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Variations in COMT Gene Interact With Parenting to Influence Attention in Early Development¹

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Abstract

Attention influences many aspects of cognitive development. Variations in the *COMT* gene, known to affect dopamine neurotransmission, have frequently been found to influence attention in adults and older children. In this paper we examined 2 year old children and found that variation in the *COMT* gene influenced attention in a task involving looking to a sequence of visual stimuli. Because the influence of another dopamine related gene (*DRD4*) has been shown to interact with parenting quality at this age, we explored parenting in relation to variations in the *COMT* gene. Variations in *COMT* interacted with parenting quality to influence our attention measure. The Val^{108/158}Met polymorphism of *COMT* is commonly used to determine allelic groups, but recently haplotypes of several polymorphisms within this gene have been shown to do a better job in reflecting perceived pain. Since attention and pain both involve the activation of the anterior cingulate gyrus in imaging studies, we compared the Val^{108/158}Met influence with the *COMT* haplotypes and found the latter to be more predictive of attention. Our results confirm that important aspects of cognitive development including attention depend on the interaction of genes and early environment.

INTRODUCTION

A central part of early cognitive development involves the development of attention networks (Posner, 2008). Two attention networks influence the ability to regulate emotions and thoughts. The executive attention network involves the anterior cingulate and plays a major role in adult regulation. The orienting network involves parietal and frontal areas, plays a particularly important role during infancy (see Colombo, 2005 for a review), and moderates parent reports of positive and negative affect by seven months (Sheese, Voelker, Rothbart & Posner, in press). Parents do not report their child's effortful control ability reliably until about 3-4 years, and of course infants and toddlers cannot perform tasks requiring verbal or key press responses. These measurement difficulties may have led to the idea that the executive attention network was not present until about 3 years of age. However, recent studies have found that infants of

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7 months show evidence of executive attention network activity when detecting errors (Berger, Tzur & Posner, 2006) and in delayed reaching to novel objects (Sheese, Rothbart, Posner, White & Fraundorf, 2007). These findings have led us to try to study how executive attention and orienting operate as control mechanisms during infancy.

One task that can be related to both orienting and executive control presents attractive stimuli in a regular sequence of fixed positions in space. Typically infants will orient by moving their eyes and/or head when a new target appears. These reactive looks are thought to involve mainly orienting mediated by the network of frontal eye field and parietal areas (Corbetta & Shulman, 2002). However, sometimes infants anticipate targets by orienting to location prior to arrival of the target. We think of these anticipatory looks as voluntary and based on learned information. They may reflect either the orienting system or elements of the executive system involved in the generation of voluntary actions, particularly where other actions conflict. Since voluntary orienting in adults can be carried out by the orienting network (Corbetta & Shulman, 2002), a different approach to determining which networks are involved is needed. In adults, the orienting network shows primarily cholinergic modulation (Greenwood, Fossella & Parasuraman, 2005), while the executive network is modulated by dopamine (Posner, 2008).

Cholinergic modulation

In a companion paper (Sheese et al in press) we examined the influence of a cholinergic polymorphism (CHRNA4) known to influence orienting in adults (Greenwood Fossella & Parasuraman, 2005) At 7 months this gene was related to the frequency of anticipations to locations in the sequence which could be related to both the orienting and executive attention systems. However, at 2 years of age a different polymorphism of this gene was related to parent reports of effortful control, which has been associated with executive attention. The operation of this gene suggested to us that it might relate to both executive and orienting control, with changes occurring over the first two years of life.

Dopaminergic Modulation

In our previous work we have examined genes linked to dopamine and thought to influence the executive attention network, which has an important node in the anterior cingulate gyrus (Posner, Rothbart & Sheese, 2007). Studies involving young children have shown a gene by environment interaction between aspects of parenting and variation in the another dopamine gene, the Dopamine D4 Receptor Gene (*DRD4*) (Bakermans-Kranenburg & van IJzendoorn, 2006; Bakermans-Kranenburg et al, 2008; Sheese et al, 2007; van IJzendoorn & Bakermans-Kranenburg, 2006). In our previous study the presence of the 7-repeat allele of the *DRD4* gene and quality of parenting were related to several dimensions of temperament including activity level, impulsivity and sensation seeking. In the absence of the 7-repeat allele no influence of parenting was found. However, in the case of the *DRD4* gene, we did not find the interaction with parenting to influence differences in attention. Because the 7-repeat allele was reported to be undergoing positive selection in human evolution (Wang, et al., 2004; 2006) we speculated that reward and punishment introduced by parents may have a larger effect on behavior for those children with the 7-repeat. The idea is that if children with the 7-repeat were more likely to be influenced by cultural factors such as parenting, this might lead to greater reproductive success and thus positive selection. It would thus be important to determine if variations in other genes might also interact with parenting.

COMT Genotype and Haplotypes

Studies of attention with older children and adults have shown that a common polymorphism in the catechol-*O*-methyltransferase (COMT) gene, Val^{108/158}Met (rs4680) results in allelic groups that differ in aspects of attention, such as the ability to resolve conflict (Blasi, et al. 2005; Diamond, et al. 2004). In this paper we examine variations in the *COMT* gene in 18 to

21 month old children. We used the eye movement tasks (Haith, et al, 1998; Johnson, et al, 1991; Rothbart, et al, 2003) described above to determine whether COMT influences the reactive looks related to orienting, and/or the anticipatory looks that might more clearly reflect executive control.

Most studies of the *COMT* gene have examined the Val^{108/158}Met polymorphism. Variation in this single gene is implicated in complex behavioral phenotypes (Stein, et al. 2006) such as anxiety (Rothe, et al. 2006), the experience of reward (Wichers, Aguilera et al. 2007), the processing of unpleasant stimuli (Smolka, et al. 2005) and the experience of physical pain (Zubieta, et al. 2003; Diatchenko, et al., 2005).

Recently, haplotypes of the *COMT* gene have been found to be more effective than the Val/Met distinction in determining pain sensitivity. Three common haplotypes of the *COMT* locus identify alleles which fall into the categories of low (LPS), intermediate (APS), and high (HPS) pain sensitivity (Diatchenko, et al. 2005). These haplotypes account for an allelic frequency greater than 95% of the population tested and include the Val^{108/158}Met variation. The other single nucleotide polymorphisms (SNPs) that constitute the haplotypes are in an intronic region with an alternate promoter, and occur as synonymous substitutions in the reading frame. These SNPs were predicted to identify mRNA conformations that were either permissive or restrictive to the translation of *COMT* (Nacklev et al, 2006). The restrictive haplotype is believed to encode a transcript that folds into a stable stem loop secondary structure; this conformation was associated with a 5-fold decrease of COMT protein in their *in vivo* assay. Thus while the Met/Val polymorphism accounts for variation in enzyme activity (Latta et al, 1995; Lachman et al, 1996) the haplotypes represent variation in both enzyme expression and activity, and pain perception is related to the inheritance of two haplotypes. Both the LPS and HPS haplotypes include the Val allele, but the HPS haplotype also has restricted translation of *COMT* and, subsequently, metabolized 11.4 times less catecholamine than the LPS haplotype in a cell culture assay. Consequently, the haplotypes are a refinement of Val^{108/158}Met genotyping where the Val allele is separated into categories of high and low expression levels of COMT. Assuming these haplotypes are expressed in the brain with the same comparative expression levels and activities, individuals homozygous for the LPS haplotype will metabolize catecholamine more efficiently, and presumably, have reduced catecholamine-mediated neurotransmission. The increased COMT activity associated with the LPS haplotype is correlated with a decreased experience of pain (Diatchenko et al 2006).

Current Study Hypotheses

A potential link exists between attention and pain in their common activation of areas of the dorsal anterior cingulate gyrus (Posner, et al 2007; Rainville, et al 1997). Thus in our study we examined attention in toddlers both in relation to the commonly studied polymorphism in *COMT*, Val^{108/158}Met, and in relation to the *COMT* haplotypes. To study attention, we used looking behavior to sequences of visual stimuli which occurred at fixed locations (Haith, et al, 1998; Johnson, et al 1991; Rothbart, et al 2003). We also examined the role of parenting to determine if there was a gene by environment (GXE) interaction with the *COMT* gene. Since attention in adults and children has been related to the rate of dopamine metabolism, we expected alleles of the *COMT* gene previously found to predict pain and attention in adults and children will influence performance in our selective looking task.

METHOD

Participants

Data for the current study are from an ongoing longitudinal study of the development of attention and temperament conducted at the University of Oregon. Families were recruited

from the local community and children were first brought into the lab when they were 6 to 8 months of age. They returned again when the children were 18 to 21 months of age. Methods and data reported here are from the 18 to 21 month assessment. The study will conclude with an assessment of attention and temperament related outcomes when the children are 4 years of age.

The sample used for the genotyping/haplotyping analyses included 45 children in the target age range (500 to 650 days), with complete data from the parenting observation, visual sequence task, and from genotyping (17 females and 28 males; 85% white and non-Hispanic, 10% Asian, 5% unreported or other).

Procedure

Families came into the laboratory for a single session lasting less than one hour. During the laboratory session, infants participated in the anticipatory looking procedure and buccal cell samples were collected for genotyping. The parent and child also participated in the parenting observation. Families were involved in additional laboratory assessments of attention, intelligence and temperament; these measures are not included in the current paper.

Genotyping/Haplotyping Procedures

COMT Genotyping—Buccal swab samples were taken from each child, and DNA was isolated from the swabs using QuickExtract V1.0 (Epicentre) according to their protocol. The Val^{108/158}Met allele (rs4680) was determined according to Daniels et al (1996). The reaction components included 0.2 μ M of each primer, 3.0mM MgCl₂, 0.2 mM each dNTP, 1.2% formamide, and 0.05 U/ul Taq polymerase with its 1x reaction buffer (NH₄)₂SO₄ (Fermentas). The PCR products were amplified at 94°C 3 min, followed by 40 cycles of 94°C 30 sec, 54°C 30 sec, 72°C 30 sec, and a final incubation at 72°C 3 min. The products were digested with the restriction enzyme NlaIII at 37°C overnight and size-separated on a 4.5% high-resolution agarose gel (A4718, Sigma) stained with ethidium bromide.

Participants were assigned to one of three groups based on genotyping: Val^{108/158} homozygous ($N = 8$), Val^{108/158} Met heterozygous ($N = 23$), and Met^{108/158} homozygous ($N = 14$).

COMT Haplotyping—Each of the four SNPs of the haplotypes were genotyped individually, then the entire region was amplified specifically and genotyped in order to determine the exact combination of SNPs on each chromosome.

The first snp of the haplotype, rs6269 was amplified with 0.2 μ M of the primers 5'-CCACACAGGACTGCCAGAG and 5'-GCTTGGAGTGCCACCATC, 2.5mM MgCl₂, 0.2 mM each dNTP, 0.05 U/ul Taq polymerase, and 1x reaction buffer (NH₄)₂SO₄. The amplification conditions were 94°C 3 min, followed by 40 cycles of 94°C 30 sec, 60°C 30 sec, 72°C 30 sec, and a final incubation at 72°C 3 min. The products were digested with the enzyme HpyCh4V (NEB) and separated on a 3% resolving agarose gel. The second snp of the haplotype, rs4633 was amplified under the same conditions, except using the primers 5'-GCTGGAACGAGTTCATCCTG and 5'-CAGCCCTATCTGGGCATATC and with the addition of 5% DMSO. The products were digested with BsaAI (NEB) and resolved on a 2% regular agarose gel (Sigma). The third snp of the haplotype, rs4818 was determined from the same PCR product as rs4680. The amplification products were digested with BclI and incubated at 50°C overnight. The digest was resolved on a 3% high-resolution agarose gel. The fourth snp of the haplotype is rs4680 and was determined in the previous section.

The entire region was amplified specifically, as determined by the 5' and 3'-most SNPs, rs6269 and rs4680, respectively. Putative carriers of the LPS haplotype were amplified with the

primers PSGF 5'-TGAACCTTGCCCCTCTGCG and PSGR 5'-ATGCACACCTTGTCCTTCAC, under conditions stringent enough to amplify those loci with the G,G alleles of rs6269 and rs4680. The amplification reaction contained 0.2 μ M of the primers, 2.5mM MgCl₂, 0.2 mM each dNTP, 0.05 U/ul Taq polymerase, and 1x reaction buffer (NH₄)₂SO₄. The amplification conditions were as follows: 94°C 3 min, followed by 35 cycles of 94°C 20 sec, 56°C 20 sec, 72°C 90 sec, and a final incubation at 72°C 3 min. Carriers of the APS haplotype were confirmed by specifically amplifying loci with the A,A alleles of rs6269 and rs4680, using the same conditions above and the primers PSAF 5'-TGAACCTTGCCCCTCTGCA and PSAR 5'-ATGCACACCTTGTCCTTCAT. Finally, the HPS haplotype was confirmed by amplifying loci with the A,G alleles of rs6269 and rs4680, respectively. The amplification reaction was the same as above, using the primers PSAF and PSGR. All PCR products were digested with the restriction enzyme BsaAI (NEB) at 37°C, then BclI (NEB) at 50°C and resolved on a 1.5% agarose gel. An LPS genotype has a 971bp product, APS has a 1357bp product, and HPS has as 1055bp product. Any other SNP combination was omitted from analysis.

Participants were assigned to one of five groups based on genotyping: HPS/APS heterozygous ($N = 7$), HPS/LPS heterozygous ($N = 1$), APS/APS homozygous ($N = 14$), APS/LPS heterozygous ($N = 16$), and LPS/LPS homozygous ($N = 7$). There were no participants in the sample with the HPS/HPS homozygous genotype.

Behavioral and Questionnaire Measures

Anticipatory Looking—Anticipatory looking, which can be elicited without verbal instructions and is measured through patterns of eye movement, presents a viable method for assessing executive attention in infancy (Clohessy, et al 2001). In anticipatory looking paradigms, predictable sequences of visual stimuli are shown to infants. Eye movements are recorded and coded for evidence of reactive looks occurring in response to the presentation of a stimulus, and anticipatory looks occurring prior to the presentation of a stimulus. Reactive looks are thought to reflect exogenous control of attention because they occur in response to the stimulus itself, and require only attentional processes associated with alerting and orienting. In contrast, anticipatory looks are thought to reflect voluntary control of attention because the infant must generate an eye movement toward a stimulus not yet present. As there is no external stimulus to elicit a response, saccades are likely to be initiated internally. Supporting the idea that anticipatory looking can be used to assess early forms of executive attention, Rothbart, et al (2003) showed that anticipatory looking in 24- and 30-month old children was related to better conflict resolution in a modified spatial-conflict task and to self-regulation as assessed through parent ratings of children's effortful control.

For the current study an anticipatory looking procedure was developed that utilized short video clips. In contrast to previous research, which used static images as stimuli, the current research used moving video clips in an effort to maximize the number of infants attending to the task. This task is referred to as the Video Anticipatory Looking (VAL) procedure. Each infant sat in a parent's lap approximately one meter in front of a 99 cm \times 69 cm display screen in a darkened laboratory room. Parents were asked to wear glasses that prohibited them from viewing the display to mitigate any potential influence they might have on their infants' attention. A camera with night vision was hidden at the bottom of the screen to record infant eye movements, with a second camera used to record the displayed images. Signals from the two cameras were sent to a digital video mixer, which combined the images for subsequent coding of target onsets and eye saccades.

Stimuli consisted of a 10 minute digital video file presenting a series of video clips (including audio) taken from popular children's television programs. Each clip was 2.33s in length. There was a 1s inter-stimulus interval (a blank screen) between each clip presentation. The order of

the clips was randomized when creating the digital video. Consequently, the presentation did not form a coherent narrative.

The presentation screen was divided into a 3×3 grid. The video clips appeared in one of three locations within this grid. Location 1 was centered horizontally and topmost vertically. Location 2 was at the right bottom. Location 3 was left bottom. The order of presentation was as follows: Location 1, 2, 1, 3, 1, 2, 1, 3 etc. This sequence repeated throughout the entire 10-minute length of the video.

Target onsets and eye saccades were coded independently by two coders using Noldus Observer Video-Pro (Noldus, et al 2000), a software package designed for observational coding. All videos were coded by one primary rater, whose ratings were used in the analyses. To assess reliability, a second rater independently coded all of the videos. Interrater agreement was excellent ($\kappa = .98$) according to the criteria of Fleiss (1981).

The VAL procedure was designed to be run continuously until participants lost interest in viewing the video clips. The procedure was stopped if participants became fussy or they not attend to the presentation for longer than 30 trials. In a small number of cases the participants attended throughout the full length of the presentation (180 trials). The *Total Trials completed* reflects the total number of video clips presented to the participant before the presentation was ended by the experimenter or the end of the video presentation was reached. This outcome may, in part, reflect variability in sustained attention and persistence in the task.

Based on the pattern of saccades, each trial (presentation of a video clip) was coded as one of the following: an Anticipatory Look, a Reactive Look, or Unattended. A response was coded as an anticipatory look if a saccade to any target location occurred in the interval following the offset of the previous target and within 10ms of the onset of the “next” target. Saccades that are initiated up to 100 ms after stimulus onset are still considered anticipatory because limitations in human reaction time. Each anticipatory look was further classified as either a correct anticipation, if the anticipatory saccade was to the location of the upcoming target, or an incorrect anticipation, if the anticipatory saccade was to any other target location. We were interested in examining overall anticipations as well as both correct and incorrect anticipations, since both reflect the endogenous control of attention, but correct looks also require participants to learn the order of the display sequence. The total number of anticipatory looks were calculated for each participant and then divided by the total number of trials attended by each participant, creating the outcome variables: percentage of looks that were anticipatory (*Total Anticipatory Looks*), percentage of looks that were correct anticipations (*Correct Anticipatory Looks*), and percentage of looks that were incorrect anticipations (*Incorrect Anticipatory Looks*).

A reactive look was coded if no anticipatory look occurred, and if a saccade to the location of the target was made within 1s of the onset of the target. The mean reaction time (RT) of all reactive looks was calculated for each participant and is referred to here as *Reaction Time*.

An unattended response was coded if no anticipatory look occurred and no reactive look occurred to the location of the Target within 1s of target onset. The total number of attended trials was summed for each participant and then divided by the total number of trials completed. This measure, the percentage of *Unattended Trials*, is distinct from the Total Trials measure in that it reflects distractibility during the procedure rather than total disengagement from the procedure.

Parental Interaction—Parenting quality was assessed using a video-taped free play procedure and a rating scheme adapted from the NICHD Study of Early Child Care (1993; see

also Egeland & Hiester, 1993). The parent was asked to play with their child for 10 minutes in a laboratory room that contained only toys and an area rug. This interaction was video-taped and subsequently rated. Raters watched the entire interaction and then used 7-point Likert scales to rate the parent on the following items (see NICHD Early Child Care Research Network, 1993 for additional details): 1. *Supportive Presence* (showing positive regard and emotional support), 2. *Respect for Autonomy* (unobtrusive in interactions with child), 3. *Stimulation of Cognitive Development* (showing directed instruction, teaching), 4. *Hostility* (showing anger, rejection, negative regard), and 5. *Confidence* (showing confidence in interactions with child). Forty four percent of the videos were coded twice to assess inter-rater reliability. Inter-rater reliability was adequate ($r = .76$). Hostility was reversed and ratings on these five items were aggregated into single parenting quality measure ($\alpha = .81$). For data analysis, parenting quality was dichotomized using a median-split to produce higher and lower quality parenting groups.

RESULTS

Four participants who attended to fewer than 30 total trials in the Visual Sequence task were excluded from data analyses. These participants exhibited fussiness prior to or early in the testing sequence and showed no evidence of initial engagement with the task. Overall descriptive statistics and intercorrelations among the Visual Sequence outcomes are presented in Table 1. The correlations indicate that toddlers showing higher rates of correct anticipations were also significantly more likely to show higher rates of incorrect anticipations. This suggests that success in the task may involve a pattern of more active anticipatory searching. Anticipatory looking was unrelated to the Total Trials completed and to reaction time. The latter finding highlights the difference between fast reaction times (toddlers who react quickly) and anticipatory looks (which occur in advance of the targets). Anticipatory looks (total and correct) were significantly related to unattended trials, such that children who showed greater anticipatory looking showed less evidence of distractibility during the task.

Total Trials Completed, Unattended Trials and Reaction Time were all significantly interrelated. Reaction Time was significantly related to Total Trials completed, with shorter RTs (faster reactions) were associated with more trials completed, and to Unattended Trials, associated with shorter RTs a lower percentage of unattended trials. Finally, toddlers who completed more Total Trials showed a lower percentage of unattended trials.

COMT haplotypes

Based on findings from Diatchenko et al. (2005), we used the COMT haplotypes to create two groups for comparison. Participants with the LPS/LPS or the LPS/APS haplotypes were grouped into a Low Pain group ($N = 23$). Participants with the APS/APS or the HPS/LPS haplotypes were grouped into a Moderate Pain group ($N = 15$). There were an insufficient number of participants with either the HPS/HPS ($N = 0$) or the HPS/APS ($N = 7$) genotype to create a High Pain group, so our initial analyses focused on just two groupings (Low pain and Moderate pain).

Analyses of covariance (ANCOVAs) were conducted treating the COMT haplotype classification (Moderate Pain vs. Low Pain) and parenting quality (lower quality parenting versus higher quality parenting) as independent variables, child age (in days) and child gender as covariates, and each of the visual sequence outcomes as separate dependent variables. Descriptive statistics are presented in Table 2.

There was a significant main effect of COMT haplotype classification predicting percentage of total Anticipatory Looks (correct and incorrect), $F(1,31) = 5.24, p = .03, partial \eta^2 = .15$. The Low Pain group ($M = .21, SD = .09$) showed a significantly higher percentage of total

Anticipatory Looks than the Moderate Pain group ($M = .15$, $SD = .07$). There was no evidence of a significant main effect for parenting quality. The COMT haplotype main effect was qualified by a significant interaction of COMT haplotype and parenting quality, $F(1,31) = 8.93$, $p = .005$, $partial\ eta^2 = .22$. This interaction, presented in Figure 1, suggests that participants in the Low Pain group only show an advantage in Total Anticipatory Looks when parenting quality is high.

We also examined correct and incorrect anticipatory looks separately. For correct anticipatory looks we found a similar COMT haplotype \times parenting quality interaction, $F(1,31) = 6.23$, $p = .02$, $partial\ eta^2 = .17$, but no evidence for main effects of either COMT haplotype or parenting quality. For incorrect anticipatory looks we found no evidence of significant effects main effects and only a marginally significant COMT haplotype \times parenting quality interaction, $F(1,31) = 4.02$, $p = .054$, $partial\ eta^2 = .12$.

There was a significant main effect of COMT haplotype classification predicting Total Trials completed, $F(1,31) = 8.03$, $p = .008$, $partial\ eta^2 = .21$, such that the Low Pain group ($M = 122.55$, $SD = 45.50$) showed significantly more trials completed than the Moderate Pain group ($M = 81.13$, $SD = 36.88$). There was no evidence of a significant main effect for parenting quality or a significant interaction of COMT haplotype and parenting quality predicting Total Trials.

There was a significant main effect of COMT haplotype classification predicting percentage of Unattended Trials, $F(1,31) = 15.30$, $p = .0005$, $partial\ eta^2 = .33$, such that the Low Pain group ($M = .06$, $SD = .05$) showed significantly lower percentage of Unattended Trials than the Moderate Pain group ($M = .19$, $SD = .15$). There was no evidence of a significant main effect for parenting quality or a significant interaction of COMT haplotype and parenting quality predicting percentage of Unattended Trials.

There was a significant main effect of COMT haplotype classification predicting Reaction Time during reactive looks, $F(1,31) = 5.25$, $p = .03$, $partial\ eta^2 = .15$, such that the Low Pain group ($M = .25$, $SD = .03$) showed significantly faster reaction times than the Moderate Pain group ($M = .30$, $SD = .08$). There was no evidence of a significant main effect for parenting quality or a significant interaction of COMT haplotype and parenting quality predicting Reaction Time.

COMT Val^{108/158}Met genotype

We re-ran our ANCOVA analyses using the traditional COMT Val^{108/158}Met genotype distinction. Due to the small number of participants with the Val^{108/158} homozygous genotype ($N = 7$), we conducted the COMT Val^{108/158}Met genotype analyses using a Val present (Val/Val and Met/Val; $N = 31$) versus Val absent (Met/Met; $N = 14$) comparison. In comparing and contrasting the results of these analyses with the haplotype analyses it should be noted that the haplotype and genotype classifications have a large degree of overlap, particularly when we aggregate participants into larger groups, and thus can be expected to produce similar outcomes.

Analyses of covariance (ANCOVAs) were conducted treating the COMT Val^{108/158} Met genotype classification (Val present versus Val absent) and parenting quality (lower quality parenting versus higher quality parenting) as independent variables, child age (in days) and child gender as covariates, and each of the visual sequence and outcomes as separate dependent variables. Descriptive statistics are presented in Table 3.

There was no evidence of significant main effects for the genotype classification or parenting quality predicting percentage of Total Anticipatory Looks, Correct Anticipatory Looks, or

Incorrect Anticipatory Looks. There was evidence of significant genotype X parenting quality interaction predicting Total Anticipatory Looks, $F(1,39) = 6.71, p = .01, \text{partial } \eta^2 = .15$. This interaction, presented in Figure 2, suggests that Val present participants only show an advantage in Total Anticipatory Looks when parenting quality is high. There was a similar, but non-significant ($p = .06$) pattern of interaction predicting Correct Anticipatory Looks and a similar significant interaction ($p = .03$) predicting Incorrect Anticipatory Looks.

There was no evidence of significant main effects for genotype classification or parenting quality and no evidence of genotype X parenting quality interactions predicting Total Trials completed, percentage of Unattended Trials, or Reaction Time. It should be noted, however, that for all three of these outcomes there was a trend of marginal main effects for genotype classification, such that participants with the Val present classification showed marginally more Total Trials completed ($p = .06$), fewer Unattended Trials ($p = .06$), and faster Reaction Times, ($p = .10$).

Comparing COMT Haplotype and Genotype

One question we were interested in examining was whether the COMT haplotype classification was significantly better at predicting Visual Sequence outcomes than the COMT Val^{108/158}Met genotype classification. While the previous analyses showed that the COMT haplotype classification produced more significant findings this does not show that the effects associated with the haplotype classification are significantly larger than the effects associated with the genotype classification. To directly examine this issue we calculated effect sizes with 95% confidence intervals for the main effects of both COMT classifications. This was done by taking the difference in means for each comparison and dividing by the pooled standard deviation (Cohen's d). Results are presented in Table 4 and plotted in Figure 3. Effect sizes for the haplotype classification ranged in size from moderate ($d = .54$) to strong ($d = 1.30$). Effect sizes for the genotype classification ranged in size from small ($d = .31$) to moderate ($d = .64$). While the COMT haplotype grouping was more successful in the sense that it produced a greater number of statistically significant findings and stronger effects, directly comparing the effect sizes associated with the COMT haplotype and genotype groupings shows that the COMT haplotype does not account for significantly more variance than the COMT genotype in any of our behavioral outcomes. As previously discussed, with the current data set the two classifications have a high degree of overlap and thus could be expected to produce similar results.

DISCUSSION

Our analysis of the *COMT* genotype and looking behavior of toddlers demonstrates anticipatory looking, where speed and persistence of looking correlate with the *COMT* haplotype groupings. The haplotypes show significant main effects predicting total anticipatory looks, total number of trials completed, percentage of unattended trials, and reaction time, where individuals with the low pain haplotypes performed better in each category. There is a significant interaction between parenting and total anticipatory looks, with percent correct anticipatory looks, and marginally, with percent incorrect anticipatory looks. The low pain LPS/LPS and APS/LPS individuals have higher levels of COMT activity and performed significantly better as compared to the HPS/LPS and APS/APS individuals of intermediate COMT activity, and this performance was enhanced in an environment of higher quality parenting.

When our data are assessed through Val^{108/158}Met genotype analysis, there were no significant main effects; however, there was a genotype and parenting quality interaction that significantly predicted total anticipatory looks and, marginally, correct and incorrect anticipatory looks. The Val-present category had more anticipatory looks in each case. This analysis only presents a partial picture of COMT: enzyme rate but not enzyme concentration Because the enzymatically

active Val allele can be abundant (LPS) or limiting (HPS) in concentration (Diatchenko et al 2005; Nackley et al, 2006), this grouping can be misleading in terms of overall COMT activity. When compared, the *COMT* haplotype gave more significant correlations but the Val^{108/158}Met genotype classification showed a similar trend. Moreover, the variance accounted for by the haplotype was measurably, but not significantly, better than that of the genotype.

Level of Dopamine

In our studies higher levels of enzyme activity and thus lower levels of dopamine transmission were related to better overall attention. The direction of these results was not as expected because previous studies have associated lower COMT activity with superior executive performance in children and adults. However, few studies have looked at the development of attention in toddlers. The dopaminergic system changes throughout the lifespan of primates, particularly during postnatal development (Goldman-Rakic, et al, 1992; Lidow, et al 1991). Cortical dopamine content is dramatically higher in postnatal monkeys (Goldman-Rakic, 2000). Tyrosine hydroxylase, the rate-limiting catalytic step of dopamine production, was measured in human cortical tissue and its concentration is highest in neonates and infants (2 months - 1 year old), by a measure of 4- and 2.5-fold, respectively, as compared to all other age groups (adolescence, young adult, adult, and aged adult) (Weickert, et al. 2007). While steady-state levels of dopamine rely both on production and degradation rates, the tyrosine hydroxylase levels likely reflect dopamine levels in cortical tissue if degradation rates do not fluctuate dramatically.

A recent study observed a maturational elevation of COMT activity in human prefrontal cortex, where COMT activity was roughly 2.5x lower in neonates and infants (1-11 months) than adults (Tunbridge, et al. 2007). In the case of toddlers, where dopamine levels are presumably much higher than in later stages of development, the higher catabolic rate of the LPS haplotype could be advantageous and determine better performance in anticipatory looking. This may be consistent with an inverse U-shaped curve response to dopamine, where cognitive performance is optimal when dopamine levels are neither too high or low (Granon, et al. 2000; Mehta, et al. 2000), and in an environment where dopamine levels are high, greater COMT activity may be optimal. Tunbridge *et al* were unable to see significant differences in COMT activity related to the Val^{108/158}Met polymorphism, but this may have been due to the small sample size and to the variation in COMT enzyme levels determined by the *COMT* haplotypes of the Val allele.

We will have an additional chance to examine the direction of the COMT variations on performance at age 4. We hope to understand these developmental changes more completely by examining the link between COMT and attention performance over time.

Influence of parenting

The *COMT* haplotypes interacted with parenting quality in their influence on attention in the visual sequence task. High quality parenting when combined with the low pain haplotype showed a higher percentage of anticipations in our looking task. Parenting quality is a composite of several dimensions including support and autonomy (see methods sections). Since these dimensions are highly correlated we do not know which of these aspects of parenting quality are most important. However, our data do show that parenting, when considered in combination with genetics, plays an important role in understanding the development of attention. It does not appear to be the case that attention simply “matures” or “unfolds” over time. Instead, higher quality parenting appears to facilitate the development of attention. From the current data it is not clear if this advantage is temporary, or if lasting advantages will be seen. However, these findings do support the idea that early environmental interventions can be used to improve domain-general cognitive functions such as executive

attention. Training studies also support the improvement of executive attention by specific experiences (Rueda et al 2005)

We had previously found that parenting quality also interacted with the 7-repeat allele of the *DRD4* gene to influence the temperamental dimension of risk taking in two year old children (Sheese et al, 2007). However, neither the *DRD4* gene nor parenting showed main effects on attention measures in our previous report. In the current data, the *COMT* gene shows a main effect on attentional tasks and also interacts with parenting to influence performance on attentional tasks. It is also unclear why variations in the *COMT* gene influence attention performance in a looking task while variations in the *DRD4* are related to parent-reported sensation seeking but not attention.

There is no evidence that *COMT* is undergoing positive selection. This casts doubt on the most general form of our hypothesis that positive selection occurs because positive selection allows more influence of cultural factors such as parenting on children. Increased cultural influence may be one factor influencing positive selection, but the current data suggest it is not the only one. Although parenting influences attentional performance, this outcome does not seem to affect reproductive success at least not sufficiently to insure positive selection. It is possible that temperamental differences such as were found with *DRD4* play a more influential role in success in reproduction.

Orienting and executive networks

It has proven difficult to separate the orienting and executive network in infancy and early childhood. Orienting tasks have been consistently related to the *CHRNA4* polymorphism in adults, sometimes in conjunction with *CHRM2* (Greenwood, Fossella & Parasuraman, 2005; Greenwood, Lin, Sundararajan, Fryxell & Parasuraman, 2009). In our data the *CHRNA 4* gene showed a relation to anticipatory looks at 7 months with the T/T polymorphism showing more correct anticipation, but at 2 years the C/C polymorphism appeared to related to effortful control in parent reports (Sheese et al, in press). Since effortful control generally reflects the executive networks, our finding suggests that orienting and executive control may be more closely linked during infancy. This may be either because they operate together in all tasks, or because the particular selective looking task we used recruits both networks.

The *COMT* gene did not show any significant relation to aspects of the sequential looking tasks at 7 months, but the *COMT* haplotypes were clearly related to anticipatory looking at 18 months to 2 years of age where they interact with parenting quality. Overall these results suggest that both the orienting and executive network are available to regulate selective looking during infancy and early childhood. Neither our experimental task nor the genetic results provide a clear separation of the two networks. However, it is possible that when these same children are given key press tasks at 4-years of age, like the Attention Network Test, that more clearly separate the networks, we will be able to determine exactly which networks mediate these early effects.

Attention is a crucial element in development of the self-regulation taking place between infancy and later childhood (Posner, et al 2007). At the age we studied, children are beginning to regulate their emotions and behaviors. As development proceeds, these differences in self-regulation are crucial to such important behaviors as the ability to delay gratification, understanding of the minds of others, and the degree of pro-social and anti-social behavior. Our new findings reveal that individual differences among children at this age depend both upon genetic variations and specific environmental influences such as parenting. The *COMT* gene interacts with parenting to influence attention. The direction of the *COMT* effect seems to suggest important differences in the endogenous level of dopamine and its regulation as a function of development. Further studies during childhood will be needed to develop a better

understanding of how the level of dopamine at a given age relates to individual differences in regulation to influence the efficiency of attention.

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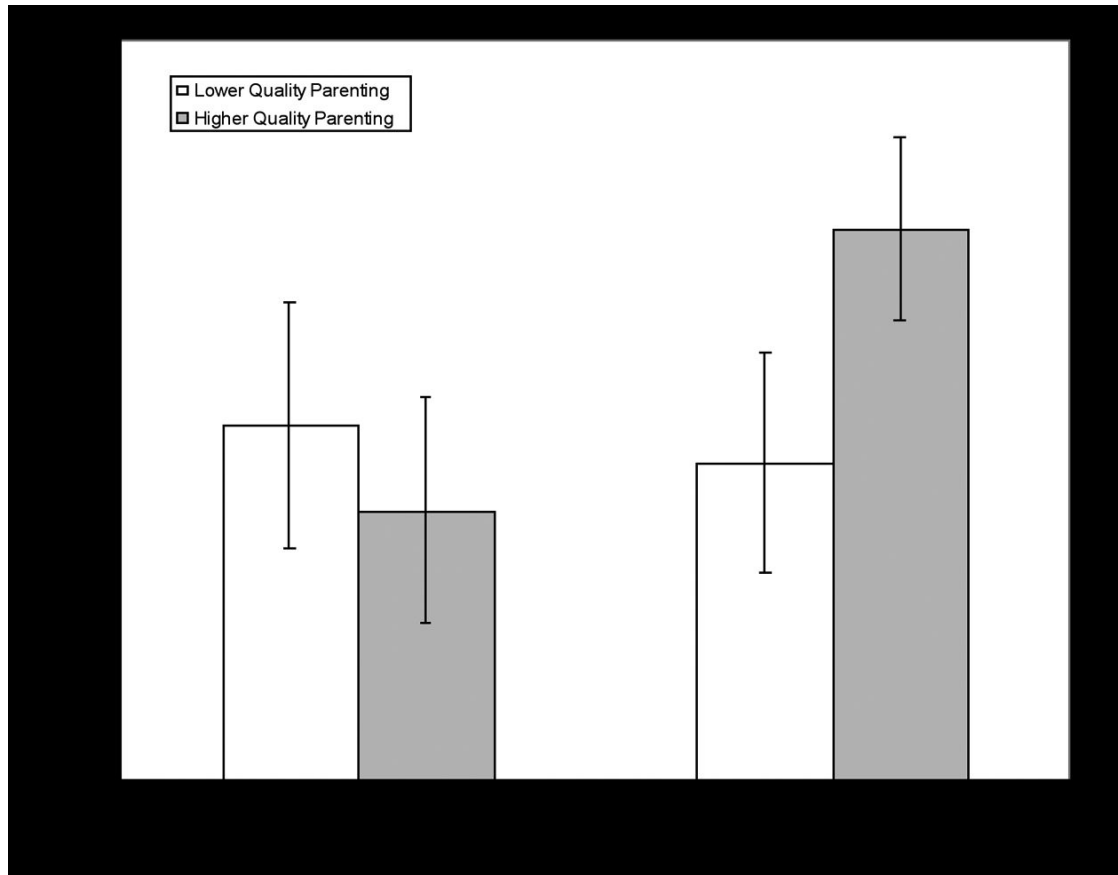


FIGURE 1. Means with 95% confidence intervals for COMT haplotype X parenting quality interaction predicting percentage of Total Anticipatory Looks.

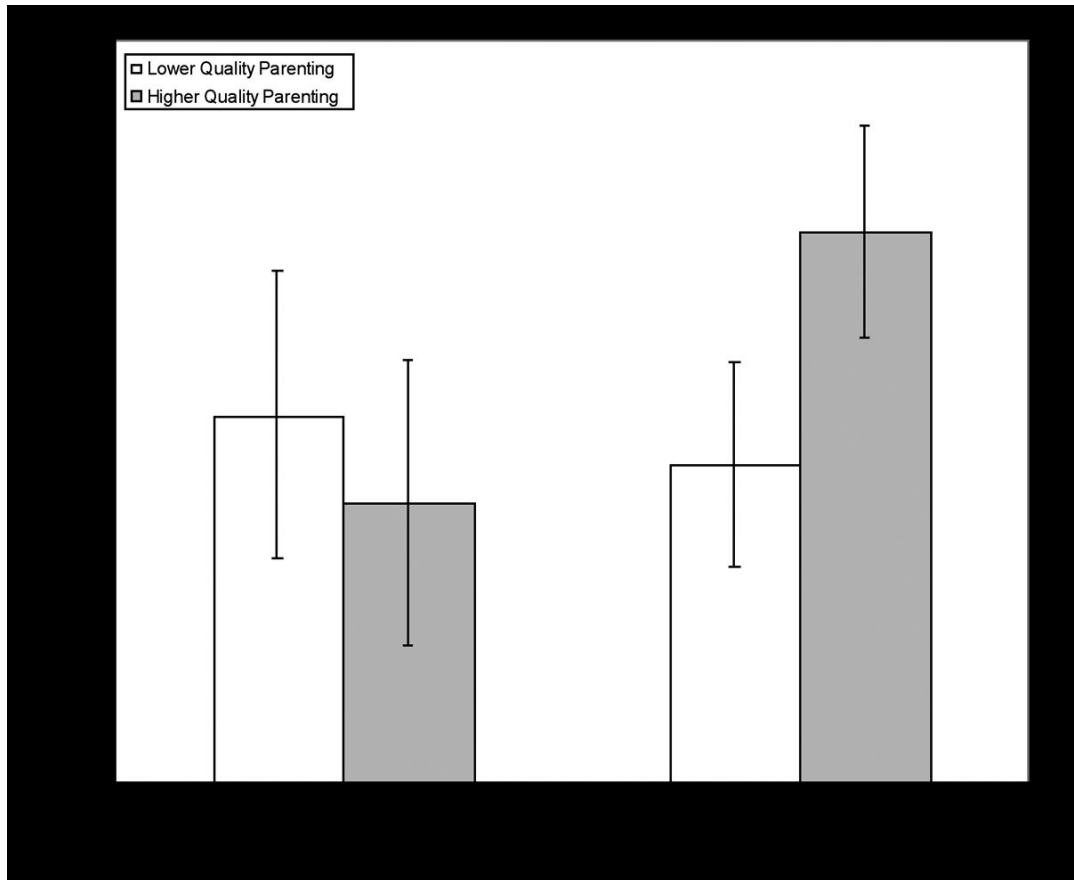


FIGURE 2. Means with 95% confidence intervals for COMT genotype X parenting quality interaction predicting percentage of Total Anticipatory Looks.

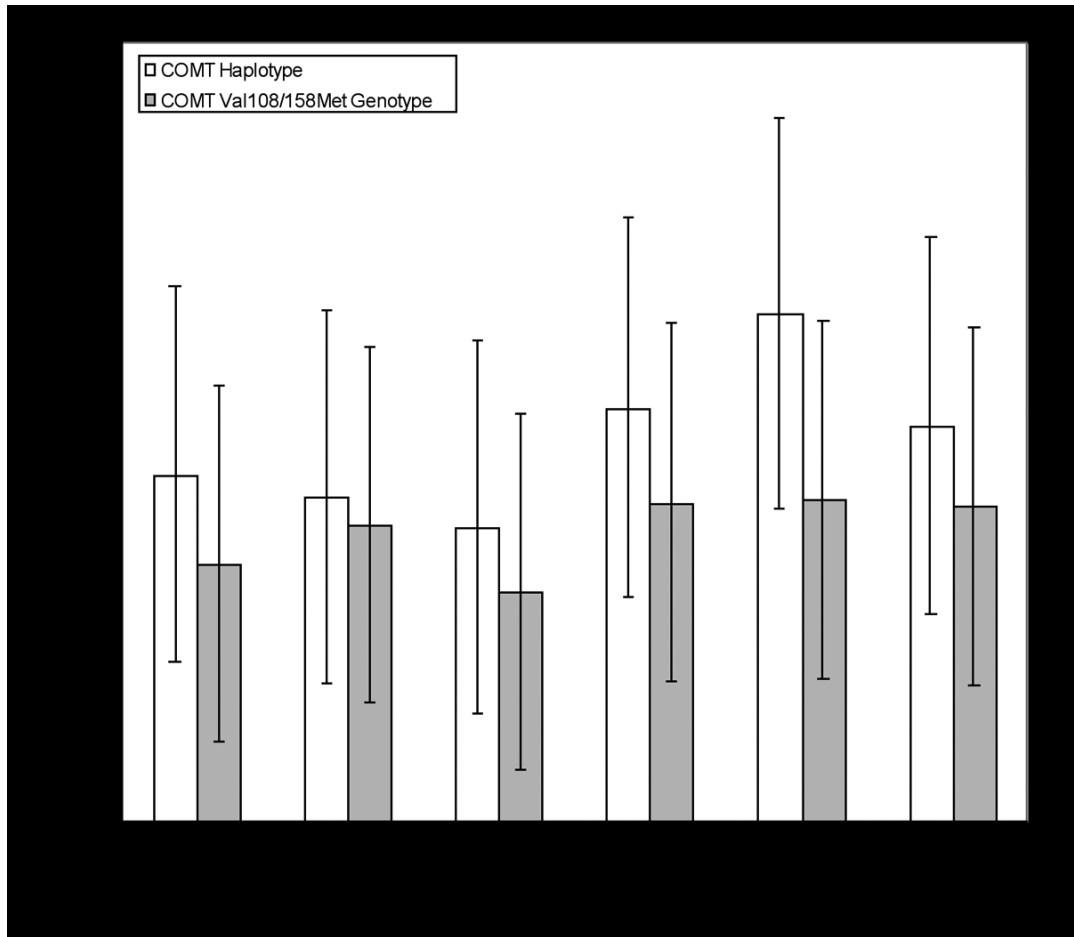


FIGURE 3. Comparison of *COMT* haplotype and genotype with varying measures of visual looking performance.

Table 1

Descriptive Statistics and Inter correlations

Visual Sequence Outcomes	M	SD	Correlations				
			1.	2.	3.	4.	5.
1. Total Anticipatory Looks %	.19	.11	1.00				
2. Correct Anticipatory Looks %	.09	.06	.86 ^{***}	1.00			
3. Incorrect Anticipatory Looks %	.11	.06	.86 ^{***}	.48 ^{***}	1.00		
4. Total Trials Completed	110.97	50.26	.18	.08	.23	1.00	
5. Unattended Trials %	.10	.11	-.32 [*]	-.34 ^{**}	-.20	-.53 ^{***}	1.00
6. Reaction Time	.27	.05	-.04	-.10	.04	-.37 ^{**}	.66 ^{***}

Note.

* indicates $p < .05$,

** indicates $p < .01$,

*** indicates $p < .001$.

Table 2

COMT Haplotype Descriptive Statistics

	COMT Haplotype																
	Moderate Pain (APS/APS & HPS/LPS)						Low Pain (LPS/APS & LPS/LPS)										
	Overall	SD	M	LQP	HQP	Overall	SD	M	LQP	HQP	Overall	SD	M	LQP	HQP		
Visual Sequence Outcomes	M	.15	.07	.18	.13	.05	.05	.04	.06	.07	.09	.21	.09	.16	.05	.25	.10
Total Anticipatory Looks %																	
Correct Anticipatory Looks %																	
Incorrect Anticipatory Looks %																	
Total Trials Completed		81.13	36.88	67.86	23.53	92.75	43.76	122.54	46.76	116.67	50.67	126.62	45.55				
Unattended Trials %		.19	.15	.21	.11	.17	.18	.06	.05	.06	.04	.06	.05				
Reaction Time		.30	.08	.30	.10	.30	.05	.25	.03	.26	.03	.25	.03				

Note. LQP denotes lower quality parenting. HQP denotes higher quality parenting.

Table 3

COMT Val¹⁵⁸Met Genotype Descriptive Statistics

	COMT Val ¹⁵⁸ Met Genotype											
	Val Present				Overall				Val Absent			
	M	SD	LQP	HQP	M	SD	LQP	HQP	M	SD	LQP	HQP
Visual Sequence Outcomes	.20	.11	.15	.26	.16	.06	.17	.26	.16	.06	.17	.26
Total Anticipatory Looks %	.09	.06	.06	.12	.06	.04	.07	.12	.06	.04	.07	.12
Correct Anticipatory Looks %	.11	.07	.09	.14	.09	.03	.11	.14	.09	.05	.11	.14
Incorrect Anticipatory Looks %	113.32	49.58	109.56	117.33	84.64	50.84	67.86	117.33	84.64	35.58	23.53	101.43
Total Trials Completed	.09	.11	.09	.09	.16	.11	.21	.09	.16	.11	.11	.12
Unattended Trials %	.26	.04	.27	.26	.29	.04	.30	.26	.29	.08	.10	.29
Reaction Time												

Note. LPQ denotes Lower Quality Parenting. HQP denotes Higher Quality Parenting.

Table 4
Effect Sizes for Genotype and Haplotype Classifications

	Effect Size		Confidence Interval for Effect Size	
	<u>Cohen's <i>d</i></u>	<u>S. E.</u>	<u>Lower</u>	<u>Upper</u>
Total Anticipatory Looks				
COMT Haplotype	.73	.34	.03	1.39
COMT Val ^{108/158} Met Genotype	.41	.32	-.23	1.04
<u>Correct Anticipatory Looks</u>				
COMT Haplotype	.65	.34	-.04	1.31
COMT Val ^{108/158} Met Genotype	.55	.33	-.10	1.18
<u>Incorrect Anticipatory Looks</u>				
COMT Haplotype	.54	.34	-.14	1.20
COMT Val ^{108/158} Met Genotype	.31	.32	-.33	.94
<u>Total Trials</u>				
COMT Haplotype	.96	.35	.25	1.63
COMT Val ^{108/158} Met Genotype	.63	.33	-.03	1.26
<u>Unattended Trials</u>				
COMT Haplotype	1.30	.37	.55	1.99
COMT Val ^{108/158} Met Genotype	.64	.33	-.02	1.27
<u>Reaction Time</u>				
COMT Haplotype	.90	.35	.19	1.56
COMT Val ^{108/158} Met Genotype	.62	.33	-.04	1.25