Genetic Vulnerability to Affective Psychopathology in Childhood: A Combined Voxel-Based Morphometry and Functional Magnetic Resonance Imaging Study

Andrea Mechelli, Stefania Tognin, Philip K. McGuire, Diana Prata, Giuseppe Sartori, Paolo Fusar-Poli, Stephane De Brito, Ahmad R. Hariri, and Essi Viding

Background: The majority of affective psychopathology is rooted early in life and first emerges during childhood and adolescence. However, little is known about how genetic vulnerability affects brain structure and function in childhood since the vast majority of studies published so far have been conducted on adult participants. The present investigation examined for the first time the effects of catechol-O-methyltransferase (COMT) valine (val) 158 methionine (met) (val158met) polymorphism, which has been shown to moderate predisposition to negative mood and affective disorders, on brain structure and function in children.

Methods: Voxel-based morphometry and functional magnetic resonance imaging were used to measure gray matter volume and emotional reactivity in 50 children aged between 10 and 12 years. We tested the hypothesis that met158 allele affects structural brain development and confers heightened reactivity within the affective frontolimbic circuit in children.

Results: The met158 allele was positively associated with gray matter volume in the left hippocampal head where genotype accounted for 59% of interindividual variance. In addition, the met158 allele was positively associated with neuronal responses to fearful relative to neutral facial expressions in the right parahippocampal gyrus where genotype accounted for 14% of the interindividual variance.

Conclusions: These results indicate that the met158 allele is associated with increased gray matter volume and heightened reactivity during emotional processing within the limbic system in children as young as 10 to 12 years of age. These findings are consistent with the notion that genetic factors affect brain function to moderate vulnerability to affective psychopathology from childhood.

Key Words: Affective psychopathology, childhood, COMT, emotional processing, hippocampus

Susceptibility for affective psychopathology depends on the dynamic interplay between genetic and environmental risk factors (1,2). The catechol-O-methyltransferase (COMT) valine (val) 158 methionine (met) (val158met) polymorphism has been shown to moderate predisposition to negative mood and affective disorders. In recent years, several imaging genetic studies have demonstrated the effects of this and other risk genes on brain structure and function in healthy adult participants (3). Given that very few psychiatric illnesses arise de novo in adulthood (4), it is important to extend the current imaging genetic work to include child samples. In the present investigation, we used voxel-based morphometry (VBM) and functional magnetic resonance imaging (fMRI) to examine the effects of COMT val158met polymorphism on brain structure and emotional processing in children aged between 10 and 12 years.

Catechol-O-methyltransferase is an enzyme that catalyzes the O-methylation of extracellular dopamine in the brain (5) and is mainly found in its membrane-bound (MB-COMT) form in postsynaptic neurons (6,7). The most abundant expression of COMT, both in terms of messenger RNA density (7,8) and enzyme activity (8,9), is found in the prefrontal cortex and the parahippocampal gyrus. The enzymatic activity of COMT is modulated by a guanine (G) to adenine (A) single nucleotide polymorphism (SNP) change (known as val158met or rs4680) in the COMT gene. This translates into a valine to methionine amino acid change in codon 158 that causes a threefold to fourfold decrease in its molecular thermostability. The alleles have been shown to be codominant with the met158 allele associated with decreased COMT activity, resulting in higher synaptic dopamine levels; the val158 allele associated with increased COMT activity, resulting in lower synaptic levels; and the heterozygote genotype (val158/met158) associated with an intermediate level of COMT activity (8).

Several studies suggest that the met158 allele is advantageous for cognitive performance (10 –15) and prefrontal function (11,15–18) not only in adults but also in children (19,20). However, a series of recent studies have also implicated the met158 allele in negative mood and affective disorders, including increased levels of anxiety in women, obsessive-compulsive disorder in men, panic disorder, alcoholism, aggressiveness, bipolar affective disorder, major depression, and higher sensitivity to pain (as reviewed by Drabant et al. [21]). The met158 allele has also been associated with a high level of anxiety (22) and early-onset antisocial behavior (23) in children and adolescents, although a recent investigation of emotional symptoms in children 6 to 7 years old did not find an association (24).

While the impact of the val158met polymorphism on prefrontal function has been characterized extensively in recent years, only a few functional imaging studies have explored the relationship between this polymorphism and brain activation during emotional processing (21,25–27). Smolka et al. (26) reported a...
dose-dependent increase in limbic and prefrontal activation associated with met158 during the processing of unpleasant but not pleasant visual stimuli in a small group of healthy volunteers (n = 35). More recently, Drabant et al. (21), using 101 healthy volunteers exposed to fearful and angry facial expressions, found met158 to be associated with a dose-dependent increase in activation within a frontolimbic circuit including the hippocampus and the ventrolateral prefrontal cortex; furthermore, in met158 homozygotes, there was increased functional coupling between limbic and prefrontal regions. These studies suggest that met158 increases reactivity within a frontolimbic circuit that is critical for emotional regulation, thereby providing support to the hypothesis that met158 increases reactivity within a frontolimbic circuit that is critical for emotional regulation, thereby providing support to the hypothesis that met158 affects structural brain development in childhood.

It is therefore unclear, however, whether the effects of the val158met polymorphism on brain responses to emotional stimuli that have been reported in adult participants are also evident in children. This is an important question since there is increasing evidence that the majority of affective psychopathology is rooted early in life and first emerges during childhood and adolescence (4). If gene-related differences in adult participants reflect alterations that occurred during childhood and adolescence, then a better characterization of these alterations during childhood is critical for understanding how genes affect brain structure and function to mediate vulnerability to affective psychopathology (31).

It is also unclear whether variation in the val158met polymorphism is associated with differences in brain morphology from early age. Dopaminergic innervation increases during brain maturation and decreases during late adolescence and early adulthood (32). Thus, it has been proposed that differences in synaptic dopamine levels associated with the val158met polymorphism may be associated with different trajectories of brain maturation (30). A recent investigation demonstrated that the impact of COMT genotype on gray and white matter density in young adults is dependent on the age of the participants in female subjects but not in male subjects (30). However, no previous studies have examined whether the val158met polymorphism affects structural brain development in childhood.

We therefore used VBM and fMRI to examine for the first time the impact of the functional val158met polymorphism in the COMT gene on brain structure and emotional processing in 50 children aged between 10 and 12 years. Participants were presented with pictures of fearful and neutral faces on a screen and were required to detect the gender of each face. We tested the hypothesis that met158 allele affects structural brain development and confers increased sensitivity to emotional stimuli within the affective frontolimbic circuit in children.

Methods and Materials

Subjects
A total of 50 boys aged 10 to 12 years old participated in the present study. Participants were recruited from the longitudinal Twins Early Development Study (TEDS) database as part of an ongoing twin neuroimaging project that included mostly typically developing children, as well as an oversample of children in the top 10% of the United Kingdom population for conduct problems (Supplement 1). The short version of the Wechsler Abbreviated Scales of Intelligence (WASI) was used to assess IQ (33). In addition, the Strengths and Difficulties Questionnaire (SDQ) (34) was used to measure emotional problems, conduct problems, hyperactivity, peer problems, prosociality, and total behavioral difficulties in all participants as rated by both parents and teachers. All subjects were genotyped for the val158met in the COMT gene (see below). Our sample of 50 volunteers comprised 14 met158/met158, 22 val158/met158, and 14 val158/val158 individuals. A one-way analysis of variance (ANOVA) revealed that the three genotype groups did not differ in age, IQ, or any of the SDQ indicators (p > .05) (Table 1).

Experimental Task
The experimental paradigm involved presenting emotional and neutral faces taken from the Pictures of Facial Affect (35) but cropped to remove hair. For each face, subjects had to make a gender classification (male or female) by pressing left or right response buttons; no explicit recognition or categorization of the emotional expression was required. Each stimulus was presented for 3000 msec and successive stimuli were separated by an interstimulus interval of 750 msec, resulting in a stimulus onset asynchrony of 3750 msec. A total of 80 stimuli were presented on a computer screen in a single scanning session that lasted 6 minutes and 24 seconds; the stimuli were arranged in 10 blocks, each comprising eight fearful or eight neutral faces. The experimental paradigm also comprised two “rest” blocks in which no faces were presented but a fixation cross remained on the screen for 32 seconds. The order of presentation of fearful and neutral faces was counterbalanced across subjects.

Genotyping
DNA was extracted from blood or cheek swabs using standard methods (36). Genotyping of the rs4680, which encodes the val158met polymorphism, was performed by KBioscience (http://www.kbioscience.co.uk; Hertz, United Kingdom) using a competitive allele-specific polymerase chain reaction (PCR) system (CASP). The region amplified was atacaccgagtaggattgcgtggcaA/Glgaaggcacgacctggtgtag. The genotyping results of a sample of 130 subjects, which included our 50 participants, were under Hardy-Weinberg equilibrium.

Image Acquisition
Structural brain images were acquired using a General Electric Signa 3.0 Telsa Excite ll magnetic resonance imaging (MRI) scanner (General Electric Medical Systems, Milwaukee, Wisconsin) at the Institute of Psychiatry. Structural scanning consisted of an isotropic resolution three-dimensional (3-D) inversion recovery prepared spoiled gradient echo. Two hundred through-plane partitions (each 1.1 mm thick) were collected, with two partitions being discarded at each end of the imaging volume to minimize wrap-round artefacts.

In addition, functional image volumes (192 scans for each subject) were collected using T2*-weighted gradient echo-planar imaging (EPI) sequence with 28 slices (slice thickness 3.5 mm, gap = .3 mm) covering the whole brain (repetition time [TR] = 2 sec, echo time [TE] = 25 msec, field of view = 220 × 220, matrix size 64 × 64). Stimuli were projected onto a high-resolution screen located in front of the participant’s head and were viewed via a mirror attached to the head coil.

Data Analysis
Behavioral Data. Analysis of response accuracy and reaction times was performed using the Statistical Package for Social Science (SPSS), version 15.0 (SPSS Inc., Chicago, Illinois). The three genotype groups were compared using a 2 × 3 ANOVA with facial expression as repeated measures. Inferences were made using a statistical threshold of p < .05.
Table 1. Participants’ Characteristics and Task Performance

<table>
<thead>
<tr>
<th></th>
<th>Met/Met</th>
<th>Met/Val</th>
<th>Val/Val</th>
<th>All Subjects</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>22</td>
<td>14</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Age in Months</td>
<td>137.8 ± 9.2</td>
<td>135.2 ± 9.8</td>
<td>140.6 ± 9.6</td>
<td>137.4 ± 9.5</td>
<td>.251</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>104.3 ± 11.9</td>
<td>102.0 ± 13.0</td>
<td>106.5 ± 9.1</td>
<td>103.9 ± 11.7</td>
<td>.534</td>
</tr>
<tr>
<td>Teacher Rated SDQ Scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>3.8 ± 2.6</td>
<td>3.7 ± 2.5</td>
<td>1.9 ± 2.5</td>
<td>3.2 ± 2.6</td>
<td>.094</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>1.6 ± 1.5</td>
<td>1.9 ± 1.6</td>
<td>1.4 ± 1.2</td>
<td>1.7 ± 1.5</td>
<td>.623</td>
</tr>
<tr>
<td>Emotional problems</td>
<td>1.9 ± 2.0</td>
<td>1.0 ± 1.3</td>
<td>1.1 ± 1.1</td>
<td>1.3 ± 1.5</td>
<td>.330</td>
</tr>
<tr>
<td>Prosociality</td>
<td>8.4 ± 1.7</td>
<td>8.3 ± 1.8</td>
<td>8.4 ± 1.4</td>
<td>8.3 ± 1.6</td>
<td>.952</td>
</tr>
<tr>
<td>Peer problems</td>
<td>.8 ± 1.4</td>
<td>1.5 ± 2.8</td>
<td>1.3 ± 2.7</td>
<td>1.2 ± 2.4</td>
<td>.735</td>
</tr>
<tr>
<td>Total difficulties</td>
<td>8.1 ± 5.2</td>
<td>7.7 ± 6.0</td>
<td>5.6 ± 5.0</td>
<td>7.2 ± 5.5</td>
<td>.442</td>
</tr>
<tr>
<td>% Correct Responses Fear</td>
<td>96.3 ± 3.5</td>
<td>93.7 ± 7.9</td>
<td>96.0 ± 4.1</td>
<td>95.1 ± 6.6</td>
<td>.063</td>
</tr>
</tbody>
</table>

Data are expressed as mean values (± standard deviation). p values for age, full scale IQ, and SDQ scores refer to a one-way ANOVA contrasting the different genotypes; p values for % correct responses and average RT refer to a 2 × 3 ANOVA contrasting the different genotypes with facial expression (Neutral, Fear) as repeated measure.

**Voxel-Based Morphometry.** Structural images were preprocessed using optimized voxel-based morphometry implemented with Statistical Parametric Mapping software (SPM5) running under Matlab 7.0 (Mathworks, Sherborn, Massachusetts). Voxel-based morphometry is a whole-brain, unbiased, semi-automated technique for characterizing regional cerebral differences in structural magnetic resonance images (Supplement 2) (37–39). Inferences were made using a statistical threshold of *p* < .05 after FDR correction for multiple comparisons across the whole brain and an extent threshold of 10 voxels. In addition to the whole-brain analysis, we performed an additional analysis with a mask that comprised six regions of interest (ROIs) with a radius of 6 mm (total size of the mask: 266). These ROIs were selected on the basis that they showed a significant effect of val158met on functional integration could be detected within our cohort of children using psychophysiological interaction (PPI) (Supplement 4) (41). Inferences were made at group level (40) using a statistical threshold of *p* < .05 after FDR correction for multiple comparisons across the whole brain and an extent threshold of 10 voxels; since no significant effects were detected using this statistical threshold, we report trends significant at *p* < .05 (uncorrected) for completeness.

**Functional Connectivity Analysis.** Functional connectivity is a measure of the temporal correlation of the blood oxygenation level-dependent (BOLD) signal in spatially remote regions and is used widely in the imaging community as a simple and robust characterization of aspects of functional integration. A previous investigation (21) found that, during the processing of emotional facial expressions, the functional coupling between limbic and prefrontal regions was increased in adult participants with the met/met variant compared with those with the val/val variant. We therefore examined whether a similar effect of COMT val158met on functional integration could be detected within our cohort of children using psychophysiological interaction (PPI) (Supplement 4) (41). Inferences were made at group level (40) using a statistical threshold of *p* < .05 after FDR correction for multiple comparisons across the whole brain and an extent threshold of 10 voxels; since no significant effects were detected using this statistical threshold, we report trends significant at *p* < .05 (uncorrected) for completeness.

**Results**

**Behavioral Performance**

Table 1 reports the response accuracy and reaction times of each genotypic group for neutral and fearful facial expressions independently. Catechol-O-methyltransferase genotype was not significantly associated with percentage of correct responses (*p* = .063) or reaction times (*p* = .319); in addition, there was no significant interaction between COMT genotype and facial expressions in adult participants with the met/met variant compared with those with the val/val variant and included the right parahippocampal gyrus (*x* = 15, *y* = −33, *z* = −7) and the right ventrolateral prefrontal cortex (*x* = 55, *y* = 22, *z* = 13). Coordinates are reported in MNI space.

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pression on percentage of correct responses \((p = .834)\) or reaction times \((p = .362)\).

**Effect of COMT Genotype on Gray Matter Volume**

There were no significant differences in gray matter volume at \(p < .05\) (corrected for multiple comparisons across the whole brain). However, when using small volume correction to examine six regions of interest where an effect of COMT had been reported in adult participants (24), we detected two significant effects (Figure 1). Individuals with the met158/met158 genotype compared with val158/val158 individuals expressed greater gray matter volume in the left hippocampal head \((x = -24, y = 4, z = -24); Z \text{ score} = 2.7; p = .026 \text{ corrected}; \text{cluster size: 33})\). A linear regression analysis in statistical parametric mapping (SPM) indicated that gray matter volume in this region was positively associated with the number of met158 alleles \((x = -24, y = 4, z = -24); Z \text{ score} = 2.6; p = .036 \text{ corrected}; \text{cluster size: 26})\). Estimate of the \(R^2\) measure in SPSS revealed that val158met genotype accounted for 59% of interindividual variance in the left hippocampal head.

We considered the possibility that the COMT-related differences in gray matter volume might be associated with intersubject differences in IQ, level of emotional problems, conduct problems, or hyperactivity. When these variables were included as covariates of no interest, the effect in the right hippocampal formation was replicated \((x = 14, y = -32, z = 0); Z \text{ score} = 3.1; p = .019 \text{ corrected}; \text{cluster size: 117})\). Estimate of the \(R^2\) measure in SPSS revealed that COMT genotype accounted for 14% of interindividual variance in BOLD signal. In contrast, we did not replicate the previous finding of greater activation in met158/met158 relative to val158/val158 individuals in the ventrolateral prefrontal cortex of adult participants.

We examined whether intersubject differences in IQ, level of emotional problems, conduct problems, or hyperactivity might account for the COMT-related difference in the right hippocampal formation. When these variables were included as covariates of no interest, the effect in the right hippocampal formation was replicated \((x = 14, y = -32, z = 0); Z \text{ score} = 2.5; p = .045 \text{ corrected}; \text{cluster size: 53})\).

**Functional Connectivity**

We used psychophysiological interaction to investigate the changes in functional integration that mediated heightened acti-

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**Figure 1.** Effects of COMT val158met polymorphism on gray matter volume \((p < .05\) after FDR correction). Sagittal view of the left hippocampal head where gray matter volume was greater for met/met relative to val/val genotype; parameter estimates are shown for each genotypic group. COMT, catechol-O-methyltransferase; FDR, false discovery rate; met, methionine; val, valine.

**Figure 2.** Regions activated for fearful relative to neutral facial expressions on average across the three genotype groups \((p < .05\) after FDR correction). The color bar indicates \(t\) scores. FDR, false discovery rate.
Estimate of the processing of fearful relative to neutral facial expressions in size: 233) (Figure 3). This area showed increased functional and the medial anterior cingulate cortex. COMT, catechol-O-methyltransferase was mediated by increased functional coupling with the anterior cingulate cortex. COMT, catechol-O-methyltransferase; FDR, false discovery rate; met, methionine; val, valine.

![Fearful > Neutral Faces in Met-Met > Val-Val](image)

**Psycho-Physiological Interaction**

**Figure 3.** Effects of COMT val158met on emotional processing (p < .05 after FDR correction). Top: the right parahippocampal gyrus expressed increased activation in response to fearful relative to neutral facial expression in met/met relative to val/val individuals; parameter estimates are shown for each genotypic group. Bottom: an analysis of psychophysiological interaction yielded a trend (p = .003 uncorrected) indicating that increased activation of the right parahippocampal gyrus in met/met relative to val/val individuals was mediated by increased functional coupling with the anterior cingulate cortex. COMT, catechol-O-methyltransferase; FDR, false discovery rate; met, methionine; val, valine.

Discussion

The aim of the present study was to investigate for the first time the impact of the COMT val158met polymorphism on brain structure and function in children aged between 10 and 12 years. In particular, we tested the hypothesis that met158 allele affects structural brain development and confers increased sensitivity to emotional stimuli within the affective frontolimbic circuit in children.

Using optimized voxel-based morphometry, we replicated the positive association between the met158 allele and gray matter volume in the left hippocampal head that had been found in a previous investigation with adult participants (28). In contrast, we did not replicate the positive association between the val158 allele and gray matter volume in prefrontal regions (28). These findings indicate that at least some of the COMT-related differences in brain structure that have been described in the adult population are already evident by the age of 10 to 12 years. In addition, they suggest a possible dissociation between the limbic system, where the effect of our polymorphism of interest was found in our cohort of children, and prefrontal regions, where no effects were detected even when lowering the statistical threshold to p < .05 (uncorrected). The lack of COMT-related differences in the prefrontal cortex can be considered surprising, given that the COMT enzyme alters extracellular dopamine levels in the prefrontal cortex and that its activity increases from neonate into adulthood (42,43).

Using functional magnetic resonance imaging, we detected increased activation in the right parahippocampal gyrus during emotional processing in met/met relative to val/val homozygotes. The parahippocampal gyrus shows abundant expression of COMT, both in terms of messenger RNA density (7,8) and enzyme activity (8,9); this provides support to the idea that met158-associated increases in dopamine level might underlie heightened reactivity of this region (21). Neuroimaging studies with human participants and animal lesion models provide converging evidence that the parahippocampal gyrus is part of a frontolimbic circuit that mediates anxious states and behaviors and is critical for emotional regulation (44–47). This has led to the suggestion that heightened reactivity to emotional stimuli in the right parahippocampal gyrus of individuals with the met158 allele might be associated with increased sensitivity to negative environmental cues (21). The absence of COMT-related differences in task performance confirms that the alteration in the right parahippocampal gyrus is likely to reflect differences in the implicit processing of the emotional content of the stimuli rather than the gender discrimination task itself. Our finding replicates the results of a previous study using the same experimental paradigm with adult participants (21). However, the present investigation expands these results by demonstrating for the first time that the COMT val158met polymorphism affects emotional processing in children. This is an important observation, since reports of an association between the met158 allele and negative mood/affective disorders have typically been based on adult participants; yet, the majority of affective psychopathology does not arise de novo in adults without any warning in childhood or adolescence (4). Our finding that the met158 allele is associated with increased sensitivity to negative environmental cues in the parahippocampal gyrus of children as young as 10 to 12 years of age is consistent with the notion that genetic factors affect brain function to moderate vulnerability to affective psychopathology from early age (31).

It may be considered surprising that we found no evidence for an effect of COMT genotype on amygdala activation, given the implication of this region in emotional processing (48). Nevertheless, human postmortem studies indicate that COMT is minimally expressed in the amygdala (49). A previous imaging genetic study reported an association between the met158 allele and amygdala reactivity to unpleasant and pleasant pictures (27); however, amygdala activation did not vary as a function of COMT genotype in another imaging genetic study that used emotional and nonemotional faces (21). These inconsistent results might be explained by differences in task design (i.e., biologically salient arousal vs. discriminating valence of complex visual scenes).

To examine the neuronal interactions that mediated the impact of the COMT val158met polymorphism in the right parahippocampal gyrus, we performed an analysis of psychophysiological interaction (41). While no effects reached signifi-

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cance after correction for multiple comparisons, we found a
trend in the medial anterior cingulate cortex. This indicated
that heightened reactivity during emotional processing in the
right parahippocampal gyrus of met158 homozygotes was
associated with heightened functional coupling with the me-
dial anterior cingulate cortex. Clearly, this finding must be
taken with caution and requires replication in future studies
since it did not reach significance at \( p < .05 \) after correction for
multiple comparisons. Nevertheless, we note that the anterior
cingulate cortex has been implicated in emotional regulation
(50), as well as negative mood and affective disorders (51). It
is also noteworthy that the genotype effect accounted for 15% of
interindividually variance in functional coupling between the
right parahippocampal gyrus and the medial anterior cingulate cortex.

In the present investigation, the effects of COMT val158met
genotype on gray matter volume and emotional processing were
localized in the left hippocampal head and the right parahip-
 hippocampal gyrus, respectively. Only one previous study had
combined structural and functional techniques to examine the
effect of COMT genotype on brain structure and function (52).
That study, which used a working memory paradigm and was
conducted with adult participants at high genetic risk for schizo-
phrenia, revealed that the val158 allele was associated with both
reduced gray matter density and increased regional activation of
the anterior cingulate cortex. In contrast, we found no evidence
for an association between COMT-related differences in gray
matter volume and COMT-related differences in emotional pro-
cessing (Supplement 5).

We also report that val158met heterozygotes expressed an
intermediate gray matter volume in the left hippocampal head
and showed intermediate reactivity in the analyses of regional
responses and functional connectivity. A similar load effect has
been found in previous neuroimaging studies that investigated
the impact of the COMT val158met polymorphism on prefrontal
function (11–15) and emotional reactivity (21,26,27). This pattern
is consistent with the results of in vitro thermostability studies
that have shown that the two alleles act codominantly (53).
Interestingly, the effects of COMT genotype on brain structure
and function were localized in the left and right hemisphere,
respectively. The left-lateralization of the structural effect might
due to limited statistical power, given that a previous inves-
tigation with a larger adult sample reported bilateral differences
(28). In contrast, the right-lateralization of the functional effect
might reflect the use of faces as stimuli, since faces are known to
preferentially activate the right hemisphere (54).

The present investigation has a number of limitations. First,
our cohort only included male subjects and therefore it is unclear
whether the results can be generalized to the female population;
an increasing number of animal and human studies indicate
that the effect of the COMT val158met polymorphism on brain
physiology may be gender-dependent (see [55] for review).
Second, the sample size was relatively small for a neuroimaging
investigation of gene-related effects but was nevertheless in line
with that of several imaging genetic studies. Our sample of 50
participants was sufficient for detecting statistically significant
effects of our polymorphism of interest on brain structure and
function, which replicated previous findings with adult partici-
pants. Third, a more comprehensive understanding of how
variation in the COMT val158met polymorphism affects brain
function in response to emotional stimuli will require investiga-
tion of interactions with other candidate genes and with envi-
nronmental factors (2).

In conclusion, this is the first investigation to examine the
effect of the COMT val158met polymorphism on brain structure
and function within a sample of children. We found that the
met158 allele is associated with increased gray matter volume of
the left hippocampal head and heightened reactivity of the
parahippocampal gyrus during emotional processing in children
as young as 10 to 12 years of age. These results suggest that the
met158 allele affects structural brain development and confers
increased sensitivity to emotional stimuli within the limbic sys-
tem before the possible manifestation of any symptoms in
adolescence and adulthood. To establish whether the genotypic
effects reported in the present investigation are related to clinical
symptomatology later in life, a longitudinal approach will be
required.

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Supplementary material cited in this article is available
online.

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