas (Neumann, Lawrence, Jennings, Ferrell, & Manuck, 2005). Genes that we examine that are related to acetylcholine include: *APOE*, *CHRNA4*, and *SLC5A7*. Even though *APOE* has been associated with cognitive disorders in older adults (Alzheimer's disease) it can also influence early development. *APOE* is highly expressed during development and is associated with both epilepsy and schizophrenia (Ziats & Rennert, 2011), which have attentional components (Espeseth, Endestad, Rootwelt, & Reinvang, 2007; Greenwood et al., 2000). *APOE* is also associated with attention in later development (Greenwood et al., 2000). *CHRNA4* has been associated with the developmental control of circuit formation and with epilepsy (Dixon-Salazar & Gleeson, 2010) and with visuospatial attention (Greenwood, Parasuraman, & Espeseth, 2012). *SLC5A7* has been associated with distractibility and ADHD (Berry et al., 2014). All these genes have been associated with some aspect of attention.

Serotonin, also a neurotransmitter and neuromodulator (Whitacker-Azmitia, Druse, Walker, & Lauder, 1996), has likewise been related to cognitive function. In particular, *BDNF* has been associated with brain development (Binder & Scharfman, 2004) and ADHD (Shim et al., 2008). *HTR4* has likewise been associated with ADHD (Faraone & Mick, 2010). Note that another gene previously mentioned, *MAOA*, which has been described previously as related to dopamine, is also related to the availability of serotonin. For a summary of the genes and markers selected, along with the rationale for each, please see Table 1.

Variation on these genes, which are associated with the neurotransmitters dopamine, acetylcholine, and serotonin, could have different impacts on reflexive attention than they do on sustained attention. For example, neurotransmitters influencing reflexive attention might

have different ideal levels in different regions of the brain and at different points in development than the ideal levels for sustained attention. There may be different ideal levels of dopamine for a single task where some subjects had “too much flexibility” (i.e., were easily distracted) and others had “too much stability or focus” (i.e., ignored pertinent information). That is, there appears to be a trade-off between flexibility and stability (Herd et al., 2014). It could also be that different tasks simply have different ideal levels of dopamine (Cools & D'Esposito, 2011). If this were true we might expect that some genes that confer “too little sustained attention” might also confer “too much reflexive attention” (distractibility). These markers would have a different direction of effect depending on which task was being examined.

On the other hand, reflexive attention could also be different if it is a precursor to sustained attention. It seems logical that people cannot sustain attention to things that have not already captured in their attention. There is evidence of this in the literature due to overlapping time courses and (in some cases) cortical areas (Beane & Marrocco, 2004). If this were true we might expect to see that genes which confer risk for problems with sustained attention tasks also confer it for problems with reflexive attention tasks.

A complex relationship between genetic risk for problems with reflexive attention and sustained attention could also exist. For example, in some brain regions increases levels of a particular neurotransmitter could be beneficial or detrimental. In other brain regions whether a neurotransmitter is beneficial or not could depend on the developmental stage or particular task (Cools & D'Esposito, 2011; Cubillo, 2012; Fallon & Cools, 2014). Whatever the nature of the relationship between genetic variation and reflexive attention, such relationships do appear worth exploring.

Method

Participants

To explore genetic associations with reflexive attention, we have collected data from 856 children for whom we had infant data. The infant data include the response time (RT) and percent correct (PC) of an adult's judgments of an infant orienting to a salient moving stimulus in the presence of other static stimuli (distractors). Using multiple-regression, we created residual scores for infant RT and PC. These scores represent the variability that remains after controlling for birthweight, gestational age, study conditions, and gender.

Of the 856 original subjects, we excluded 230 children who could not be located 10–15 years after they were first tested; 26 children who had a sibling in the study (to avoid genetic associations due to non-independence); and 82 children who lived more than 35 miles from the Waisman Center. Remaining children who lived in the Madison, Wisconsin area and who were in the upper or lower one third of the infant distribution of residual PC scores were invited to visit the Waisman Center to complete two attention-related tasks ($n = 345$). Children who did not live in the Madison area or who were in the middle one-third of the infant distribution were invited to participate by mail ($n = 255$). Of the 345 invited to participate in person, 201 participated. An additional 129 participated by mail. All subjects provided a saliva sample and had parents who completed the questionnaire, but only the in-

person subjects completed the computer tasks, and only the attention task that was similar to the task they completed as infants (the eye movement [EM] task) is described in this paper. This is a 58% participation rate of those invited for the in-person visit. These values are similar to those for other long-term longitudinal follow-up studies (Capaldi & Patterson, 1987; Cotter, Burke, Loeber, & Mutchka, 2005; Ribisl et al., 1996; Tebes, Snow, & Arthur, 1992) especially without intervening contact over 10–15 years. Because the children in the middle one-third of the infant distribution did not complete the computer task they are not included in the current analyses. It was anticipated that inviting the lower and upper thirds of the infant distribution would lead to greater opportunity to find between group differences. This is a modified extreme group design in that we used performance on an earlier measure (in infancy) to form groups at a later time point (in childhood). The attention task completed by the 201 children available to travel to the Waisman Center is described under Measures.

Exclusion criteria—Of the 201 children who completed the task, additional children were excluded. Namely, children whose parents reported that their child had at least one non-Caucasian biological parent ($n = 11$) were excluded to avoid population stratification (Thomas & Witte, 2002). In addition, we excluded 2 children with error rates over 40%, 2 children with a neurological diagnosis, 3 children with an uncorrected vision impairment, and 3 children who were taking medications with side effects related to attention. These considerations excluded the data of 21 children, leaving for analysis the data of 180 children.

Of the 180 children in the analyzed data set, 88 (49%) were female. The mean age was 12.96 years ($SD = 1.74$). Eighty-six (44 female) were in the lower infant subsample (those in the lower one-third of residual infant PC scores) and 94 (44 female) were in the upper infant subsample. Those in the upper and lower infant subsamples (180) completed the Eye Movement (EM) task described below.

Measures

Infant scores—When the children were infants (approximately 2 to 6 months of age), they were shown a display with a single moving bar in a field of static bars (see Figure 1). The static bars were expected to exert potentially distracting effects on looking behaviors such as eye and/or head movements. The PC score for each infant indicates the percentage of trials that an adult observer watching the infant correctly determined the side of the display with the moving bar. The observer did not know the right/left location of the moving bar on any trial. This task is a variant of Teller's (1974) Forced Choice Preferential Looking technique (FPL). The RT for each trial indicated the length of time required for the adult observer¹ to make her judgment. The same observer was used for all infants in the data set. The validity of the judgments was apparent in comparison to the actual external stimulus (the left or right location of the moving bar). The external stimuli are also useful in assessing reliability and indicate that the observer's performance at predicting the location of the bar was well above chance ($M = 70\%$, $SD = 12\%$). In other words, we have evidence that the infants could detect the moving target and the observer could read infant cues indicating the bar's location

¹Jackie Roessler, whom we thank for this effort.

(Dannemiller, 2000). This makes possible the use of infant PC and RT scores in data analyses.

PC and RT scores from the infant task required transformation. PC scores are proportions (which have residuals that are not normally distributed). Therefore, scores were logit transformed prior to creating the residual scores. As commonly expected, RT scores had a positive skew and, therefore were transformed using a base-10 log transform (Tabachnick & Fidell, 2007). Transformed scores were regressed on relevant factors (birthweight, infant age corrected for gestation, study conditions, and gender), and residual scores were used in analyses. Residual PC scores were also used to determine whether children would be invited to participate by mail or in-person and to determine infant subsample group for comparison purposes.

Child scores—As previously described, children who were in the upper or lower one-third on the infant PC scores were invited to visit the Waisman Center. These children provided a saliva sample for genotyping and completed the eye movement task. Their parents completed a questionnaire that included behavior ratings. Each measure is described below.

Genetic data: We selected markers on 11 genes: *APOE*, *BDNF*, *CHRNA4*, *COMT*, *DRD4*, *HTR4*, *IGF2*, *MAOA*, *SLC5A7*, *SLC6A3*, and *SNAP25*. Because we were interested in discovering if the same genes related to sustained attention were also related to reflexive attention, these genes were primarily chosen based on a literature review of genetic associations with sustained attention even though we suspect that the direction of association (i.e., which allele actually confers “risk”) will not always be the same. As described previously, they are related either to the availability of neurotransmitters such as acetylcholine, dopamine, and serotonin and/or to growth, brain development, or general cognition.

Because very few genetic studies on reflexive attention exist, most of the genes were selected because they are related to sustained attention or some aspect of cognition. If the direction of an effect is in the “expected direction,” then this means the effect we found was with the same risk allele as identified in the literature as associated with another cognitive task or disorder. If the same direction of effect is found as for sustained attention, then this indicates that the markers have the same direction of effect for both types of attentional task.

Multiple markers were used for each gene. These markers are single nucleotide polymorphisms (SNPs; which show variation in the general population at a single base-pair) and variable number tandem repeats (VNTRs; which show variation on the number of short sequences of base-pairs). Each SNP or VNTR was chosen based on prior literature (when available), a sufficient minor allele frequency (generally MAF > .10), and the Illumina system’s ability to assay a particular marker. Risk alleles for deficits in some aspect of attention or cognition are known for 29 of the 43 markers (41 SNPs and 2 VNTRs). See Table 1 for a list of all markers used.

Genetic material was collected from each participant using an Oragene-500 kit (DNA Genotek, Kanata, Ontario, Canada). Each kit collects approximately 2 ml of saliva, which

can then be purified to obtain DNA, and nucleotides can be tagged with a fluorescent dye. Genotyping was performed at the Heflin Center for Genomic Science at the University of Alabama-Birmingham using the GoldenGate assay on the BeadXpress system (Illumina, Inc.). Once the array had been visualized with the BeadXpress reader, wavelength and intensity values of the fluorescence were used to determine genotype. Allele detection and genotype calling were performed using GenomeStudio software v2011.1 (Illumina, Inc.). For each SNP, a child was identified as having 0, 1, or 2 risk alleles which were associated with some aspect of attention or a disorder with attentional symptoms. These were the genetic variables to be associated with infant and child EM task scores.

Eye movement: The child eye movement task (EM) was similar to that used in our previous infant studies (Dannemiller, 2000). Participants were digitally recorded with a low-light video camera in a darkened room while performing this task. There were eight practice trials and 16 data-collection trials. We used the same trial order for each participant. Stimuli were presented on a computer with a 60 Hz refresh rate. Each trial consisted of a medium gray background with an equal number of lighter and darker gray bars (14) per side. Within two seconds after the trial began, one of the bars began to oscillate. The moving bar was presented randomly across trials on either the left or the right side and as either lighter or darker than the background. The bar moved 2.02 degrees of visual angle per second. All participants were instructed to look initially at a central fixation cross (presented as black on a white background) and told that a field of bars would appear; Figure 1). Each child was instructed to then look directly at the moving bar as soon as he/ she saw it begin to move. The onset of the moving bar triggered the initiation of a time stamp imprinted on the digital video. Two raters coded offline the 16 trials of each subject for latency (RT) and the direction of the first eye movement. We performed inter-rater reliability (IRR) analysis prior to aggregating data from several raters. Of 3232 direction judgments, 104 were missing (i.e., 3% of trials could not be coded). Overall IRR across all dyads was .95 for RT and .93 for direction, indicating sufficient agreement. Therefore, the raters' judgments were averaged for each trial's RT and direction separately. For each subject, we calculated PC for left, right, and all trials; we also calculated RT for *correct* left, right, and all trials. These were the EM variables used in analyses.

Questionnaire: While the children completed the computer task, the parents completed a questionnaire that included the McArthur Health and Behavior Questionnaire-Parent Version (HBQ-P) (Armstrong, Goldstein, & The MacArthur Working Group on Outcome Assessment, 2003; Essex et al., 2002). The HBQ-P is a parent-report measure that has been successfully used in a variety of studies (Burghy et al., 2012; Lemery-Chalfant, Doelger, & Goldsmith, 2008). Parents used a three-point Likert scale (0–3) to indicate agreement with statements about the distractibility, concentration, and organization of their children. For this study, we used summary scores for *Inattention* (which included six items), *Impulsivity* (which included nine items), and *ADHD Symptoms* (which is a summary of *Inattention* and *Impulsivity*). These scores were used in an attempt to establish heterotypic continuity (Lavigne, Gouze, Bryant, & Hopkins, 2014; Miller, Vaillancourt, & Boyle, 2009; Putnam, Rothbart, & Gartstein, 2008) between the infant reflexive attention task and later child behavior.

Statistical Analyses

We have described the collection of data from genetic, computer task, and parent behavior ratings. We screened data prior to main analyses to detect skew, outliers, and missing data. Logit and log transformations are described above, under Infant scores. We excluded as errors incorrect (wrong side) and RTs under 100 msec or over 2000 msec. We also excluded data from two children who had error rates over 40% on the eye movement task (previously described under exclusions). We used error percent as a covariate for the remaining children. Very few participants had missing genetic information. All 84 alleles on all 42 markers were genotyped in more than 96% of participants (the average success rate per marker was 98%). In MANCOVA analyses, individuals with missing data on any variable are automatically excluded from analysis. MANCOVAs were used to help address issues of Type I error due to multiple comparisons.

Due to a failure to replicate the findings of some genetic studies, the potential for Type I error in genetic studies has received additional attention (Gorroochurn, Hodge, Heiman, Durner, & Greenberg, 2007; Hirschhorn & Altshuler, 2002; Ioannidis, 2003). To help address these concerns, we have taken several steps. First, by focusing on genes that influence the availability of neurotransmitters we are prioritizing genes with a plausible biological pathway for influence on attention (Caporaso, 2002; Hegele, 2002; Hill, 1971; Swanson, 2001). Second, by using a candidate gene approach for genes associated with attention deficits, brain development, and cognition we are attempting constructive replication (Lykken, 1968). Third, we limited our data collection to children with Caucasian parents and from the same geographical location, thus reducing the risk of spurious effects due to population stratification (Wacholder, Rothman, & Caporaso, 2002). Finally, we have used statistical protections including MANCOVAs to analyze data and only considered genetic associations with a task when both the MANCOVA and accompanying ANOVA have pointed to a clear association with a specific outcome measure (including survival following Bonferroni correction maintaining a familywise error rate of .05).

A first set of MANCOVAs tested all the markers on a given gene for significant association with the infant residual PC, residual RT, and composite scores as dependent variables. Composite scores were created from the residual PC and reversed residual RT scores. The residual scores already account for pertinent covariates, and thus there are no covariates in these analyses. A second set of MANCOVAs tested all the markers on a given gene with derived EM outcomes (PC for left targets, PC for right targets, PC for all targets, RT for left targets, RT for right targets, and RT for all targets) using child age, error percent and gender as covariates. Interactions between genetic marker and infant subsample groups were also examined.

In cases of significant findings on any on the MANCOVAs, we examined the univariate ANOVAs that are reported with the MANCOVA. Below, we report all significant ($p < .05$) MANCOVAs for which we also obtained a clear ANOVA result. We also report overall behavioral data.

Results

Behavioral Data

Consistent with previous research, infant response times ($M = 1801.44$ msec; $SD = 370.88$ msec) were slower than child response times Child RT ($M = 358.73$ msec; $SD = 41.69$ msec). This is consistent because infants might be expected to have slower responses generally. In addition, with the infant task there is an observer who is marking the response for the infant and this will add time. Likewise, the infant PC ($M = .72$; $SD = .12$) is lower than the child PC ($M = .86$; $SD = .11$), but not as dramatically.

Infant and child task performance scores were only weakly correlated. Infant RT and child RT were somewhat negatively correlated ($r = -.14$, $p = .06$). This correlation improves slightly when all Caucasian children are examined ($r = -.15$, $p = .045$), probably due to the slight increase in numbers of children (188 vs. 180). In both cases, there was a tendency for the faster identification of the observer as to where the infant was looking to be associated with slower RTs for child eye movements. Child and infant PC scores were positively correlated ($r = .18$, $p = .01$) and this correlation remains significant when all Caucasian children are examined ($r = .18$, $p = .01$). If an infant tended to look at the moving bar as opposed to elsewhere in the display, then as a child they also tended to look first at the moving bar.

Infant RT (but not PC) scores were also correlated with parent ratings of child behavior 9–16 years after infant testing. We used three HBQ-P scores anticipated to be associated with attention-related behaviors. *Impulsivity* was correlated with Infant RT ($r = -.14$, $p = .03$), indicating that slower RTs were related to lower impulsivity. The *ADHD Symptoms* score (a composite of *Impulsivity* and *Inattention*) was also slightly correlated ($r = -.14$, $p = .06$). However, the *Inattention* score was not correlated with either infant RT ($p = .17$) or PC ($p = .98$) scores. The somewhat weak correlation between infant and child task scores is not surprising given the time lapse. Nevertheless, the correlation with *Impulsivity* reassures us that the RT infant measure is associated with a child attention-related outcome and can therefore demonstrate heterotypic continuity and can be used in analyses.

Linkage Disequilibrium

Prior to tests for association between behavioral measures and genetic markers we report on two characteristics of our genetic data. First, all SNPs were in Hardy-Weinberg equilibrium (all P s $> .39$). This indicates that the genotypes are in the expected proportion given the allele frequencies. Second, we provide information of linkage disequilibrium for alleles that were included in HapMap2 (Gibbs et al., 2003). Linkage indicates the tendency of alleles to be inherited together. We analyzed SNPs in HaploView (Barrett, Fry, Maller, & Daly, 2005) for genes with more than one SNP in the study. For *HTR4*, three SNPs had available data in HapMap2. Linkage disequilibrium is indicated between SNPs rs12374521 and rs1833710 ($r^2 = .04$ and $D' = .71$) but negligible for all other pairs ($D' < .20$ and $r^2 = 0$). For *IGF2*, two SNPs had available data in HapMap2 (rs10770125 & rs734351), with linkage disequilibrium ($r^2 = .19$ and $D' = .56$). Many SNPs on *MAOA* have been found to be in linkage (Gabriel et al., 2002), and all SNPs for which data were available in HapMap2 (rs909525, rs6323,

rs3027400, rs2072743, rs1137070) had linkage disequilibrium ($r^2 > .59$; $D' > .93$). For *SLC6A3*, five SNPs had data available in HapMap2 (rs2042449, rs2617605, rs2937639, rs463379, and rs6350). There is relatively high linkage between SNPs rs463379 and rs6350 ($r^2 = .16$; $D' = .84$); rs6350 and rs2937639 ($r^2 = .10$; $D' = 1$); rs2042449 and rs463379 ($r^2 = .11$; $D' = 1$); and rs2617605 and rs6350 ($r^2 = .17$; $D' = 1$). Two other SNP pairs showed more moderate linkage: rs2042449 and rs2617605 ($r^2 = .08$; $D' = .47$); and rs2617605 and rs2937639 ($r^2 = .19$; $D' = .59$). The remaining three SNP pairs on *SLC6A3* showed negligible linkage ($r^2 < .02$; $D' < .10$). Finally, there were two SNPs on *SNAP25* with HapMap2 data that showed moderate linkage: rs362570 and rs3746544 ($r^2 = .08$; $D' = .48$). SNPs that are in high linkage are likely to each show association with the same behavioral outcomes.

MANCOVAs with Infant task

To answer questions about genotype associations with the infant outcome measures, we conducted 11 MANCOVAs, one for each gene. For each MANCOVA, we used all the candidate markers on a given gene as predictors. The residual scores used as the dependent measures already control for birthweight, gestational age, study conditions, and gender. We used Pillai's Trace to determine statistical significance. For the infant outcomes, the only SNP with significance to pass Bonferroni procedures was rs2937639 (on *SLC6A3*), which was associated with the composite of infant residual PC and RT scores as well as with PC and RT scores separately. For a tabular summary of the significant findings, please see Table 2.

MANCOVAs with Child task

As mentioned previously, we used an eye movement task for children that was similar to the eye movement task for infants. The MANCOVAs for the child EM task used child age, error percent, and gender as covariates. There were separate MANCOVAs for each of the eleven genes, using the markers on a given gene and side of target (right vs. left) as predictors of outcomes for the EM task. Four of the 11 genes had at least one SNP that was statistically significant after Bonferroni correction. These genes were *CHRNA4*, *COMT*, *DRD4*, and *MAOA*. Interactions with subsample (high and low infant score groups) were also tested to examine differences between those in the lower or upper third of the infant distribution. For a tabular summary of the results, please see Table 3.

Discussion

The findings presented in this paper are particularly interesting for at least two reasons. First, they provide evidence that there are different genetic associations with reflexive attention at different times during development, whereas some other researchers have assumed that reflexive attention did not differ in the course of its development or between groups (Enns, 1990; Enns & Trick, 2006; Plude et al., 1994). In this regard, our findings also extend our earlier study with adults (Lundwall et al., 2012) which indicated between-group differences based on genotype. The second reason these findings are particularly interesting is because they suggest that, while some of the same genes that are related to reflexive attention are also related to sustained attention, there are sometimes either different risk alleles or the

version of the allele that indicates poorer reflexive attentional performance depends on infant subsample. As a reminder, our use of the term “risk allele” indicates that such polymorphisms influence individual differences in behavior, even when there is no clinical disorder.

Infant Measures

One of the primary questions of this study is whether candidate genes are associated with reflexive attention in infants. The answer appears to be that at least one specific gene is related to residualized infant PC, infant RT, and the composite of RT and PC scores.

Dopamine Related Markers—One marker on the *SLC6A3* gene survived Bonferroni correction for association with infant attention measures. *SLC6A3*, also known as *DAT1*, controls the amount of dopamine transporter (more transporter leads to less dopamine in the synapse). Rs2937639 was associated with all three infant reflexive attention scores. In particular the G allele was identified as the risk allele in prior literature with children. In our infant sample A was associated with the best performance (on infant composite scores) but was the worst performing genotype group for infant RT and for infant PC (where heterozygotes performed better). These results are not entirely consistent with the findings for sustained attention with a reversed trend from that seen with sustained attention for RT and with a heterozygote advantage for PC. However, other possible explanations exist. First, it is possible that sustained attention tasks require relatively more dopamine for best performance while reflexive attention tasks are more sensitive to having an optimal level of dopamine (Cools & D'Esposito, 2011). Infant RT scores are associated such that those with one or two risk alleles for ADHD (Brookes et al., 2006) are performing best and those with no risk alleles are performing worst. The risk allele was selected based on associations between rs2937639 and sustained attention; therefore, it is possible that the gene has a different impact on reflexive attention. This is plausible if the amount of dopamine considered optimal for one task is not optimal for the other task.

Another possibility is that the reversed association occurs because dopamine is highly expressed in infancy (Bonnin, Peng, Hewlett, & Levitt, 2006; Lambe, Fillman, Webster, & Weickert, 2011; Rothmond et al., 2012). This suggests that gene expression in infancy might produce very different results from gene expression for the same gene in childhood.

In summary, we found a genetic association with the infant task but it is not as clear linear trend as might be expected from a gene-dose perspective where the number of copies of the risk allele (identified from the literature) is negatively associated with high performance on a task. Nevertheless, our study appears to demonstrate that studies which investigate the associations between genes and reflexive attention tasks are warranted. In particular, future research could answer the question of whether the direction of the associations is opposite for reflexive and sustained attention.

Child Measures

Another question of this study is whether any of the candidate genes are associated with reflexive attention in children. The child eye movement (EM) task is similar to the infant

task previously described. Genetic associations with the child EM task are organized according to the associated neurotransmitter.

Acetylcholine related—After Bonferroni correction, one of the markers (rs1044396 on *CHRNA4*) was associated with the RT to right-sided targets in the child eye movement (EM) task in interaction with infant subsample group. *CHRNA4* encodes a nicotinic acetylcholine receptor that can open a channel across the plasma membrane. Recall that infant subsample groups were assigned based on infant task performance. The risk allele (G) represents risk for an attentional deficit (Reinvang, Lundervold, Rootwelt, Wehling, & Espeseth, 2009). In the lower infant subsample (lower residual PC scores in infancy), children with two risk alleles were fastest and those with zero or one risk alleles performed similarly, but in the upper infant subsample those with zero risk alleles were fastest and those with two risk alleles were much slower. This result highlights the importance of examining subsample differences and suggests that the direction of the genetic association with childhood attention reverses across the infant subsample classification. We can only speculate as to the particular cause of this reversal. However, we note that between early infancy and later childhood there are changes the expression of genes that influence neurotransmitter availability (Dixon-Salazar & Gleeson, 2010; Ziats & Rennert, 2011). In the case of dopamine, the greatest abundance is generally during prenatal and early postnatal periods (Rothmond et al., 2012). The reduced availability of neurotransmitters that were previously plentiful (including via receptors) may lead to a reversal of cognitive effects when compared to a later point in development due to increased sensitivity of certain cognitive tasks to dopamine levels (Cools & D'Esposito, 2011; Fera et al., 2007; Kroener, Chandler, Phillips, & Seamans, 2009; Monte-Silva et al., 2009). The same may be true with acetylcholine.

Another possibility is that there is an interaction between genes, environment, and development. It is interesting to note that for *CHRNA4* (and as we will discuss later, for *COMT*) the interactions are such that the best performing child group consists of those in the lower infant subsample with two copies of the risk allele and the worst performing group consists of those in the upper infant subsample with two copies of the risk allele (see the column for Genotype 3 in Table 3). Several researchers have concluded that a risk allele is often not an indication of risk *per se*, but of susceptibility (Brody et al., 2013; Nilsson, Comasco, Hodgins, Orelund, & Aslund, 2014). The susceptibility might be associated with infant subsample via temperament. Relaxed, slow to orient infants may invite more enriching social interactions with a caregiver (Rothbart & Derryberry, 1981). *CHRNA4* encodes a nicotinic acetylcholine receptor and is associated with circuit formation (Dixon-Salazar & Gleeson, 2010). Early in development the circuits may not be well formed in any infants and the high and low performing groups have their performance influenced by other genes. However, later in development those with plentiful receptors may have well-formed attentional circuits for acetylcholine and those with the risk allele show problems unless the environment compensates based on something that is also genetically influenced (such as temperament) (Bale, 2014; Bjorklund, Ellis, & Rosenberg, 2007; Korosi et al., 2012; Martinez, 2009; Vrieze, Iacono, & McGue, 2012). All these possibilities are consistent with *CHRNA4*'s influence during development.

Dopamine related—Dopamine is also highly influential during development. After Bonferroni correction, three dopamine-related genes (four markers) showed significance with the child task outcomes. The G allele on *COMT*rs165599 has been associated with several psychiatric disorders which show attentional deficits (Funke et al., 2005). *COMT* produces an enzyme that catabolizes dopamine. Increased levels of the enzyme reduce levels of dopamine and impair neural messaging. Children in the lower infant subsample performed best (had higher PC) if they had two risk alleles; however, children in the upper infant subsample best if no risk alleles. This pattern is very similar to the pattern seen with *CHRNA4* that we suggest is a susceptibility pattern.

DRD4 (rs11246227), which codes for a dopamine receptor, shows a somewhat different pattern in interaction with infant subsample. Nevertheless, the pattern is the same for all three RT outcomes. In each lower infant subsample group (for RT left, right, and all targets), the best performing genotype group was the group with two copies of the risk allele. The worst performing group was the heterozygote group. In each upper infant subsample group, the best performing group was the heterozygote group and the worst performing group was the group with no risk alleles. In these cases it cannot be simply that the risk allele is actually a susceptibility allele. However, it still seems reasonable to assume that there is some other gene or environmental factor (including temperament) that is beneficial to those in the lower infant subsample. For them, it appears that fewer dopamine receptors are beneficial. For those in the upper infant subsample, more dopamine receptors are problematic. Since dopamine is known to be highly expressed in infancy and influences brain development, those infants who tend to produce more dopamine may actually have too much and be assigned to the lower infant PC group. Later, lower dopamine may improve performance on a reflexive attention task for which distraction is not a problem. Those in the upper infant subsample may have performed better on the infant task because they had less dopamine and this was beneficial with the already plentiful dopamine in early brain development. There is some evidence from the infant task that those with a gene that is associated with less dopamine tend to perform better (see Table 2). However, when there was a reduction in dopamine due to typical developmental changes, those subjects (now children) performed worse than their peers. If fewer “distracting” neural messages are transmitted, then this may be beneficial. Later, when dopamine subsides, these children do not have enough dopamine receptor to pass neural messages efficiently.

There were four associations with dopamine related markers that were not involved in interactions. *DRD4*rs7124601 was associated with child PC scores such that those with the GG genotype have the lowest PC scores. This SNP is not commonly tested in cognition tasks and the risk allele is unknown, but our finding suggests that for reflexive attention in children G is the risk allele. The 30 bp VNTR on *MAOA* was also associated with child PC scores for left targets (in girls) in a way that is consistent with risk for sustained attention deficits. The same VNTR was also found to be associated with child task RT such that those with two copies of the risk allele performed best on the reflexive attention task (for both RT all and RT left, although the RT left pattern looks similar to heterozygote disadvantage). *MAOA* is associated with both dopamine and serotonin and is located on the X chromosome. Seeing results for both measures at once suggests that it is possible that

decreased availability of dopamine may be associated with reduced accuracy (lower PC scores) but better (lower) RT scores. This is the only genetic marker which was associated with both PC and RT measures. This suggests the possibility of dopamine's influence on impulsivity. However, *post hoc* analyses indicate that there was not an association between this *MAOA* VNTR and impulsivity in this study.

In summary, the consistent pattern seems to be that the risk allele for poorer performance on a reflexive attention task is not the same as the risk allele for sustained attention and this gets particularly interesting when we look at interactions with infant task performance (subsample). Sensitivity to environment, rather than risk *per se* seems to explain the best performance with the pre-identified risk allele. This suggests that for these infants risks are reversed from what is expected from sustained attentional studies in children and adults. However, studies may inadvertently only have tested children who would have been in the upper infant subsample. Or perhaps reflexive attention is really different from sustained attention as far as which alleles confer risk. Some might have expected a dose-response in which the number of copies of the risk allele (identified from the literature) is negatively associated with high performance on a task. That is not what is demonstrated here. A more complex picture appears to be likely for both how risk is conferred for different attention tasks, for whom it actually becomes a risk (perhaps depending on environmental factors induced by genetic factors like temperament), and whether it is really risk or just sensitivity that is conferred.

Study Limitations

There is always some risk that the results of a study are spurious and this study is no exception. Particular limitations of this study that might give rise spurious results include issues with recruitment, the possibility of measurement variance, and the absence of physiological measures of gene expression. In regard to recruitment, a better picture of the development of reflexive attention might have been obtained if a greater proportion of families would have been able to participate. As mentioned previously, we recruited 201 follow-up participants from a potential sample of 498 children who participated as infants in visual attention studies (Dannemiller, 2004) and were in the middle one-third on infant performance. This is a 60% attrition rate. Even though this is not unusually high for a 15 year gap without intervening contact, we considered that those who participated could be different in some way from those who did not participate and this could impact the generalizability of the results. For general comparison purposes, note that differences between those who did and did not participate for any reason were not significantly different in terms of age ($t[851] = -.19, p = .85$; 13.53 years for children retained in the study vs. 13.55 years) or birthweight ($t[851] = -1.05, p = .30$; 3634 grams for children retained in the study vs. 3601 grams), or residual infant PC scores ($t[850] = -.70, p = .48$; .03 for children retained in the study vs. $-.02$). This gives some reassurance that the results are generalizable.

Another limitation concerns the possibility of measurement variance. In this case, measurement invariance refers to the construct similarity between measures of attention at the two ages. The infant and child eye movement (moving bar) tasks are nearly identical in stimuli presentation and scoring. However, the infant and child scores were only weakly

correlated. This is likely due to either or both of two aspects of development. First, even though the task does not change, the child has had life experiences which may lead to their interaction with the task being different. Developmental studies frequently have issues of this kind of construct shift because the meaning of a specific behavior changes from infancy to childhood. Infants are not and cannot be instructed to look at the moving bar, but children expect instruction and will invent rules if not provided with instruction. The task may be somewhat similar in meaning, but not identical. One way to determine more thoroughly if the same underlying construct is being measured would require the same sub-measures at each time point that capture an underlying construct. For example, data on speed, accuracy, and the influence of crowding within a single task may together capture the underlying construct of reflexive attention and these could be measured at several time points from infancy through childhood. If this is done then structural equation modeling can be used to determine if the sub-scales actually capture the same underlying construct at different ages. Another possibility is to use several different tasks at each time point in an overlapping design and use structural equation modeling to track constructs through time. This method was successfully used by Petersen, Bates, Dodge, Lansford, and Pettit (2014). Thus, there are ways to investigate the meaning of the weak correlation between infant and child task performance in future studies.

A second explanation for the weak correlation between infant and child measures is that gene expression has changed over the course of development and impacted the child's behavior. That is, other environmental (including epigenetic) and genetic (including developmental) factors could be influencing whether a child is producing, relative to his/ her peers, more or less of a gene product (Feil, 2006; Vrieze et al., 2012). These influences would include epigenetic modifications of gene expression based on early environmental factors (Brummett et al., 2008) and developmentally programmed changes in gene expression (Calabrese, Scapagnini, Ravagna, Giuffrida Stella, & Butterfield, 2002; Li et al., 2009). These developmental forces are quite powerful and seem likely to be the more impactful influence on which genes correlate at which ages than modest shifts in the meaning of a nearly identical task.

However, the demonstration of even a weak correlation between infant and child measures seems very interesting and worth further investigation if the infant task also predicts child behavior. This is demonstrated in the correlation between infant RT scores and parent rated child behaviors a decade or more later. This demonstrates a kind of correlation that is called heterotypic continuity (Lavigne et al., 2014; Miller et al., 2009; Putnam et al., 2008). So, while the weak correlation is a weakness, there are some indications that the genetic association are valid.

The final limitation that we will address is the absence of physiological measures of gene expression. In this study, we have used genetic markers such as for one side of the association and responses to suddenly appearing or moving stimuli as the other side of the association. However, because the amount of gene product that is produced by a gene can vary for several reasons (e.g., epigenetic factors or development), a gene expression study might be an excellent supplement to our data. However, such studies have been difficulties of their own. They can be invasive and are often impractical in humans because gene

expression can be particular to the tissue of interest (the brain, in this case). Therefore, animal or other models may be the necessary approach.

While difficulties with recruitment, the possibility of measurement variance, and the absence of physiological measures of gene expression may have increased the chance of spurious results to some extent, we have handled threats to the validity of our findings with care. Those who participated in the study were not significantly different from those who did not participate in terms of age, gender, birthweight, or residual infant scores. Second, the infant and child eye movement tasks are nearly identical such that the weak correlation is more likely to come from changes in development (including gene expression) rather than differences between the underlying construct being measured. Third, while gene expression information would have been very useful, this information would have needed to be collected at both time points and was not possible given the follow-up nature of this study.

Contributions and Future Directions

This study has several strengths. First, it represents a follow-up longitudinal approach across a period of approximately 10–15 years. These types of studies are rare but necessary for understanding developmental changes. For example, we found that the genetic influence on reflexive attention appears to vary by age (associations differed in infancy, childhood, or, in a previous study of adulthood). Second, we examined reflexive attention to see how the risk alleles for sustained attention compare. Several markers were associated with reflexive attention on five genes. Third, examining interactions with subsample (based on infant PC scores) led to the discovery of significant differences in the genetic associations. In particular, it appears that risk varies by whether the child performed well on the infant task or not. The differences by infant subsample highlight the importance of considering what genetic (e.g., gene expression) and environmental (e.g., gestational events or nutrition) factors may be impacting performance. They also suggest the importance of considering that genes may confer sensitivity to the environment rather than risk *per se*. Overall, this study is useful because it gives a more complete picture of the nature of attention by investigating reflexive attention in the same group of children tested as infants and considering interactions between genes and infant task performance in considering child task performance.

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Research Highlights

- This is a follow-up longitudinal study (testing children who were tested as infants) in which we use a behavioral genetics approach to address developmental aspects of attention.
- We find that genetic influence on reflexive attention involves some of the same genetic markers which are also involved with sustained attention, but that the risk alleles for reflexive and sustained attentional deficits sometimes varied.
- Genetic influence on reflexive attention also appears to vary by age (infant or child) and by whether the children were in the lower or upper third of the distribution of infant scores. That is, different populations appear to have different risk alleles.
- Including reflexive attention in genetic studies of attentional deficits gives a more complete picture of the nature of attention.

Figure 1.
Schematic representation of display eye movement task used in both infancy and childhood.

Table 1

List of genetic markers tested for association with task scores.

Gene	SNPs	Risk allele	Cognitive Process	Citation
<i>APOE</i>			cognition generally	Greenwood and Lambert (2005)
	rs429358	C	sleepiness (T allele); Alzheimer's disease (C allele)	Kripke et al. (2010); Belbin et al. (2007) (in haplotype with rs7412)
	rs7412	C	Alzheimer's disease	Belbin et al. (2007) (in haplotype with rs429358)
<i>BDNF</i>			brain development, ADHD	Binder and Scharfman (2004); Shim et al. (2008)
	rs1491850	T	strong LDAEP (low serotonin activity)	Juckel et al. (2010)
	rs2203877	NA		dbSNP
	rs6265	G	episodic memory	Egan et al. (2003)
<i>CHRNA4</i>			visuospatial attention, cognition generally	Greenwood et al. (2012)
	rs1044396	T	both sustained and reflexive attention	Greenwood et al. (2012), Reinvang et al. (2009)
	rs1044397	G	nicotine dependence	Feng et al. (2004)
	rs2273502	C	nicotine dependence	Spruell et al. (2012)
	rs6090387	G	ADHD	Wallis et al. (2009) (as part of haplotype with rs6090384)
<i>COMT</i>			sustained attention	Bellgrove, Domschke, et al. (2005)
	rs165599	G	psychiatric disorders	Funke et al. (2005) (as part of 4 SNP haplotype)
	rs737865	T	psychiatric disorders	Funke et al. (2005) (as part of 4 SNP haplotype)
<i>DRD4</i>			ADHD	Gorlick et al. (2015); Kegel and Bus (2013); Szekely et al. (2011)
	rs11246227	T	inattentive symptoms	Lasky-Su, Lange, et al. (2008)
	rs1800955	C	novelty seeking, impulsivity	Munafò et al. (2008)
	rs7124601	NA		dbSNP
<i>HTR4</i>			ADHD	Faraone and Mick (2010)
	rs12374521	NA		dbSNP
	rs1363545	NA		dbSNP
	rs1862345	NA		dbSNP
<i>IGF2</i>			cognition, attention; memory	Alfimova, Lezheiko, Gritsenko, and Golimbet (2012); Cordova-Palomera et al. (2014)
	rs10770125	A	maternal glucose concentration (paternally transmitted allele)	Petry et al. (2005)
	rs734351	NA		dbSNP
	rs7924316	T	maternal glucose concentration	Petry (2011)
<i>MAOA</i>			ADHD; aggression, impulsivity	Lawson et al. (2003); Manuck et al. (2000)
	rs1137070	A	visuospatial working memory in girls	Rommelse et al. (2008) (haplotype with rs12843268 and rs3027400)
	rs12843268	T	visuospatial working memory in girls	Rommelse et al. (2008) (haplotype with rs1137070 and rs3027400)
	rs2072743	A	depression in males	Zhang et al. (2010)

Gene	SNPs	Risk allele	Cognitive Process	Citation
<i>SLC5A7</i>	rs3027400	T	visuospatial working memory in girls	Rommelse et al. (2008) (haplotype with rs1137070 and rs12843268)
	rs6323	G	ADHD	Domschke et al. (2005); Xu et al. (2007)
	rs909525	NA		dbSNP
	30bp promoter VNTR	3R	ADHD; impulsivity	Manor (2002); Manuck et al. (2000)
			distractibility; ADHD	Berry et al. (2014); English et al. (2009)
	rs1013940	C	ADHD	English et al. (2009)
	rs2114635	NA		dbSNP
	rs333229	T	heart rate variability; ADHD	English et al. (2009) (in haplotype with rs1013940); Neumann et al. (2005)
	rs3806536	NA		dbSNP
	rs4676169	NA		dbSNP
<i>SLC6A3</i>			ADHD	Cornish et al. (2008)
	rs2042449	C	ADHD	Friedel et al. (2007)
	rs2617605	G	spatial working memory	Shang and Gau (2014)
	rs27047	NA		dbSNP
	rs2937639	NA		dbSNP
	rs463379	C	ADHD	Friedel et al. (2007)
	rs6350	C	ADHD	Friedel et al. (2007); Konrad et al. (2010)
	30bp VNTR (intron 8 3'UTR)	6R	orienting task	Bellgrove et al. (2007); Lundwall et al. (2012)
			ADHD	Feng et al. (2005)
	rs362570	NA		dbSNP
<i>SNAP25</i>	rs3746544	T	ADHD	Feng et al. (2005); Kim et al. (2007)
	rs6032846	NA		dbSNP
	rs6077690	T	ADHD; major depression	Faraone and Mick (2010) (review); Kim et al. (2007)

Note. Some SNPs do not have specific citations for association with cognitive processes because they were selected for having a higher minor allele frequency (MAF) and being near (and likely in linkage with) SNPs that did have literature indicating association with cognitive processes but had a MAF < .05 or otherwise were not assayable by Illumina's GoldenGate system. dbSNP information can be obtained from <http://www.ncbi.nlm.nih.gov/snp>.

Table 2

Summary of Significant Findings for the Infant Eye Movement Task.

Genetic Marker	Specific Outcome ^a	MANCOVA ^b	ANOVA	Genotypes ^c	Genotype 1 Mean (SD) n	Genotype 2 Mean (SD) n	Genotype 3 Mean (SD) n
<i>SLC6A3</i> rs2937639	Infant PC	3.78 (4.322), $p = .01$, $\eta_p^2 = .04$	5.60 (2.161), $p = .004$ ($\alpha = .05$), $\eta_p^2 = .06$	AA;AG;GG	.76 (0.13) 30	.70 (0.12) 81	.74 (0.12) 55
<i>SLC6A3</i> rs2937639	Infant RT	***	6.05(2.161), $p = .003$ ($\alpha = .03$), $\eta_p^2 = .07$	“ “	1821.33 (372.96) 30	1793.46 (331.11) 81	1799.45 (430.31) 55
<i>SLC6A3</i> rs2937639	RT & PC composite ^d	($\alpha = .05$)	7.89 (2.161), $p = .001$ ($\alpha = .02$), $\eta_p^2 = .09$	“ “	.50 (0.68) 30	-.20(0.88) 81	.27 (1.00) 55

^aOnly statistically significant ($p < .05$) MANCOVA outcomes are reported in this table. ANOVA results are those provided by SPSS accompanying each MANCOVA.

^bThe “” symbol indicates ‘as above.’

^cGenotypes indicate the order of presentation for the Mean (SD) information in the right three columns. When risk allele is known, the two-risk allele group is always the last one in the list (and in the right-most column). For ease of comparison with Table 3, the column headings are the same in this table. Possible genotypes vary by marker and do not have their own column headings.

^dPositive values indicate better than mean; negative scores indicate worse than mean.

Table 3

Summary of Significant Findings for the Child Eye Movement Task.

Genetic Marker	Specific Outcome ^d	MANCOVA	ANOVA	Genotypes ^b	Genotype 1 Mean (SD) n	Genotype 2 Mean (SD) n	Genotype 3 Mean (SD) n
<i>CHRNA4</i> rs1044396 (chr20)*subsample ^c	RT right (lower infant group)	1.99 (10,282), $p = .03$, $\eta_p^2 = .07$	5.12(2,144), $p = .003$ ($\alpha = .01$), $\eta_p^2 = .07$	CC;CT;TT	360.17 (59.54) 15	361.65 (43.13) 41	346.99 (37.10) 23
“ “	RT right (upper infant group)	“ “	“ “	“ “	363.31 (39.02) 23	373.04 (60.09) 51	409.66 (77.79) 12
<i>COMT</i> rs165599 (chr22)*subsample	PC left (lower infant group)	1.98(10,288), $p = .03$, $\eta_p^2 = .06$	6.44(2,147), $p = .002$ ($\alpha = .01$), $\eta_p^2 = .08$	AA;AG;GG	.88 (.13) 50	.90 (.11) 20	.96 (.06) 9
“ “	PC left (upper infant group)	“ “	“ “	“ “	.88 (.13) 43	.87 (.15) 37	.70 (.25) 7
<i>COMT</i> rs165599 (chr22)*subsample	PC all (lower infant group)	“ “	6.17(2,138), $p = .01$ ($\alpha = .02$), $\eta_p^2 = .08$	“ “	.82 (.12) 50	.86 (.11) 20	.89 (.12) 9
“ “	PC all (upper infant group)	“ “	“ “	“ “	.85 (.13) 43	.84 (.12) 37	.69 (.17) 7
<i>DRD4</i> rs7124601 (chr11)	PC left	1.91(10,278), $p = .04$, $\eta_p^2 = .06$	5.15(2,142), $p = .007$ ($\alpha = .008$), $\eta_p^2 = .07$	GG;GT;TT (unknown)	.84 (.14) 55	.90 (.14) 87	.89 (.13) 24
<i>DRD4</i> rs11246227 (chr11)*subsample	RT left (lower infant group)	2.47(10,278), $p = .01$, $\eta_p^2 = .08$	4.69(2,142), $p = .01$ ($\alpha = .03$), $\eta_p^2 = .06$	CC;CT;TT (unknown)	358.84 (40.36) 21	365.44 (50.04) 48	338.95 (36.73) 9
“ “	RT left (upper infant group)	“ “	“ “	“ “	372.87 (30.02) 25	352.16 (36.53) 41	352.46 (32.98) 21
<i>DRD4</i> rs11246227 (chr11)*subsample	RT right (lower infant group)	“ “	4.57(2,142), $p = .01$ ($\alpha = .02$), $\eta_p^2 = .06$	“ “	350.48 (32.91) 21	358.86 (48.14) 48	349.27 (30.65) 9
“ “	RT right (upper infant group)	“ “	“ “	“ “	400.05 (76.60) 25	361.81 (48.89) 41	369.68 (36.06) 21
<i>DRD4</i> rs11246227 (chr11)*subsample	RT all (lower infant group)	“ “	5.91(2,142), $p = .003$ ($\alpha = .01$), $\eta_p^2 = .08$	“ “	355.13 (32.18) 21	362.43 (44.11) 48	344.47 (30.96) 9
“ “	RT all (upper infant group)	“ “	“ “	“ “	385.78 (44.07) 25	357.06 (35.95) 41	360.11 (29.75) 21
<i>MAOA</i> 30bp VNTR (girls)	PC left	3.23(10,112), $p = .001$, $\eta_p^2 = .22$	3.99(2,59), $p = .02$ ($\alpha = .02$), $\eta_p^2 = .12$	no 2R or 3R; one 2R or 3R; two 2R or 3R	.91 (.13) 37	.87 (.16) 31	.84 (.13) 12
<i>MAOA</i> 30bp VNTR (girls)	RT all	“ “	3.19(2,59), $p = .02$ ($\alpha = .03$), $\eta_p^2 = .12$	“ “	365.16 (41.40) 37	366.42 (34.54) 31	358.94 (45.26) 12
<i>MAOA</i> 30bp VNTR (girls)	RT left	“ “	10.25(2,59), $p < .001$ ($\alpha = .01$), $\eta_p^2 = .26$	“ “	353.96 (32.12) 37	358.33 (31.75) 31	352.49 (52.59) 12

^a Only statistically significant ($p < .05$) MANCOVA outcomes are reported in this table.

^bWhen the genetic marker includes „subsample” this indicates an interaction and the ANOVA provided is for the interaction.

^cGenotypes indicate the order of presentation for the Mean (SD) information in the right three columns. When risk allele is known, the two-risk allele group is always the last one in the list (and in the right-most column). The “*” symbol indicates ‘as above.’

^dIf an interaction between infant subsample group (assigned according to high v. low infant PC residual scores) was significant, then a breakout of means and standard deviations by subsample group is provided.

^eAll = both left and right-sided targets combined.

^fBoys were tested separately because the marker is on an X chromosome and boys cannot have 2 risk alleles. There were no significant differences for boys.