Developmental Science

Developmental Science 16:1 (2013), pp 13–23 DOI: 10.1111/j.1467-7687.2012.01180.x

PAPER

The *COMT* Val/Met polymorphism is associated with reading-related skills and consistent patterns of functional neural activation

Nicole Landi, Stephen J. Frost, W. Einar Mencl, Jonathan L. Preston, Leslie K. Jacobsen, Maria Lee, Carolyn Yrigollen, Kenneth R. Pugh and Elena L. Grigorenko

Yale Child Study Center, USA

Abstract

In both children and adults there is large variability in reading skill, with approximately 5–10% of individuals characterized as having reading disability; these individuals struggle to learn to read despite adequate intelligence and opportunity. Although it is well established that a substantial portion of this variability is attributed to the genetic differences between individuals, specifics of the connections between reading and the genome are not understood. This article presents data that suggest that variation in the COMT *gene, which has previously been associated with variation in higher-order cognition, is associated with reading and reading-related skills, at the level of both brain and behavior. In particular, we found that the* COMT *Val/Met polymorphism at rs4680, which results in the substitution of the ancestral Valine (Val) by Methionine (Met), was associated with better performance on a number of critical reading measures and with patterns of functional neural activation that have been linked to better readers. We argue that this polymorphism, known for its broad effects on cognition, may modulate (likely through frontal lobe function) reading skill.*

Introduction

Reading disability (RD) has been characterized as a brain-based difficulty in acquiring fluent reading skills, typically associated with phonological deficits, that affects significant numbers of children (Lyon, Shaywitz & Shaywitz, 2003).[1] Evidence from epidemiological population studies suggests that RD symptomatology likely reflects normally distributed variation in behavior (Jorm, Share, Maclean & Matthews, 1986; Shaywitz, Escobar, Shaywitz, Fletcher & Makuch, 1992; Stevenson, 1988), and thus might be more accurately viewed as a dimensional, rather than a discrete developmental disorder (Fletcher, 2009). This evidence motivates the study of neural and genetic correlates of reading skill across a broad spectrum of levels rather than limiting our approach to extreme variation in reading skill (e.g. RD).

[1] This prevalence depends, in part, on definitional criteria applied (i.e. discrepancy–poor reading, usually bottom 25%, and 'normal' or above normal IQ; achievement–poor reading despite IQ; or Response to Intervention–poor reading despite adequate pedagogical treatment), thus prevalence estimates can vary from 5 to 20%.

The acquisition of reading skill is likely to be influenced by multiple genes and gene–environment co-actions. Moreover, the psychological texture of reading skill is complex because it weaves in not only reading-specific processes (e.g. decoding) but also more generic cognitive characteristics of the reader (e.g. working memory). Given the role of *COMT* in dopamine regulation and the observed associations between *COMT* and a variety of skills important for reading (e.g. attention, working memory), we have chosen to focus on the variation in this gene and its putative association with reading skill. The *COMT* gene codes for the Catechol-*O*-methyltransferase enzyme, which metabolizes released dopamine in the prefrontal cortex and, as such, is a strong regulator of prefrontal dopamine levels. Moreover, multiple loci within the *COMT* intronic and promoter regions have been found to modify gene expression and function (e.g. Chen, Lipska, Halim, Quang, Matsumoto, Melhem, Kolachana, Hyde, Herman, Apud, Egan, Kleinman & Weinberger, 2004). Given the role of the variation in *COMT* in prefrontal functioning and skill, we suggest that variability in the *COMT* genotype may modulate

Address for correspondence: Nicole Landi, Yale Child Study Center, Haskins Laboratories, 230 S. Frontage Road, New Haven CT 06519, USA; e-mail: Nicole.landi@yale.edu

skilled reading development; that is, we suggest that variation in the *COMT* gene may be associated with reading skill acquisition through the connection between reading skills and higher-level cognitive skills, which, in turn, are connected to the activity in the prefrontal cortex.

Variation at codon 158 of the *COMT* gene (captured as rs4680) results in a valine (Val)-to-methionine (Met) substitution, which has been associated with increased performance on tasks that heavily recruit prefrontal regions and more efficient physiological response in prefrontal cortex (Egan, Goldberg, Kolachana, Callicott, Mazzanti, Straub, Goldman & Weinberger, 2001). Behaviorally, this polymorphism in adults and late adolescents has been associated with memory, executive function, attention, low-level auditory ERP response and reading comprehension (e.g. Chen *et al.*, 2004; Lebedeva, Korovaitseva, Lezheiko, Kaleda, Abramova, Barkhatova & Golimbet, 2009; Grigorenko, Deyoung, Getchell, Haeffel, Klinteberg, Koposov, Oreland, Pakstis, Ruchkin & Yrigollen, 2007). Extant research on *COMT* has largely focused on memory and/or executive function in typical and atypical (e.g. schizophrenic patients) individuals because of the role that prefrontal dopamine is thought to play in these functions and illnesses. Despite these positive associations, a recent meta-analysis (Barnett, Scoriels & Munafò, 2008) of this particular *COMT* polymorphism yielded mixed results, indicating that there may be little role for this polymorphism in cognitive behavior. However, meta-analytic approaches depend upon the quality and the validity of the individual studies included. In fact, Barnett *et al.* (2008) conclude that the *COMT* Val/Met polymorphism remains a viable candidate gene that may contribute to variation in cognitive function, and that continued investigation of the relationship between properly characterized complex cognitive phenotypes and the variation in the *COMT* gene is important.

Although the literature examining the effects of this *COMT* polymorphism on functional MRI (fMRI) activation is relatively small, and thus far largely limited to studies of adults, multiple studies have found that Val carriers produce greater prefrontal activation than Met carriers despite comparable levels of working memory performance, indicating that cognitive processing may be less efficient in these individuals (e.g. in schizophrenic patients during an N-back task, Egan *et al.*, 2001; in healthy adults in a verbal and spatial memory task, Bishop, Fossella, Croucher & Duncan, 2008; in healthy adults in a word recall task, Schott, Seidenbecher, Fenker, Lauer, Bunzeck, Bernstein, Tischmeyer, Gundelfinger, Heinze & Düzel, 2006; in healthy adults during mathematic and temporal transformations that tax working memory, Tan, Chen, Goldberg, Mattay, Meyer-Lindenberg, Weinberger & Callicot, 2007). However, other studies have found greater activity for Met carriers, including a recent study by Stokes, Rhodes, Grasby and Mehta (2011) who found reduced activation in the right posterior cingulate cortex for healthy adults with the Val/Val genotype relative to Val/Met and Met/Met genotypes during an N-back task and a go-no-go task (see also Stokes *et al.*, 2011 and Mier, Kirsh & Mayer-Lindenberg, 2010 for a summary of Val/Met, Met/Met and Val/Val patterns of activation across reports/tasks). Stokes and colleagues (2011) and Tan and colleagues (2007) suggest that the difference in findings reflects the use of tasks or subprocesses within tasks that have differential sensitivity to dopamine levels and/or function. Further, another recent meta-analysis of the neural substrates associated with *COMT* (Mier *et al.*, 2010) found that in general, executive cognition tasks favored Met carriers while emotional processing tasks favored Val carriers, further validating the pleiotropic effects of *COMT* variation.

Recently, our group established a complex association between variation in the *COMT* gene across multiple SNPs (using a haplotype analysis) and reading comprehension skill in incarcerated adolescents[2] (Grigorenko *et al.*, 2007). This relationship suggests that the action of the *COMT* gene is related to complex multi-layered tasks such as reading comprehension, which involves low-level skills such as pseudoword decoding, intermediate-level skills such as lexical-semantic processing, and high-level skills such as executive functioning that are required for maintaining coherent text representations (Locascio, Mahone, Eason & Cutting, 2010; Landi, 2010). This article presents data from a study that follows up on this work by examining whether variability in *COMT* is associated with multiple aspects of reading skill (word reading, pseudoword reading, passage comprehension) and reading-related tasks (phonological awareness [PA], spelling and oral language skills) in young children and/or brain activation measured with fMRI. Given that the *COMT* gene regulates dopamine in left frontal cortical regions that are altered in RD, particularly in beginning readers (Shaywitz, Shaywitz, Pugh, Mencl, Fulbright, Skudlarski, Constable, Marchione, Fletcher, Lyon & Gore, 2002), we hypothesize that variation in this gene may contribute to individual differences in reading skill and its acquisition. Specifically, we suggest that for young readers, learning to read should be viewed as acquiring a new expertise and, as such, prefrontal systems should play an important role. Therefore, we propose that the variation in *COMT* via its impact on prefrontal systems function will be associated with reading-related behavior indicators, and associated patterns of activation in brain.

[2] Note that this finding was obtained in the context of studying reading comprehension performance and self-reported characteristics of maternal upbringing; this was not a case-control study of reading comprehension.

Methods

Participants

Eighty-six individuals between the ages of 6 and 10, mean age = 8.28, were enrolled in this study; these participants were split into three groups based on *COMT* genotype (see Group details below). Mean ages and gender for the three groups are as follows: Met/Met, Mean age = 8.35 (11 males, 12 females); Val/Met, mean age = 8.06 (24 males, 18 females); Val/Val, mean age = 8.40 (15 males, 6 females). These individuals participated as part of an ongoing study of individual differences in behavioral, neurobiological and genetic contributions to reading skill. Our participants were selected from the larger sample because they had usable MRI data (see MRI analysis) and usable DNA (see DNA collection and analysis). All participants had normal or corrected-to-normal vision and had normal hearing, assessed by an audiometer to be between −20 and 20 dB. No participants had a history of neurobiological insult, psychiatric condition, or developmental disability other than RD (primary), ADHD and/or speech delay (secondary).

Behavioral assessments

Participants were all administered a standard battery of reading and language assessments as well as a screener for ADHD, and educational and neuropsychological history evaluations. Several assessments of reading, language and academic skills were used. Specifically, the three genetic groups (Val/Val, Val/Met, and Met/Met) were compared on several assessments from the Woodcock-Johnson Achievement battery (Woodcock, McGrew & Mather, 2001) including: *Word reading measures*: Word Attack (pseudoword reading, or pseudoword decoding) and Reading Comprehension. *Oral Language Measures*: the Oral Comprehension and Oral Expression composites. *Spelling* was measured with the Spelling subtest. We also administered a measure of *Phonological Awareness* from the Comprehensive test of Phonological Processing (CTOPP; Wagner, Torgesen & Rashotte, 1999), which includes measures of elision and blending. Finally, we also measured *IQ*, in both the Performance and Verbal domains (the latter serves as a measure of expressive vocabulary as well) using the WASI (Psychological Corporation, 1999).

fMRI task

All participants were administered a neuroimaging task that was designed to look at word–level print processing. Specifically, children viewed pictures of common objects and printed words or pseudowords that either matched or did not match the object (e.g. they saw an image of a dress and saw the word 'dress' or a similar pseudoword 'dreak'). Critically, pictures came on the screen before the words and remained on the screen for six trials; this was done to ensure that picture processing was not part of what was being measured during the trials of interest. Real words were high frequency, 4–5 letter words, pseudowords were also 4–5 letters long. Participants were asked to press one button when the word matched the image and another when the image did not match the word (see Frost, Landi, Mencl, Sandak, Fulbright, Tejada, Jacobsen, Grigorenko, Constable & Pugh, 2009; Preston, Frost, Mencl, Fulbright, Landi, Grigorenko, Jacobsen & Pugh, 2010; Preston, Felsenfeld, Frost, Mencl, Fulbright, Grigorenko, Landi & Pugh, in press, for a more detailed task description). Behavioral accuracy in this task was greater than 80% (M = 84%), which is consistent with performance reported in other analyses with this sample (see Frost *et al.*, 2009). This task has been previously shown to discriminate good from poor readers as well as children with more general language problems (Frost *et al.*, 2009; Preston *et al.*, 2010; Preston *et al.*, in press).

fMRI data processing and analysis

Twenty axial-oblique anatomic images were acquired, parallel to the intercommissural line based on sagittal localizer images. At these same 20 slice locations, activation images were acquired using single shot, gradient echo, echo-planar acquisitions. High-resolution anatomical images were collected for 3D reconstruction. Images were sinc-interpolated to correct for slice acquisition time, motion-corrected with SPM2 (Friston, Ashburner, Frith, Poline, Heather & Frackowiak, 1995) and spatially smoothed with a 5.15-mm FWHM Gaussian filter. Images were excluded if they exceeded a tolerance of 2 mm displacement or 2° rotation from the first image in the functional series, or if they exceeded an image-to-image change of 1 mm displacement or 1° rotation. Regression-based estimation was used for the hemodynamic response at each voxel and for each condition, without prior specification of a reference function (Miezin, Maccotta, Ollinger, Petersen & Buckner, 2000). These parameters estimated the mean response for each condition from −3 to + 15 s relative to stimulus onset, and individual activation maps were created to estimate the mean difference between a baseline (0–3 sec before onset) and an activation period (3–8 sec post-onset). Prior to across-subjects analysis, participants' data were transformed to standardized reference space defined by the Montreal Neurological Institute (MNI) by mapping to the high-resolution anatomic to the 'Colin' brain, using linear and nonlinear registration parameters obtained with BioImage Suite (www.bioimagesuite.org; Papademetris, Jackowski, Schultz, Staib & Duncan, 2003).

The three genotype groups were compared on indicators of behavioral performance and initially across three fMRI conditions (printed words [match and non-match] and pseudowords) in a repeated-measures ANOVA;

patterns of activation between the two groups did not differ between word and pseudoword conditions and thus these three conditions were collapsed. Planned contrasts within this ANOVA were used to compare groups for the main effect of print processing conditions (collapsed across words and pseudowords) at each voxel separately. The univariate *p*-values from this ANOVA then corrected for multiple comparisons using the False Discovery Rate [FDR] correction with q = 0.001, effectively thresholding the univariate *p*-values at .01, corrected for multiple comparisons (Genovese, Lazar & Nichols, 2002). No cluster threshold was applied in this analysis or for display purposes. We also ran an omnibus ANOVA to examine which regions overlapped for the overall effect of *COMT* and the individual group comparisons. For the most part regions that showed significant activation differences in the individual group comparisons were also significantly active in the Omnibus ANOVA (Appendix Table A4 and Appendix figure 1).

DNA collection and analysis

DNA was extracted from saliva samples collected using sterile Oragene kits (DNA Genotek) during behavioral testing sessions with participants using DNA Genotek's protocol. After extraction of DNA from samples we used the Applied Biosystems Inc. (ABI) Taqman protocol for SNP genotyping. Specifically, the Assays-on-Demand SNP Genotyping Product containing forward and reverse primers as well as the probe for the SNP of interest was utilized. Taqman polymerase chain reaction (PCR) was used to amplify the region of DNA contained in the genomic region (*COMT* rs4680) under investigation. PCR was carried out using MJ Research Tetrad Thermocycler on a 384-well plate format. Taqman reactions include 50 ng of genomic DNA, 2.5 μl of ABI Taqman® Universal PCR Master Mix, 0.2 μl of ABI 40X Assays-on-Demand SNP Genotyping Assay Mix (assay ID C__25746809_50), 2.0 ul of sterile H_2O and 0.5 μl of Bovine Serum Albumin (BSA). The call rate for genotype identification was 87% (i.e. 28/209 from the entire study sample failed due to the quality of DNA).

Group details

Participants were genotyped (see details above) and grouped into three genotype groups: Val/ Val (n = 23), Val/Met (n = 42), and Met /Met (n = 21). There were no significant differences in age $F(2, 83) = .915$, $p = .405$ or gender ($X^2 = 2.09$, $p = .351$) between the three *COMT* groups. With respect to race, almost all participants were of European Caucasian ancestry with the two African-American participants in the Met/Met group and one in the Val/Met and only Caucasian participants in the Val/Val group.[3] With respect to handedness across the groups, the majority of participants were right handed with 27% left handed in the Met/Met group; 11% left handed in the Val/Met group and 9% in the Val/Val group ($X^2 = 5.103$, $p = .277$).

[3] Behavioral assessments and fMRI analyses were run with and without the two African-American participants in the Met carrier groups, and the pattern of significant findings remained the same.

Results

Behavioral

Performance on behavioral assessments was first analyzed using a MANOVA with group as a fixed factor, followed by pair-wise comparisons for each assessment. The MANOVA was significant $F(2, 75)$, $p = .03$. Because of a few missing cells in the phonological awareness and IQ subtests, the group *N*s for the MANOVA were Met/Met = 20; Val/Met = 40; and Val/ Val = 19; findings reported in Table 1 show means and standard deviations for the two groups on each of the behavioral assessments (means are based on the full sample for most assessments, Ns are provided for each test). Table 2 shows statistical results from the MANOVA including F values, *p* values and effect sizes for the group comparisons, and Table 3 shows the pairwise comparisons for each group relative to the other group in order to distinguish which group comparisons are driving the overall group effect. For both Met/Met vs. Val/Val and Val/Met vs. Val/Val we observed significant differences for Phonological Awareness and Spelling, and a marginal effect for Decoding. There were no significant differences between Met/Met

Table 1 *Means and standard deviations for the two groups on our behavioral assessments*

Test	Group	*N*	Mean	*SD*
WordAttack	Met/Met	23	110.17	13.90
	Val/Met	42	110.60	13.71
	Val/Val	21	103.71	11.93
PassageComp	Met/Met	23	106.39	16.98
	Val/Met	42	106.52	13.88
	Val/Val	21	100.71	13.40
OralComprehension	Met/Met	23	117.17	14.10
	Val/Met	42	115.98	12.24
	Val/Val	21	116.81	11.89
OralExpression	Met/Met	23	113.52	14.38
	Val/Met	42	114.41	10.61
	Val/Val	21	116.48	11.80
PhonoAwareness	Met/Met	23	114.32	17.80
	Val/Met	42	108.49	13.94
	Val/ Val	21	99.05	9.95
Spelling	Met/Met	23	110.39	19.67
	Val/Met	42	108.71	19.92
	Val/Val	21	96.29	16.52
PIQ	Met/Met	22	104.77	14.82
	Val/Met	42	110.81	17.81
	Val/Val	21	108.81	15.19
VIQ	Met/Met	22	106.77	16.32
	Val/Met	42	112.29	14.84
	Val/Val	21	107.57	15.37

Table 2 *F-values, p-values and effect sizes (r) for the three group comparison (MANOVA) on our behavioral assessments. Significant and marginal effects (based on effect size are bolded)*

Test	*F*	*p*	*R*
WordAttack	2.070	**0.133**	**0.412**
PassageComp	0.994	0.375	0.212
OralComprehension	0.115	0.681	0.067
OralExpression	0.386	0.681	0.110
PhonoAwareness	5.818	**0.004**	**0.859**
Spelling	3.953	**0.023**	**0.694**
PIQ	0.983	0.379	0.215
VIQ	0.848	0.432	0.191

Table 3 *Pairwise t-values from the three group comparisons (MANOVA) on our behavioral assessments. Significant and marginal effects (based on p-value, are bolded)*

Test	Group	*p*
WordAttack	Met/Met vs. Val /Met	.999
	Met/Met vs. Val/Val	**.092**
	Val/Met vs. Val/Val	**.059**
PassageComp	Met/Met vs. Val /Met	.946
	Met/Met vs. Val/Val	.257
	Val/Met vs. Val/Val	.181
OralComprehension	Met/Met vs. Val /Met	.874
	Met/Met vs. Val/Val	.772
	Val/Met vs. Val/Val	.633
OralExpression	Met/Met vs. Val /Met	.661
	Met/Met vs. Val/Val	.383
	Val/Met vs. Val/Val	.573
PhonoAwareness	Met/Met vs. Val /Met	.141
	Met/Met vs. Val/Val	**.001**
	Val/Met vs. Val/Val	**.020**
Spelling	Met/Met vs. Val /Met	.752
	Met/Met vs. Val/Val	**.014**
	Val/Met vs. Val/Val	**.014**
PIQ	Met/Met vs. Val /Met	.170
	Met/Met vs. Val/Val	.573
	Val/Met vs. Val/Val	.497
VIQ	Met/Met vs. Val /Met	.206
	Met/Met vs. Val/Val	.631
	Val/Met vs. Val/Val	.502

and Val/Met groups, though for some of our tasks there was a trend for means to be higher for Met/Met in the reading and reading-related tasks. There were no significant differences between any of the groups in Oral Language skills, Passage Comprehension, Performance IQ or Verbal IQ. These findings suggest that Met/Met and Val/Met carriers had superior performance relative to Val/Val carriers on reading-related skills (PA, Spelling), and marginally better performance for Decoding but not on more general language skills (Oral Language, Comprehension) or IQ. Note that superior performance for the individuals possessing Met/Met relative to Val/Val is consistent with previous behavioral data as noted above, though none of these studies examined reading or reading-related skills; this study is the first to use this approach to investigate reading and language skills and their relationship to *COMT*.

fMRI

Met/Met vs. Val/Val

Comparisons of the two homozygous groups revealed many regions of differential brain activation, with the Met/Met group showing several regions of greater activation relative to the Val/Val group. Moreover, the pattern of neural activation observed for Met/Met was more consistent with previously identified patterns of neural activity in good readers relative to poor readers (e.g. Landi, Mencl, Frost, Sandak, Chen & Pugh, 2010; Pugh, Mencl, Jenner, Katz, Frost, Lee, Shaywitz & Shaywitz, 2000; Pugh, Frost, Sandak, Landi, Rueckl, Constable, Seidenberg, Fulbright, Katz & Mencl, 2008). Specifically, individuals in the Met/Met group showed greater activation in a large region covering the left occipitotemporal junction (OT) and fusiform gyrus, sometimes referred to as the visual word form area (VWFA) and the left middle temporal gyrus (MTG). In addition, they also showed greater activation in a region of right frontal cortex and right parietal cortex, consistent with the idea that the frontal cortex may be involved in the relationship between *COMT* and reading (Figure 1; Appendix Table A1).

Met/Met vs. Val/Met

Likewise, as shown in Figure 1, the comparison of Met/Met and Val/Met groups indicated several regions of differential brain activation, in this case with Met/Met carriers showing significantly greater activation relative to individuals with the Val/Met genotype. The areas of greater activation for Met/Met relative to Val/Met overlap with those observed to be more active for Met/Met relative to Val/Val. In particular, greater activation in many of these regions is typically observed in relative to less skilled readers, including left OT, left STG and left MTG, (Figure 1; Appendix Table A2).

Val/Met vs. Val/Val

The comparison of Val/Met with Val/Val revealed many fewer regions of differential activation and the pattern of regional activation differences is primarily isolated to the left precentral gyrus and right occipital temporal gyrus with additional differences in extrastriate regions. Val/Val carriers also showed several areas of greater activity relative to Val/Met carriers, including in the parahippocampal gyrus and in several small regions of the frontal cortex and in the cerebellum.

Covariate analysis

Because *COMT* regulates dopamine levels and the degree to which these levels are modulated varies by gender, we chose to include gender as a covariate. Similarly, because the *COMT* Val/Met polymorphism has been associated

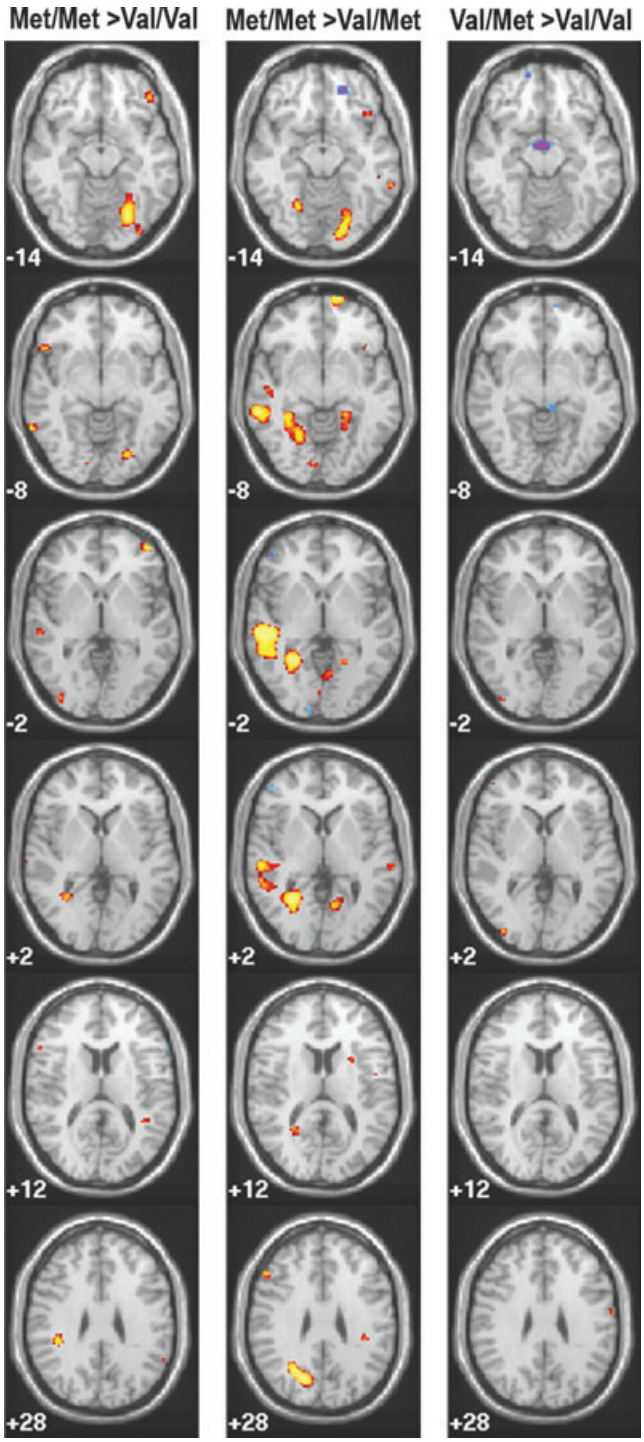

Figure 1 *Patterns of activation are shown for Met/Met > Val/Val, Met/Met > Val/Val and Val/Met > Val/Val in response to printed stimuli. Areas in yellow show greater activity for genotype listed first, Areas in purple show greater activity for the genotype listed second Z coordinates are listed in the bottom left corner, and pictures are presented in radiological convention (left, right reversed).*

with ADHD (Gothelf, Michaelovsky, Frisch, Zohar, Presburger, Burg, Aviram-Goldring, Frydman, Yeshaya, Shohat, Korostishevsky, Apter & Weizman, 2006), diagnosis of ADHD was included as a covariate as well. In addition, because of its known effect on hemispheric laterality, handedness was also included as a covariate. Finally, because of the relatively large age range in our study we also included age. To examine the role that gender, handedness, ADHD and age might play in our behavioral and/or our fMRI findings, we conducted two ANCOVAs, the first on all of our statistically significant behavioral variables, the second on our regions of interest (all regions in which group activations significantly differed). We first conducted the analysis with all covariates at once and if a significant effect for any covariate was identified or if the effect of group became non-significant we ran each covariate separately to determine which covariate was modifying our results. For the behavioral data, none of the covariates modified our effects (either entered in combination or independently). For the MRI data, we found small effects in two regions for one of our group comparisons; specifically, for the comparison of Val/Met > Val/Val the inclusion of all of the covariates made the middle occipital effect marginal (p = .07). This was also true for each of the covariates entered on their own (p-values for the effect of *COMT* group ranged from p = .07 to .09) except handedness, which did not modify observed effects of interest. Thus the middle occipital effect in this contrast may not be robust.

Discussion

We present an initial report on the relationship between a relatively common genetic mutation, the *COMT* Val/Met polymorphism found at SNP rs4680, and reading and reading-related skills. Associations were found between variation in the *COMT* gene and performance on behavioral measures; specifically, pairwise comparisons of each genotype revealed significantly better performance for Met/Met relative to Val/Val and Val/Met relative to Val/Val on several reading related skills, namely phonological awareness and spelling as well as a marginal effect of better performance on decoding (Word Attack), but no significant effects or trends for other skills we measured (e.g. comprehension, oral language, IQ). We suggest that these particular skills were more strongly associated with frontal lobe function (relative to the other skills measured) because these skills, which emphasize phonological processing, decoding and orthographic awareness, are of particular importance for children in this age range who are just beginning to acquire these skills. Moreover, we also observed strong associations between *COMT* and patterns of brain activation (BOLD); specifically, we found that Met/Met relative to Val/Val and Met/Met relative to Val/Met carriers presented more like better readers (identified in our previous work, e.g. Pugh *et al.*, 2000; Landi *et al.*, 2010). That is, in both cases the Met/Met carriers had greater activation in the OT region and in temporal regions of the left hemisphere. Moreover, Met/

Met carriers had greater activation in left prefrontal regions, consistent with the role of *COMT* in modulating prefrontal function. The comparison of Val/Met to Val/Val revealed fewer regions that distinguished the groups, and although the Val/Met carriers showed greater activation in some reading-related regions, they did not show the same global pattern of 'looking like better readers'. This is somewhat in conflict with the behavioral findings, which demonstrated behavioral differences between these groups. However, upon further inspection at a lower threshold ($p < .05$, FDR corrected) many more regions associated with reading including the OT were indeed more strongly activated for the Val/Met relative to the Val/ Val group.

It is noteworthy that many previous fMRI studies of this *COMT* Val/Met genotype have often identified greater activation for Val/Val carriers particularly in frontal regions, which has been associated with decreased efficiency (Bertolino, Rubino, Sambataro, Blasi, Latorre, Fazio, Caforio, Petruzzella, Kolachana, Hariri, Meyer-Lindenberg, Nardini, Weinberger & Scarabino, 2006; Bishop *et al*., 2008; Blasi Mattay, V.S., Bertolino, A., Elvevag, B., Callicott, J.H., Das, S., Kolachana, Egan, Goldberg & Weinberger, 2005; Caldu, Vendrell, Bartres-Faz, Clemente, Bargallo, Jurado, Serra- Grabulosa & Junqué, 2007; Egan *et al*., 2001; Kempton, Haldane, Jogia, Christodoulou, Powell, Collier, Williams & Frangou, 2008; Mattay, Goldberg, Fera, Hariri, Tessitore, Egan, Kolachana, Callicott & Weinberger, 2003). In our study the Val/Val group generally showed reduced activation, particularly in areas of interest for reading, including a left frontal region; however, as discussed above, several studies have also found greater activity for Met carriers, in a variety of regions including frontal sites (Drabant, Hariri, Meyer-Lindenberg, Munoz, Mattay, Kolachana, Egan & Weinberger, 2006; Smolka, Bu̇hler, Schumann, Klein, Hu, Moayer, Zimmer, Wrase, Flor, Mann, Braus, Goldman & Heinz, 2007; Smolka, Schumann, Wrase, Grusser, Flor, Mann, Braus, Goldman, Büchel & Heinz, 2005; Stokes *et al*., 2011). This discrepancy from the literature might be explained by two factors: first, the nature of our task (reading) and second the regions involved. The existing work that has identified greater activation for Val/Val has been focused on executive function (EF), attention and memory; these tasks and their associated patterns of regional activations are quite different from our assessments and in-scanner tasks, which primarily involve word reading. In particular, work on memory and EF routinely identifies increased activation in prefrontal regions as indicating reduced efficiency; however, in studies of reading, increased activity in reading and language-related areas is associated with superior performance. The second factor may be the age of our participants; the majority of the imaging work investigating *COMT* variation has been done with adults and not with young children. Although it is difficult to predict how exactly this would affect the data, it is known that tonic and phasic levels of dopamine in the cortex change throughout the aging process. Indeed, Wahlstrom, White, Hooper, Vrshek-Schallhorn, Oetting, Brott and Luciana (2007) found that superior performance in children and adolescents was associated with the heterozygous Val/Met genotype in contrast to most of the work on adults which has demonstrated superior performance for individuals with the Met/Met genotype (see also Wahlstrom, White & Luciana, 2010, for a review on the this work and related findings). Moreover, two existing studies of effects of *COMT* genotype on brain in children (though not on reading) indicate that 11–12-year-old children with the Met/Met genotype have increased gray matter volume and increased functional activity in the hippocampus during and emotional processing task (Mechelli, Tognin, McGuire, Prata, Sartori, Fusar-Poli, De Brito, Hariri & Viding, 2009) and that children between the ages of 9 and 16 who are Met/Met carriers have greater regional perfusion (measured by arterial spin-labeling) than Val/Val homozygotes in both cortical and sub-cortical regions, including frontal and temporal cortices, insula, caudate, brainstem, and lateral cerebellum. Although these tasks and methods are different from those used in the current study, these findings suggest that patterns of activation for Met/Met vs. Val/Met and Val/Val carriers may differ based on task, regions being explored, and participant age.

With regard to the association between this polymorphism and our behavioral data, we argue that, based on the literature, this polymorphism has broad cognitive effects and may modulate both acquisition and realization of reading skill via its impact on frontal lobe function. More specifically, we believe that the link to frontal lobe function may be via the metacognitive skill of phonological awareness (PA), which is strongly predictive of reading skill in the early grades (see Frost *et al*., 2009); this hypothesis is supported by our behavioral data which show that Met carriers have better PA. An alternative hypothesis is that polymorphism affects reading via fronto-striatal networks; recent work from our lab (Preston *et al*., 2010; Pugh, Landi, Preston, Mencl, Austin, Sibley, Fulbright, Seidenberg, Grigorenko, Constable, Molfese & Frost, in press) implicates the thalamus and putamen as important in reading and related skills (and these regions are apparent in the data presented here as well; Appendix Tables A1–A3). In our earlier work, we have further hypothesized that these regions are critical because of the sensori-motor procedural learning that takes place when children acquire phonological awareness and then reading (cf. Ullman & Pierpont, 2005). Specific mechanisms aside, because the Val/Met polymorphism represents a common variant in the population, it may account for a meaningful amount of the variability in reading and other domain-specific abilities (again, via domain-general mechanisms associated with cognition) in the general population. Thus, we suggest that *COMT* may be more relevant in the general population and associated distribution of reading skill

than any single rare mutation, which can be a powerful causal factor in a single family or a few families, but is unlikely to be generalizable to the general population.

Despite its limitations (i.e. sample size in particular), this study contributes to a growing literature that stresses the importance of considering common genetic variants in understanding the etiology of cognitive differences, especially in samples drawn from the general population. Although such variants might not target a particular cognitive skill or process, because of their critical role in brain function, they appear to be pleiotropic in their impact, affecting multiple skills or components of these skills. While these findings should be viewed with caution, they contribute to the literature by demonstrating the complexity of the *COMT* Val/Met polymorphism in its relationship to multiple cognitive skills. To understand this complexity, it is important to carry out multi-level modeling, bringing genetic, brain, and behavior data into vertical structures allowing investigations of the direct and indirect effects of genetic variants on characteristics of brain and behavior functions. Although such modeling cannot be carried out in this work due to sample size limitations, the current results provide evidence for the importance of such multi-level investigations.

Acknowledgements

This study was supported by several NIH grants including R01 HD 048830 (K. Pugh, PI); PO1 HD052120, (R. Wagner, PI); P01 HD 01994 (C. Fowler, PI); R03 HD053409 (N. Landi, PI). We also want to thank Beth Eaton and Annie Stutsman for behavioral assessment of children, as well as Teri Hickey, HedySerofin and Cheryl McMurray for imaging participants, and Cheryl Lacadie for fMRI preprocessing. Finally we thank the many families and children for their participation, with special thanks to the Windward School for their collaboration.

References

Barnett, J.H., Scoriels, L., & Munafò, M.R (2008). Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. *Biological Psychiatry*, **64**, 137–144.

Bertolino, A., Rubino, V., Sambataro, F., Blasi, G., Latorre, V., Fazio, L., Caforio, G., Petruzzella, V., Kolachana, B., Hariri, A., Meyer-Lindenberg, A., Nardini, M., Weinberger, D.R., & Scarabino, T. (2006). Prefrontal-hippocampal coupling during memory processing is modulated by COMT val158met genotype. *Biological Psychiatry*, **60**, 1250–1258.

Bishop, S.J., Fossella, J., Croucher, C.J., & Duncan, J. (2008). COMT val158met genotype affects recruitment of neural mechanism supporting fluid intelligence. *Cerebral Cortex*, **18**, 2132–2140.

Blasi, G., Mattay, V.S., Bertolino, A., Elvevag, B., Callicott, J. H., Das, S., Kolachana, B.S., Egan, M.F., Goldberg, T.E., & Weinberger, D.R. (2005). Effect of catechol- O-methyltransferase val158metgenotype on attentional control. *Journal of Neuroscience*, **25**, 5038–5045.

Caldu, X., Vendrell, P., Bartres-Faz, D., Clemente, I., Bargallo, N., Jurado, M.A., Serra- Grabulosa, J.M., & Junqué, C. (2007). Impact of the COMT Val108/158 Met and DAT genotypes on prefrontal function in healthy subjects. *NeuroImage*, **37**, 1437–1444.

Chen, J., Lipska, B., Halim, N., Quang, D.M., Matsumoto, M., Melhem, S., Kolachana, B.S., Hyde, T.M., Herman, M., Apud, J., Egan, M., Kleinman, J.E., & Weinberger, D.R. (2004). Functional analysis of genetic variation in catechol-omethyltransferase (COMT): effects of mRNA, protein, and enzyme activity in postmortem human brain. *American Journal of Human Genetics*, **75**, 807–821.

Drabant, E.M., Hariri, A.R., Meyer-Lindenberg, A., Munoz, K.E., Mattay, V.S., Kolachana, B.S., Egan, M.F., & Weinberger, D.R. (2006). Catechol O-methyltransferase ValÂ1-sup-5-sup-8Met genotype and neural mechanisms related to affective arousal and regulation. *Archives of General Psychiatry*, **63**, 1396–1406.

Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Goldman, D., & Weinberger, D.R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences, USA*, **98**, 6917–6922.

Fletcher, J. (2009). Dyslexia: the evolution of a scientific concept. *Journal of the International Neuropsychological Society*, **15**, 501–508.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.-B., Heather, J.D., & Frackowiak, R.S.J. (1995). Spatial registration and normalization of images. *Human Brain Mapping*, **2**, 165–189.

Frost, S.J., Landi, N., Mencl, W.E., Sandak, R., Fulbright, R.K., Tejada, E.T., Jacobsen, L., Grigorenko, E.L., Constable, R.T., & Pugh, K.R. (2009). Phonological awareness predicts activation patterns for print and speech. *Annals of Dyslexia*, **59**, 78–97.

Genovese, C.R., Lazar, N.A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage*, **15**, 870–878.

Gothelf, D., Michaelovsky, E., Frisch, A., Zohar, A.H., Presburger, G., Burg, M., Aviram-Goldring, A., Frydman, M., Yeshaya, J., Shohat, M., Korostishevsky, M., Apter, A., & Weizman, A. (2007). Association of the low-activity *COMT* ^{158}*Met* allele with ADHD and OCD in subjects with velocardiofacial syndrome. *International Journal of Neuropsychopharmacology*, **10**, 301–308.

Grigorenko, E.L., Deyoung, C.G., Getchell, M., Haeffel, G.J., Klinteberg, B.A.F., Koposov, R.A., Oreland, L., Pakstis, A. J., Ruchkin, V.V., & Yrigollen, C.M. (2007). Exploring interactive effects of genes and environments in etiology of individual differences in reading comprehension. *Developmental Psychopathology*, **19**, 1089–1103.

Jorm, A.F, Share, D.L., Maclean, R., & Matthews, R. (1986). Cognitive factors at school entry predictive of specific reading retardation and general reading backwardness: a research note. *Journal of Child Psychology and Psychiatry*, **27**, 45–54.

Kempton, M.J., Haldane, M., Jogia, J., Christodoulou, T., Powell, J., Collier, D., Williams, S.C., & Frangou, S. (2008). The effects of gender and COMT Val158Met polymorphism on fearful facial affect recognition: a fMRI study. *International Journal Neuropsychopharmacology*, **12**, 371–381.

Landi, N. (2010). An examination of the relationship between reading comprehension, higher-level and lower-level reading sub-skills in adults. *Reading and Writing*, **23**, 701–717.

Landi, N., Mencl, W.E., Frost, S.J., Sandak, R., Chen, H., & Pugh, K.R. (2010). An fMRI comparison of semantic and phonological processing in non-impaired and reading disabled adolescents. *Annals of Dyslexia*, **60**, 102–121.

Lebedeva, L.S., Korovaitseva, G.I., Lezheiko, T.V., Kaleda, V. G., Abramova, L.I., Barkhatova, A.N., & Golimbet, V.E. (2009). Influence of genetic variants modulating dopamine activity on brain processing of auditory information (the P300 paradigm). *Human Physiology*, **35**, 21–24.

Locascio, G., Mahone, E.M., Eason, S.H., & Cutting, L.E. (2010). Executive dysfunction among children with reading comprehension deficits. *Journal of Learning Disabilities*, **43**, 441–454.

Lyon, G., Shaywitz, S., & Shaywitz, B. (2003). A definition of dyslexia. *Annals of Dyslexia*, **53**, 1–14.

Mattay, V.S., Goldberg, T.E., Fera, F., Hariri, A.R., Tessitore, A., Egan, M.F., Kolachana, B., Callicott, J.H., & Weinberger, D.R. (2003). Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proceedings of the National Academy of Sciences, USA*, **100**, 6186–6191.

Mechelli, A., Tognin, S., McGuire, P.K., Prata, D., Sartori, G., Fusar-Poli, P., De Brito, S., Hariri, A.R., & Viding, E. (2009). Genetic vulnerability to affective psychopathology in childhood: a combined voxel-based morphometry and functional magnetic resonance imaging study. *Biological Psychiatry*, **66**, 231–237.

Mier, D., Kirsh, P., & Mayer-Lindenberg, A. (2010). Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Molecular Psychiatry*, **15**, 918–927.

Miezin, F.M., Maccotta, L., Ollinger, J.M., Petersen, S.E., & Buckner, R.L. (2000). Characterizing the haemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *NeuroImage*, **11**, 735–759.

Papademetris, X., Jackowski, A., Schultz, R.T., Staib, L.H., & Duncan, J.S. (2003). Computing 3D non-rigid brain registration using extended robust point matching for composite multisubject fMRI analysis. *Medical Image Computing and Computer Aided Intervention (MICCAI) Part II LLNCS 2879* (pp. 788–795). New York: Springer-Verlag.

Preston, J.L., Felsenfeld, S.F., Frost, S.J., Mencl, W.E., Fulbright, R.K., Grigorenko, E., Landi, N., & Pugh, K.R. (in press). Functional brain activation differences in school-age children with speech sound errors: speech and print processing. *Journal of Speech, Language and Hearing Research*. doi:10.1044/1092-4388(2011/11-0056).

Preston, J.L., Frost, S., Mencl, W.E., Fulbright, R.K., Landi, N., Grigorenko, E., Jacobsen, L., & Pugh, K.R. (2010). Early and late talkers: school-age language, literacy and neurolinguistic differences. *Brain*, **133**, 2185–2195.

Psychological Corporation (1999). *Wechzrsler Abbreviated Scale of Intelligence*. San Antonio, TX: Harcourt Brace & Co.

Pugh, K.R., Frost, S.J., Sandak, R., Landi, N., Rueckl, J.G., Constable, R.T., Seidenberg, M.S., Fulbright, R.K., Katz, L., & Mencl, W.E. (2008). Effects of stimulus difficulty and repetition on printed word identification: an fMRI comparison of nonimpaired and reading-disabled adolescent cohorts. *Journal of Cognitive Neuroscience*, **20**, 1146–1160.

Pugh, K.R., Landi, N., Preston, J.L., Mencl, W.E., Austin, A., Sibley, D., Fulbright, R.K., Seidenberg, M.S., Grigorenko, E., Constable, R.T., Molfese, P., & Frost, S.J. (in press). The relationship between phonological and sensorimotor processing skills and the neurocircuitry for reading in emergent readers. *Brain and Language*.

Pugh, K.R., Mencl, W.E., Jenner, A.R., Katz, L., Frost, S.J., Lee, J.R., Shaywitz, S.E., & Shaywitz, B.A. (2000). Functional neuroimaging studies of reading and reading disability (developmental dyslexia). *Mental Retardation & Developmental Disabilities Research Reviews*, **6**, 207–213.

Schott, B.H., Seidenbecher, C.I., Fenker, D.B., Lauer, C.J., Bunzeck, N., Bernstein, H.G., Tischmeyer, W., Gundelfinger, E.D., Heinze, H.J., & Düzel, E. (2006). The dopaminergic midbrain participates in human episodic memory formation: evidence from genetic imaging. *Journal of Neuroscience*, **26**, 1407–1417.

Shaywitz, S.E., Escobar, M.D., Shaywitz, B.A., Fletcher, J.M., & Makuch, R.W. (1992). Evidence that dyslexia may represent the lower tail of a normal distribution of reading ability. *New England Journal of Medicine*, **326**, 145–150.

Shaywitz, B.A., Shaywitz, S.E., Pugh, K.R., Mencl, W.E., Fulbright, R.K., Skudlarski, P., Constable, R.T., Marchione, K.E., Fletcher, J.M., Lyon, G.R., & Gore, J.C. (2002). Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biological Psychiatry*, **52**, 101–110.

Smolka, M.N., Bühler, M., Schumann, G., Klein, S., Hu, X.Z., Moayer, M., Zimmer, A., Wrase, J., Flor, H., Mann, K., Braus, D.F., Goldman, D., & Heinz, A. (2007). Gene–gene effects on central processing of adverse stimuli. *Molecular Psychiatry*, **12**, 307–317.

Smolka, M.N., Schumann, G., Wrase, J., Grusser, S.M., Flor, H., Mann, K., Braus, D.F., Goldman, D., Büchel, C., & Heinz, A. (2005). Catechol-O- methyltransferase val158met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. *Journal of Neuroscience*, **25**, 836–842.

Stevenson, J. (1988). Which aspects of reading disability show a 'hump' in their distribution? *Applied Cognitive Psychology*, **2**, 77–85.

Stokes, P.R., Rhodes, R.A., Grasby, P.M., & Mehta, M.A. (2011). The effects of the COMT val (108/158)met polymorphism on BOLD activation during working memory, planning, and response inhibition: a role for the posterior cingulate cortex? *Neuropsychopharmacology*, **36**, 763–771.

Tan, H.Y., Chen, Q., Goldberg, T.E., Mattay, V.S., Meyer-Lindenberg, A., Weinberger, D.R., & Callicot, J.H. (2007). Catechol-O-methyltransferase Val158Met modulation of prefrontal-parietal-striatal brain systems during arithmetic and temporal transformations in working memory. *Journal of Neuroscience*, **27**, 13393–13401.

Ullman, M.T., & Pierpont, E.I. (2005). Specific language impairment is not specific to language: the procedural deficit hypothesis. *Cortex*, **41**, 399–433.

Wagner, R.K., Torgesen, J.K., & Rashotte, C.A. (1999). *Comprehensive Test of Phonological Processing*. Austin, TX: Pro-Ed.

Wahlstrom, D., White, T., Hooper, C.J., Vrshek-Schallhorn, S., Oetting, W.S., Brott, M.J., & Luciana, M. (2007). Association of the Catechol-O-methyltransferase (COMT) gene to prefrontally-mediated cognitions in adolescents. *Biological Psychiatry*, **61**, 626–632.

Wahlstrom, D., White, T., & Luciana, M. (2010). Neurobehavioral evidence for changes in dopamine system activity during adolescence. *Neuroscience and Biobehavioral Reviews*, **34**, 631–648.

Woodcock, R.W., McGrew, K.S., & Mather, N. (2001). *Woodcock-Johnson III NU tests of achievement*. Rolling Meadows, IL: Riverside Publishing.

Appendix

Table A1 *For all regions showing significant differences between the two groups (Met/Met > Val/Met), Brodman Area (BA), volume in mm^3, MNI coordinates at peak, p-value for peak activation. The sign of the p value indicates directionality of the observed effect*

Region	BA	Vol.	X	Y	Z	*p*-value
Precuneus	7	12616	28	−54	16	<.0001
Superior Temporal Gyrus	21/22	6400	56	−28	−1	<.0001
Parahippocampa Gyrus	19	5080	28	−51	−2	.0002
Middle Occipital Gyrus	18	1496	−18	−86	−15	.001
Parahippocampa Gyrus	30	1048	−22	−42	−6	.0017
Lingual Gyrus	18	952	−10	−64	2	.0023
Precentral Gyrus	6	944	−34	−14	44	.0006
Superior Temporal Gyrus	42	664	70	−24	10	.0005
Superior Parietal Lobule	7	584	−44	−62	54	.0002
Insula	13	584	−42	−36	24	.0028
Superior Frontal Gyrus	10	504	−10	68	−6	.0007
Culmen		480	24	−60	−30	.0011
Precuneus	7	408	−20	−82	50	.0018
Middle Frontal Gyrus	46	376	52	29	30	.0008
Postcentral Gyrus	43	368	70	−14	20	.0029
Lingual Gyrus	18	328	6	−86	−6	.0034
Culmen		296	12	−42	−24	.0035
Middle Temporal Gyrus	20	272	−64	−46	−16	.0012
Inferior Frontal Gyrus	47	216	−42	22	−14	.005
Middle Temporal Gyrus	21	144	−64	−30	0	.0049
Precentral Gyrus	6	120	20	−16	54	.0042
Superior Frontal Gyrus	10	112	30	62	−4	.0067
Culmen	36	104	−12	−46	−24	.0064
Angular Gyrus	39	88	−54	−62	36	.0051
Lentiform Nucleus		80	30	−16	−6	.0037
Inferior Frontal Gyrus	11	1416	12	36	−22	−.0002
Middle Frontal Gyrus	11	520	−20	44	−12	−.0005
Cuneus	19	296	12	−96	24	−.0003
Inferior Frontal Gyrus	10	168	48	48	0	−.0013
Cuneus	17	88	10	−98	0	−.0068

Table A2 *For all regions showing significant differences between the two groups (Met/Met > Val/Val), Brodman Area (BA), volume in mm^3, MNI coordinates at peak, p-value for peak activation. The sign of the p value indicates directionality of the observed effect*

Region	BA	Vol.	X	Y	Z	*p*-value
Fusiform Gyrus	19	2048	−24	−70	−14	.0008
Cerebellar Tonsil	19	1664	6	−56	−43	.0004
Inferior Parietal Lobule	40	1480	40	−36	32	.0001
Medial Frontal Gyrus	6	1040	18	−16	54	.0006
Precentral Gyrus	4	992	−32	−20	46	.0002
Parahippocampa Gyrus	30	480	32	−56	2	.0029
Precuneus	7	344	16	−46	54	.0023
Inferior Occipital Gyrus	18	328	40	−86	−3	.0039
Paracentral Lobule	6	320	−6	−30	54	.0044
Middle Temporal Gyrus	37	312	64	−58	−6	.0008
Superior Temporal Gyrus	22	288	30	−54	16	.0011
Inferior Frontal Gyrus	47	280	−46	38	−15	.0029
Middle Frontal Gyrus	10	280	−44	54	−2	.0006
Fusiform Gyrus	37	248	38	−52	−20	.0047
Inferior Occipital Gyrus	18	208	−38	−88	−16	.0034
Precuneus	7	208	24	−60	56	.0041
Superior Temporal Gyrus		160	56	−28	−1	.0048
Declive	18	144	4	−64	−30	.0045
Precuneus	7	136	−20	−70	40	.0046
Fusiform Gyrus	37	136	36	−40	−9	.0048
Inferior Frontal Gyrus	47	120	52	22	−8	.0036
Inferior Frontal Gyrus	45	112	58	20	10	.0041
Superior Frontal Gyrus	8	96	8	50	44	.0055
Superior Temporal Gyrus	38	88	−24	22	−34	.0017
Fusiform Gyrus	19	80	24	−62	−12	.0059
Inferior Frontal Gyrus	47	520	−34	14	−19	−.0001
Uncus		512	2	−8	−40	−.0004
Inferior Frontal Gyrus	47	376	20	10	−22	−.0017
Uncus		288	−4	−8	−20	−.0031
Inferior Frontal Gyrus	11	264	20	38	−24	−.001
Caudate		240	−22	−32	24	−.0025
Caudate		104	24	−36	22	−.004

Table A3 *For all regions showing significant differences between the two groups (Val/Met> Val/Val), Brodman Area (BA), volume in mm^3, MNI coordinates at peak, p-value for peak activation. The sign of the p value indicates directionality of the observed effect*

Region	BA	Vol.	X	Y	Z	*p*-value
Precentral Gyrus	6	1104	−32	−16	64	.001
Fusiform Gyrus	19	272	10	−58	−44	.003
Middle Occipital Gyrus	18	256	40	−88	0	.0023
Uncus		1544	−2	−10	−18	<.0001
Inferior Frontal Gyrus	47	704	20	12	−24	−.0003
Uncus		384	−4	−12	−36	−.0028
Insula	13	352	−32	−38	18	−.0013
Insula	13	192	34	−8	24	−.0039
Inferior Frontal Gyrus	47	168	−34	16	−18	−.0026
Superior Frontal Gyrus	10	152	−10	60	−6	−.0025
Parahippocampal Gyrus	30	144	−8	−34	−8	−.0053
Superior Frontal Gyrus	11	136	16	58	−15	−.0022
Thalamus		96	−12	−28	20	−.0072

Table A4 *For all regions showing significant differences between among the groups (omnibus ANOVA), Brodman Area (BA), volume in mm^3, MNI coordinates at peak, and the p-value for peak activation*

Region	BA	Vol.	X	Y	Z	*p*-value
Superior Temporal Gyrus		3240	56	−28	−1	.0001
Parahippocampa Gyrus	19	1800	32	−50	−4	.0006
Precuneus	7	1448	22	−56	54	.0015
Precuneus	7	1352	18	−70	30	.0005
Lingual Gyrus	18	1200	−24	−74	−14	.002
Uncus		1016	−2	−10	−18	.0002
Culmen		832	28	−54	16	.0001
Declive		808	6	−56	−43	.0012
Precentral Gyrus	4	680	−32	−18	46	.0005
Inferior Frontal Gyrus	11	648	12	36	−22	.0011
Inferior Parietal Lobule	40	632	40	−36	32	.0005
Precuneus	7	544	−20	−70	40	.0017
Uncus	34	488	20	10	−24	.001
Fusiform Gyrus	19	416	24	−62	−12	.0013
Superior Frontal Gyrus	10	384	−10	66	−6	.0007
Insula	13	320	−34	−38	18	.0016
Inferior Frontal Gyrus	47	312	−34	14	−19	.0004
Superior Parietal Lobule	7	304	−44	−62	54	.0005
Uncus		296	2	−8	−40	.0016
Precentral Gyrus	6	256	−32	−16	64	.0041
Precentral Gyrus	6	240	20	−16	54	.0017
Middle Frontal Gyrus	11	200	−20	44	−12	.0019
Superior Temporal Gyrus	42	168	70	−24	10	.0021
Declive		136	24	−60	−30	.0046
Middle Temporal Gyrus	37	112	64	−58	−6	.0024
Cuneus	19	104	12	−96	24	.0014
Insula	13	104	−42	−34	24	.0062
Middle Frontal Gyrus	46	88	52	29	30	.0033

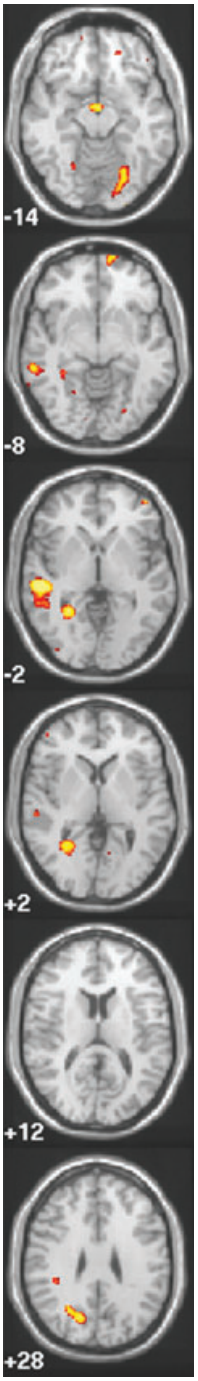

Figure A1 *Omnibus ANOVA: overall effect of COMT.*