Influence of the *COMT* genotype on working memory and brain activity changes during development

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Abstract

Background: The Val^{158}Met polymorphism of the catechol-O-methyltransferase (*COMT*) gene leads to lower enzymatic activity and higher dopamine availability in Met carriers. The Met allele is associated with better performance and reduced prefrontal cortex (PFC) activation during working memory (WM) tasks in adults. Dopaminergic system changes during adolescence may lead to a reduction of basal dopamine levels, potentially affecting Met allele benefits during development.

Methods: We investigated the association of *COMT* genotype with behavioral (N=322) and magnetic resonance imaging (MRI) data (N=81-84) collected during performance of a visuospatial WM task and potential changes in these effects during development (reflected in age x genotype interactions). Data were collected from a cross-sectional and longitudinal typically developing sample of 6 to 20 year-olds.

Results: Visuospatial WM capacity exhibited an age x genotype interaction, with a benefit of the Met allele emerging after 10 years of age. There was a parallel age x genotype interaction on WM-related activation in the right inferior frontal gyrus and intraparietal sulcus (IPS), with increases in activation with age in the Val/Val group only. Main effects of *COMT* genotype were also observed in the IPS, with greater gray matter volumes bilaterally and greater right IPS activation in the Val/Val group compared to the Met carriers.

Conclusion: These results suggest that *COMT* genotype effects on WM brain activity and behavior are not static during development. The full developmental picture should be considered when trying to understand the impact of genetic polymorphisms on the mature cognition of healthy adult or psychiatric populations.

Introduction

The gene coding for the catechol-O-methyltransferase (COMT) enzyme, which mediates the degradation of catecholamines, in particular dopamine, has attracted considerable attention as a promising candidate gene for studying variance in cognitive function and mental illness (1,2). Developmental studies of this gene could inform us on the typical development of the dopamine system and provide a reference for the study of developmental disorders which have been linked to dopamine system dysfunction, such as schizophrenia (3), for which COMT function may be relevant (2, 4,5), although the evidence is inconsistent (e.g. 1).

The common rs4680 Val^{158}Met single nucleotide polymorphism (SNP) leads to a reduction of COMT enzymatic activity in Met carriers (6-8). The effect of rs4680 on cognition has been extensively studied in adults, both in typical and neuropsychiatric populations. Better working memory (WM) performance (e.g. in N-back tasks), fewer perseverative errors, and higher IQ tend to be associated with the Met allele in healthy individuals (9-11), although some studies have failed to replicate these effects (see 10). In functional magnetic resonance imaging (fMRI) studies Val/Val adults tend to exhibit greater prefrontal cortex (PFC) activation during WM tasks than Met/Met individuals (12,13). Structural imaging studies report less consistent results (14-16).

In children and adolescents effects of *COMT* genotype in specific age groups have been reported on brain structure (17-19), resting brain perfusion (20) and brain activation in response to emotional stimuli (17). Behavioral findings are mixed (21-23). This lack of consistency may arise from age differences in the effect of *COMT* genotype on cognition.

Dopamine effects on behavior follow an inverted U-shaped dose-response curve, with both deficient and excessive amounts of dopamine activity predicting poor cognitive tasks performance (24,25). Met/Met adults are thought to be near the apex of this curve, while Val carriers lay towards the lower end because of the increased dopamine metabolism rate associated with the Val allele (2,26,27).

There is some evidence that the dopamine system undergoes changes during childhood and adolescence. In the rhesus monkey, dopamine concentration in the PFC and dopamine synthesis in the PFC and parietal cortex peak around puberty (2-3 years), while dopamine concentration in the parietal cortex remains stable from 5 months of age (28,29). Dopaminergic input in the PFC also peaks around puberty, both in terms of length of the axons and density of varicosities (30-32). In humans, postmortem studies of the PFC have shown that dopamine concentration is highest during early postnatal development (33), while D1 receptor density peaks in adolescents (age 14-18) and young adults compared to neonates, infants, adults and aged adults (33). In the living brain, a decrease in D1 receptor binding was observed in the PFC and parietal cortex over an age span of 10 to 30 years (34). These results overall suggests a decrease in dopamine levels from puberty to adulthood (23). Little information is available regarding potential sex differences.

A decrease in basal dopamine level between childhood and adulthood could affect the position of the Val^{158}Met genotypes on the inverted U-shaped curve and lead to a differential effect of rs4680 during development. We tested the hypothesis of a change in the effect of *COMT* genotype with age on behavioral and neuroimaging data associated with visuospatial WM, a cognitive ability which develops during childhood and adolescence (35).

Methods and Materials

Participants and genetic data

Participants in nine different age groups (6, 8, 10, 12, 14, 16, 18, 20 and 25 years) were recruited using random sampling from the population registry in Nynäshamn in Sweden ('Brainchild' study, (36)). Informed consent was obtained from the participants and from the parents of children under 18. The study was approved by the local ethics committee of the Karolinska University Hospital, Stockholm. See **Table 1** and **Figure 1** for a description of included participants. Deoxyribonucleic acid (DNA) was extracted either from blood or saliva. *COMT* is located on chromosome 22q11.2 and SNP rs4680 is in exon 4 of the gene (see Supplemental Information for details of the genetic analyses and excluded participants).

Assessment of working memory

Participants completed a large neuropsychological battery administered individually and in a quiet room. Visuospatial working memory (WM) was assessed using a grid task (Dot Matrix) from the AWMA battery (37). This computerised task involves remembering the location and order of dots displayed sequentially in a four-by-four grid, for 1000 ms each, with a 500 ms interval between dots. After training with one, two and three dots, the test started with one dot. Each level consisted of six trials. Four correct answers were required for moving to the next level, where one more dot needed to be remembered. The test terminated when three errors were committed on one level. The score used was the total number of correct trials.

Dot Matrix statistical analyses

Linear mixed model analyses, which allow the inclusion of data from participants who have not attended all testing waves and adjust for inter-correlation between testing waves (38-40), were performed using the PASW 18.0 statistical package (41). A compound symmetry covariance structure was used and Dot Matrix score was treated as a repeated measure (rounds 1 and 2). We first identified how to best model changes in WM capacity with age, including the leveling of performance during mid-adolescence. We compared entering the age variable as age without transformation (linear effect), the inverse of age (age^{-1}) and the natural logarithm of age (ln(age)) (42,43). In all cases, age was transformed into Z scores to evaluate effects

of interest at the mean age of our sample and reduce collinearity between main effects and interactions (44). Sex and sex x age were entered as covariates. The best model was identified using Akaike's (AIC) and Schwartz's information criteria (SBC or BIC) (45,46).

We then tested whether including *COMT* genotype and age x *COMT* genotype as additional fixed effects improved the model. Genotype x sex and genotype x age x sex interactions were also included to test for potential sex differences in the effect of *COMT* genotype (47). Although the effect of rs4680 on dopamine degradation is additive, the effect on cognition is suggested to follow a non-linear, inverted U-curve. In order to allow the detection of such effects, we evaluated both additive (0=Met/Met, 1=Val/Met, 2=Val/Val) and dominance models (Val dominance: 0=Met/Met, 1=Val carriers; Met dominance: 0=Met carriers, 1=Val/Val) (similarly to (9,48)).

Brain imaging (fMRI)

MRI data was collected on a 1.5 T Siemens scanner (see Supplementary Information). Participants performed two 5 min sessions each including 16 WM and 16 Control trials in a pseudo-randomized order. Dots were presented sequentially in a four-by-four grid. To reduce potential age or genotype differences in behavior, the task included load 2 (two dots) and 4 (four dots) trials only. After the last dot was shown a number was presented in the grid. Participants were asked to indicate whether the number and its position in the grid matched. For example "2?" would prompt the participant to indicate whether the second circle had appeared in the grid position filled by the number. In the Control condition, the dots were presented in the corners of the grid and the cue ("8?") always required a "no" response.

Preprocessing and statistical analysis (see (36)) were carried out with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). Contrast images comparing WM and Control conditions, irrespective of load, for each participant, were used in flexible factorial design second-level analyses which modelled whether the contrasts were from the same or different participants by including

subject and testing round as factors. This permitted the inclusion in a single analysis of participants with and without longitudinal data. Age in months was transformed into Z score (age_Z).

First age_Z and sex were entered as covariates and the main WM-Control contrast was performed correcting for multiple comparison across all voxels within the brain, with a false discovery rate (FDR) threshold of $p < 0.05$, to identify regions recruited during the task. Then, genotype and genotype x age_Z were entered as additional covariates. Genotype was entered with an additive, Met dominant or Val dominant effect. In each model a single F-test was performed to test whether any main effect of genotype or age x genotype interaction could be observed (FDR, $p < .05$). Contrasts were inclusively masked by the WM-Control main effect previously defined. Results were plotted on a surface-based human atlas (PALS)(49,50) using the Caret software (51; http://www.nitrc.org/projects/caret/). Mean parameter estimates from the first level contrasts were obtained in the significant clusters using MarsBar (52) and further analysed using linear mixed models with PASW 18.0.

Brain imaging (Voxel-based morphometry)

Structural T1-weighted spin echo images were acquired with a 3D MPRAGE sequence (FOV = 256 x 256 mm, 256 x 256 grid, 1 mm^3 voxel size). Voxel-based morphometry (VBM) was performed using SPM5. Following segmentation of the T1-weighted images, high-dimensional normalization was performed using the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) toolbox in SPM (53). The modulated warped gray matter (GM) images were then smoothed with an 8 mm Gaussian kernel. The same flexible factorial analyses and statistical thresholds as those used for the fMRI data were used for the VBM GM data, with the addition of total GM volume as a covariate.

Results

Analyses combined data from all participants and both testing rounds using linear mixed models. The complicated non-independent design did not allow the calculation of standardised effect statistics (54). Effect sizes from analyses performed on the round 1 data only are reported in the Supplementary Information.

Behavioral analysis

WM capacity development

Behavioural data were available for 322 participants, including 260 with longitudinal data. We first compared the information criteria of three different models (with the age variable as age_Z, age^{-1}_Z or $ln(age)_Z$) to identify the best model of WM capacity development. Linear mixed model analyses included Dot Matrix score as the dependent variable, sex, age, and their interaction were entered as fixed effects. The best model was where WM capacity was explained by age^{-1}_Z, with a steeper change in WM capacity over younger ages and then flattening to an asymptote.

Influence of COMT *genotype on WM capacity development*

We then tested whether including the main effect of *COMT* genotype and the genotype x age interaction improved this model. Genotype x sex and genotype x age x sex interactions were also included. Genotype was modelled with an additive effect, Val dominance, or Met dominance.

Only the Val dominance model led to a significantly improved fit of the data compared with the age and sex only model (likelihood-ratio test, $D = 9.77$, 4 degrees of freedom, $p = .045$). The only significant effects observed in this full model were a main effect of age^{-1}_Z ($F(1,502.7) = 171.01$, $p < .001$) and an interaction between genotype (Met/Met vs. Val carriers) and age^{-1}_Z ($F(1,500.1) = 4.40$, $p = .036$). Met/Met individuals switched from being poorer performer during childhood to being the better performers from mid-adolescence onwards (**Figure 2**). According to the model estimates, the cross-over occurred at 10.2 years of age. Neither sex, nor interactions between sex and other variables had a significant effect on behavior.

FMRI analysis

In-scanner performance

FMRI data were available for 81 participants, including 44 with longitudinal data. Accuracy was high overall. Participants were less accurate in the WM condition (WM: mean 90.6 % ± SD 10.6; Control: 98.4 % ± 3.5) ($t(124) = 9.52$, $p < .001$), as well as slower to respond (correct trials only, WM: 1277 ms ± 360; Control: 738 ms ± 215) ($t(124) = 25.11$, $p < .001$). The difference between WM and Control conditions decreased with age in terms of both accuracy and reaction time (main effect of age^{-1}_{Z} respectively $F(1,87.8) = 10.06$, $p = .002$, and $F(1,97.1) = 32.05$, $p < .001$), however there was no main effect of genotype or age by genotype interaction (all p*s* > 0.29). Genotype thus did not affect WM vs. Control condition performance. Furthermore only correct trials were used in the brain activity analyses.

WM-Control main effect

FMRI data were analysed using a flexible factorial second level analysis of the WM-Control contrast which coded subject and testing round as factors and age_Z and sex as covariates. Because of the smaller sample size of the fMRI data, only the linear effect of age was tested in SPM analyses. The resulting WM-Control contrast image (FDR, $p < .05$) was saved and used as a mask for the subsequent analyses. A large frontoparietal network of regions was more active in the WM than the Control condition (**Figure 3a**).

Effect of COMT *genotype on the WM-Control contrast*

COMT genotype and genotype x age_Z were added as additional covariates in the flexible factorial analysis. Genotype was entered as an additive effect, with Val or with Met dominance. Interactions between genotype and sex, and genotype, sex and age were included in the follow up analyses only. In each analysis a single F-test assessed whether genotype or genotype x age_Z had significant effects (FDR, $p < .05$, within WM-Control mask). Only the Met dominance model resulted in significant clusters, located in the right inferior frontal gyrus (IFG) and in the posterior section of the right intraparietal sulcus (IPS)/angular gyrus (**Table 2, Figure 3b** and **Figure S1**).

Mean parameter estimates from the individual first level WM-Control contrasts were obtained for these two clusters. Linear mixed level model analyses demonstrated (see **Table 2** for statistics) that the parietal cluster exhibited both a main effect of genotype, with greater activation in Val/Val participants than Met carriers, and an age by genotype interaction, with an increase in activation with age in the Val/Val participants only (Val/Val, $F(1,22.5) = 21.5$, $p < .001$; Met carriers, $p > .2$). The frontal cluster exhibited an age by genotype interaction, with a similar pattern (Val/Val, $F(1,20.3) = 25.9$, $p < .001$; Met carriers, $p > .4$) (**Figure 3**). Note that for both clusters the genotype effects were significant when using age^{-1}_z but the information criteria indicated that the models including age_z were a better fit of the data. **Figure 4** relates our findings to the suggestion that PFC functioning and WM performance follow an inverted-U curve function of dopamine levels.

The main effect of genotype and age x genotype interaction remained significant (ps ≤ .001) when including genotype x sex, age x sex, and genotype x age x sex interactions in the model. In the IPS, the main effect of genotype tended to be greater in males, while in the IFG the interaction between age and genotype tended to be greater in males (**Table 2**).

Further analyses (see Supplemental Information, Figures S2, S3) indicated that activations in the IFG and IPS clusters were more strongly correlated in the Val/Val group and that these participants also showed a positive correlation between IFG activation and Dot Matrix performance.

Voxel-based morphometry

Structural MRI data were available for 84 participants, including 47 with longitudinal data. rs4680 effects on GM volumes were analysed in the same way as for the fMRI data. Total GM $volume_z$ was included as an additional covariate to permit the study of regional rather than global effects. However, similar results were obtained when total GM volume was not included.

Again only the Met dominance model resulted in significant clusters, located in the lateral bank of the IPS bilaterally (see **Table 2, Figure 3c** and **Figure S1**). Individual mean GM volumes were calculated for each cluster. Linear mixed level model analyses indicated that all three clusters showed a main effect of genotype, with greater GM volumes in Val/Val participants than Met carriers. There was a weak trend in the largest cluster for a genotype by age interaction, with a steeper decrease in GM with age in the Val/Val individuals than Met carriers. The main effects of genotype in the three clusters remained significant (all *p*s ≤ .0001) when including genotype x sex, age x sex, and genotype x age x sex interactions in the model. Significant interactions between sex and genotype were observed bilaterally (**Table 2**). In both cases, the effect of genotype was greater in males than females.

Discussion

This longitudinal and cross-sectional study of 6 to 20 year-olds combined a large sample and full age range of participants to investigate developmental changes in the effect of a functional polymorphism of the *COMT* gene on cognition, brain structure and brain function. Previous studies of children and adolescents observed inconsistent *COMT* genotype effects and were restricted by either a small age range (21) or a small sample size (22,23). Our results show that the adult pattern of the effects of the *COMT* Val^{158}Met polymorphism on brain and behavior during the performance of a visuospatial WM task emerges during adolescence. Met/Met individuals showed a steeper increase in performance with age than Val carriers, while Val/Val individuals exhibited an increase in activation in the right IFG and right IPS/angular gyrus with age. Additional main effects of genotype were observed in the parietal cortex for both fMRI and gray matter data, with larger activation and GM volumes in Val/Val participants than Met carriers.

Differences in genotype effects on the behavioral and neuroimaging data, such as the Val vs. Met dominance effects, may have been driven by a range of factors. For example the fMRI visuospatial WM task included only relatively low WM loads and a control task while the behavioral score reflected the performance achieved up to the participants' maximum WM load level. In addition, behavior may reflect more complex and global dopamine effects on brain activity and structure in a wide network of brain regions.

Behavioral results of the Dot Matrix task indicated that Met/Met homozygotes switched from being the underperformers to follow the adult pattern of better WM performance at around the age of 10-12 years old, typically considered as the start of puberty. Barnett et al. (21) reported a greater effect of COMT genotype on verbal IQ in 8 year-old boys who were pubertal at age 9 compared to prepubertal boys or girls. This pattern was not observed on other measures, including a counting span measure of WM. The present study did not evaluate pubertal state. However, WM capacity showed no significant effect of sex or interaction between sex and age or gene. We therefore interpret the observed interaction of *COMT* genotype by age as a result of a changing dopamine system during development, independent of possible

additional interactions with hormonal effects. Note however that substance use was not recorded in this study and is a potential confound of the age effect observed here (55). In Sweden, daily or almost daily smoking increases during adolescence from < 1 % at age 11-12 to a 12 % at age 18-20 (56,57), and the *COMT* Val allele has been shown to be a small risk factor (odds ratio 1.12) for smoking (58). Smoking is associated with lower WM in adults, while the evidence is mixed in younger samples (59). The increasingly poorer WM performance in Val carriers compared to Met/Met individuals may thus partly reflect increased smoking during adolescence particularly in Val carriers. However, smoking rate is low, the associations between the Val allele and smoking, and between smoking and WM, are weak and therefore unlikely to explain the entire effect observed here.

The effects of genotype and genotype x age interactions also remained significant in the neuroimaging data when interactions with sex were included in the models. In the IPS both brain activity (trend in the right IPS) and GM volumes (bilateral IPS) exhibited an interaction between sex and genotype, with greater genotype effects in males than females. In addition a greater interaction effect on IFG activation tended to be observed in males. There is widespread but weak evidence of an interaction between sex and rs4680 on behavior, brain structure and the incidence of psychiatric disorders (47). Estrogens have been implicated to explain these sex differences, as they are thought to down-regulate COMT activity (47). The current study included only small age groups when split for sex. This limitation and the lack of pubertal stage information prevented us from investigating sex differences during development in more detail.

Our findings of rs4680 effects on GM volumes are consistent with previous evidence for an effect of this polymorphism on both adolescent and adult GM volumes (14,16) and cortical thickness (15,18). However, the locations of the observed effects differ between studies, which may be due to differences in methodology and age of the participants. rs4680 is a functional variant and could be thought to affect brain function but not brain structure. However, the pruning of synapses and axons during development is affected by synaptic functioning (60,61). Thus, during maturation, genotype effects on brain function could gradually impact on brain structure and GM volumes in particular. The weaker genotype by age interaction

observed in the VBM compared to the fMRI and behavioral data may be due to the fact that these processes occur over protracted period and are not as flexible and rapid as functional changes in brain activity.

It is unclear yet what the greater parietal GM volumes observed in Val/Val individuals across ages precisely reflect, and why the Val carriers are those with greater volumes. Further investigation using a combination of cortical thickness, cortical surface area and volume data may provide more insight on the underlying developmental changes in structure (62). A possible interpretation of the results of this study relates them to the altered trajectories of brain structure maturation reported in developmental psychiatric disorders (63). For example, delayed peaks in cortical thickness in Attention-Deficit/Hyperactivity Disorder (ADHD) (64), a disorder associated with visuospatial WM impairments (65), lead to increased cortical thickness in ADHD during late childhood and early adolescence. In the current study, Val/Val participants had greater gray matter volumes in the parietal cortex and show poorer WM capacity from mid-adolescence onwards.

The effects of *COMT* genotype we observed were not limited to the PFC. In line with these results, dopamine D1 receptors availability (34) and correlation between D1 receptors availability and *COMT* genotype (66) are similar throughout the cortex, and dopamine D1 receptors density and change in WM capacity after training are correlated in both prefrontal and parietal cortex (67). Recent multimodal studies combining positron emission tomography (PET) and fMRI data to study the dopamine system in adults have repeatedly identified parietal and lateral PFC regions similar to the clusters observed in the present study and provide independent evidence that these regions are sensitive to basal dopamine levels and dopamine levels in interconnected subcortical regions (68-70).

In both the behavioral and fMRI data sets, we observed a gradual emergence from age 12 of the adult pattern of *COMT* genotype effects. PFC functioning and WM performance have been suggested to follow an inverted-U curve function of dopamine levels (24), with adult rs4680 Met/Met individuals near the apex of this curve (2). The pattern observed in children (**Figure 4**) resembles the reduction of lateral PFC

activation and improvement in WM performance observed in Val/Val adults administered amphetamine, which increases basal dopamine levels (27). Thus our findings are compatible with a decrease in basal dopamine levels during adolescence (23), providing indirect evidence for the development of the dopamine system in humans.

Increased prefrontal activity could reflect top-down boosting of WM capacity in the parietal cortex (71). Val/Val individuals showed an increase in prefrontal and parietal activation during adolescence, a greater correlation between the activation in these two clusters than Met carriers, and a correlation between greater WM activity in the right IFG and better WM capacity outside the scanner. Together these results suggest that a top-down excitation from frontal to parietal cortex may be gradually implemented during adolescence in Val/Val individuals to compensate for deficient amounts of dopamine levels and parietal functioning.

Given that the onset of many psychiatric conditions occurs during adolescence (72), and that genotype variations have been associated with the incidence of developmental psychiatric disorders, elucidating the role of genetics in determining brain function during childhood and adolescence is critical to our understanding of the development of these disorders. The findings presented here show that the full developmental picture should be considered when trying to understand the impact of genetic polymorphisms on the mature cognition of healthy adult or psychiatric populations.

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Figure legends

Figure 1: Distribution of the data points across round 1 and round 2 according to age and *COMT* genotype in each of the three analyses. For each age group, the number of participants from round 1 and round 2 is indicated above each bar (round 1 N / round 2 N).

Figure 2: Working memory capacity as a function of each age year group at testing and *COMT* Val^{158}Met polymorphism. The bars are included for illustrative purposes only and represent the mean and standard error (SE) of WM capacity, as measured by the Dot Matrix score, in each age group, collapsing across longitudinal and cross-sectional data. Participants tested at both rounds are included as two data points. Analyses were performed with age as a covariate rather than considering the age groups separately. The lines represent the mean predicted Dot Matrix score for each genotype group, as obtained from the mixed model analysis using the inverse of age as a factor and genotype effects with Val dominance.

Figure 3: FMRI and VBM results. **a)** Render of the fMRI main effect WM – Control (FDR, $p < 0.05$) on a surface-based human atlas (see Methods and Materials). From left to right: lateral view of the left and right hemisphere, dorsal view of the left and right hemispheres. This contrast was used as a inclusive mask for the tests of the effect of COMT genotype presented in **b** and **c**. **b)** F-test of *COMT* genotype or genotype x age effects on the fMRI WM – Control contrast (FDR, $p < 0.05$). Mean parameter estimates of the WM – Control contrast at the first level were calculated and plotted for the parietal and frontal clusters observed in the right hemisphere. Full lines connect those participants who participated to both testing rounds. Dashed lines are the predicted fit from linear mixed models including sex, age_Z, *COMT* genotype (with Met dominance) and genotype x age_Z interaction as covariates. The age by genotype interaction was significant in both clusters. There was an additional main effect of genotype in the parietal cluster. **c)** F-test of *COMT* genotype or genotype x age effects on the VBM gray matter data (FDR, $p < 0.05$). Mean gray matter volume were calculated and plotted for the two largest parietal clusters (see **Table 2**). Full lines connect those participants who participated to both testing rounds. Dashed lines are the predicted fit from linear mixed

models including sex, age_Z, total gray matter volume (Z), *COMT* genotype (with Met dominance) and genotype x age_Z interaction as covariates. The main effect of genotype but not the age x genotype interaction was significant in both clusters. (see also Figure S1)

Figure 4: *COMT* genotype, WM capacity and WM activity and their relation to a hypothetical basal dopamine concentration. Brain activity is from the right lateral PFC. 8 and 18 year-old age groups were chosen to illustrate the changes in the influence of *COMT* genotype on WM function during development. On the top row, WM capacity Z scores were calculated using the Dot Matrix scores of the 8 and 18 year-olds separately and are plotted in the inset bar charts for each *COMT* genotype. The three *COMT* genotypes were accordingly located on the hypothetical inverted U-curve of prefrontal functioning as a function of dopamine concentration proposed from adult and animal data (e.g. 25, 27). Here an arbitrary Gaussian curve was used. On the bottom row, similar steps were applied to the WM – Control activation in the right lateral PFC. Note that greater brain activation is associated with worse performance (27) and thus the y-axis is inverted to highlight the similarities between the behavioral and imaging results. 8 year-olds showed a detrimental effect of the Met allele, while 18 year-olds showed the typical adult pattern of a beneficial effect of the Met allele, with higher WM capacity and lower brain activity in the frontal cortex. This pattern of change in genotype effect with age can be regarded as a shift during development of the position of the *COMT* Val^{158}Met genotypes on the inverted-U curve of PFC function relative to dopamine levels in the direction of lower basal dopamine levels.

Figure 1

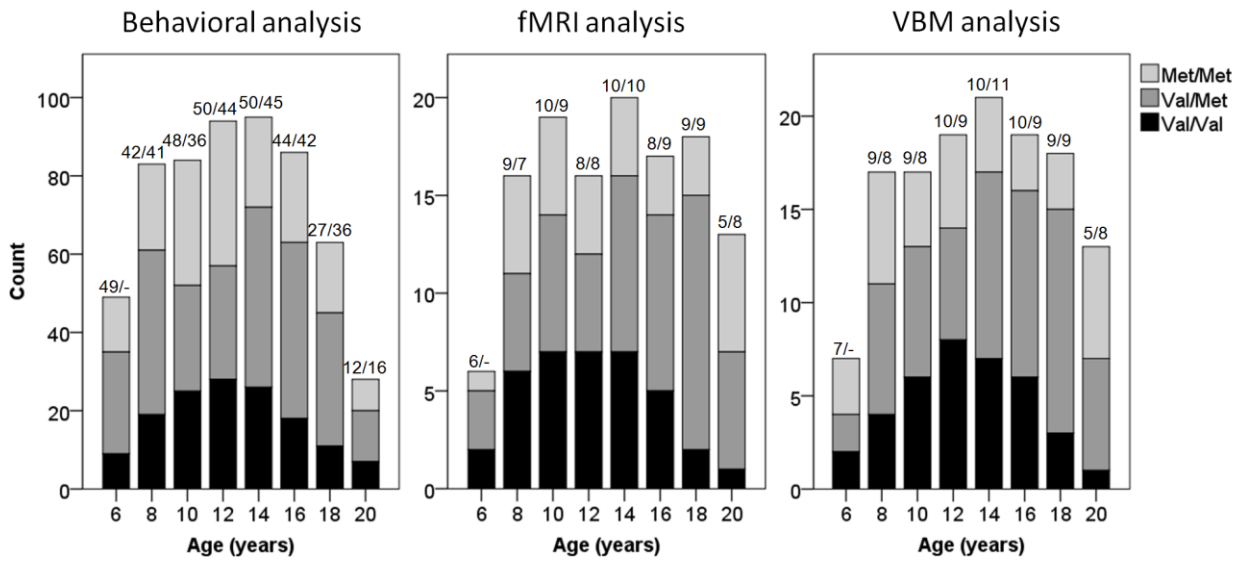


Figure 2

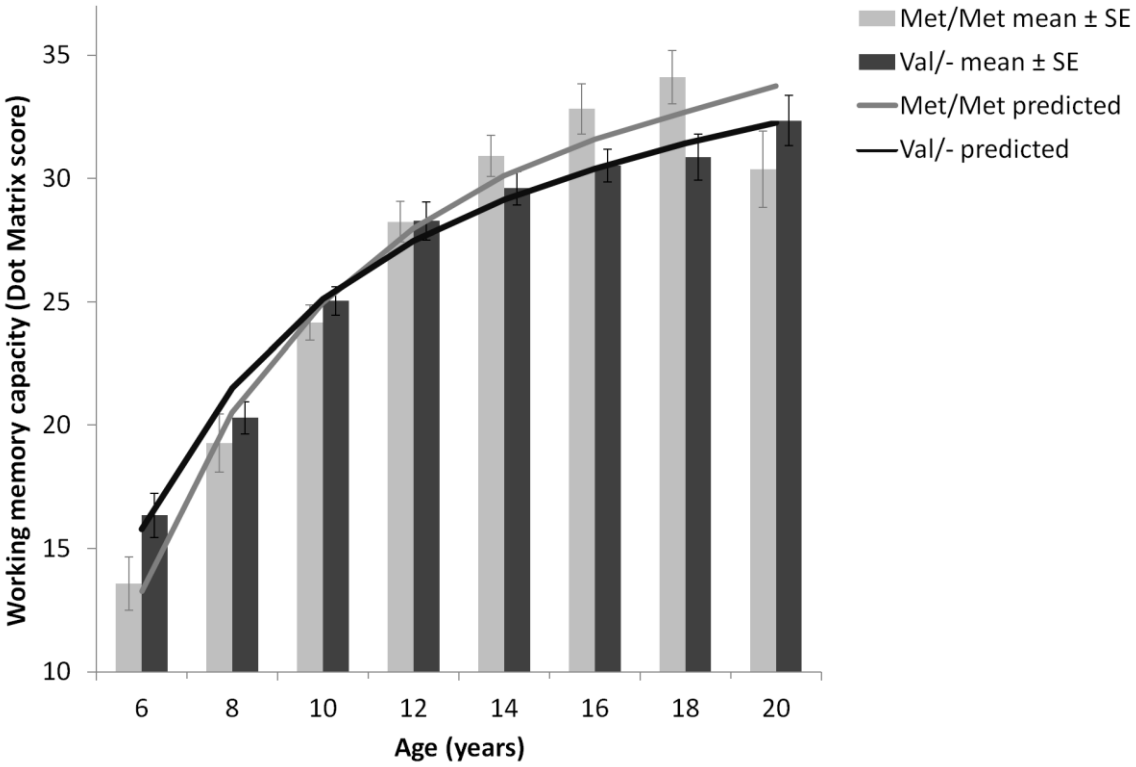


Figure 3

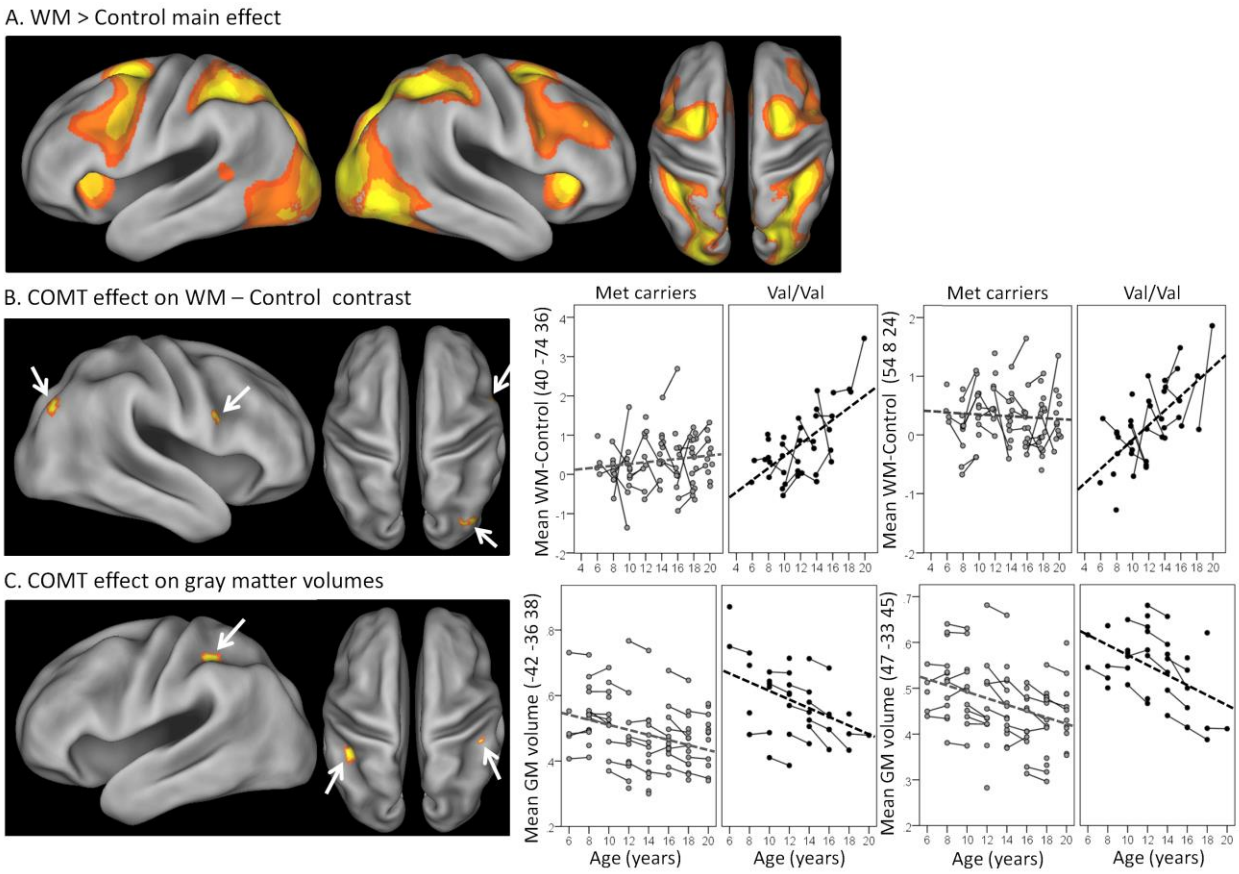
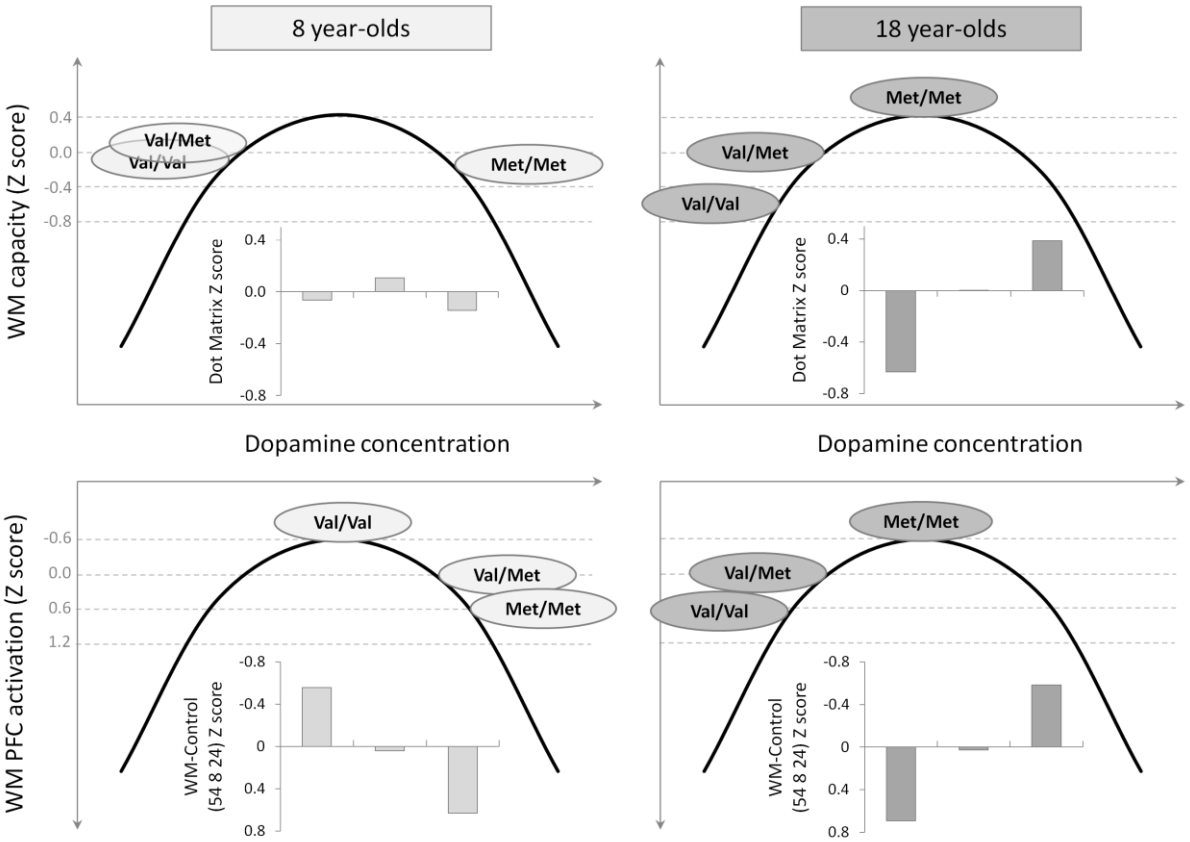

A. WM > Control main effect
B. COMT effect on WM – Control contrast
C. COMT effect on gray matter volumes
Met carriers
Val/Val
Met carriers
Val/Val
Mean WM-Control (40 -74 36)
Mean WM-Control (54 8 24)
Mean GM volume (-42 -36 38)
Mean GM volume (47 -33 45)
Age (years)
Age (years)
Age (years)
Age (years)

Figure 4


8 year-olds
18 year-olds
WM capacity (Z score)
0.4
0.0
-0.4
-0.8
Val/Met
Val/Val
Met/Met
Dot Matrix Z score
0.4
0.0
-0.4
-0.8
Dopamine concentration
WM PFC activation (Z score)
-0.6
0.0
0.6
1.2
Val/Val
Val/Met
Met/Met
WM-Control (54 8 24) Z score
-0.8
-0.4
0
0.4
0.8