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Relations between catechol-O-methyltransferase Val158Met genotype and inhibitory control development in childhood

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Abstract

The Val158Met rs4680 single nucleotide polymorphism (SNP) at the catechol-O-methyltransferase (*COMT*) gene, primarily involved in dopamine breakdown within prefrontal cortex, has shown relations with inhibitory control (IC) in both adults and children. However, little is known about how *COMT* genotype relates to developmental trajectories of inhibitory control throughout childhood. Here, our study explored the effects of the *COMT* genotype (Val/Val, Val/Met, and Met/Met) on IC trajectories between the ages of 5 and 10 years. Children (n=222) completed a Go/Nogo task at ages 5, 7, and 10; IC was characterized using signal detection theory to examine IC performance (d') and response strategy (criterion). *COMT* genotype was not related to initial levels of IC performance and response strategy at age 5 or change in response strategy from ages 5 to 10. In contrast, *COMT* genotype was related to change in IC performance between 5 and 10 years. While Val/Val children did not differ from Val/Met children in development of IC performance, children with the Met/Met genotype exhibited more rapid development of IC performance when compared to Val/Met peers. These results suggest that *COMT* genotype modulates the development of IC performance in middle childhood.

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Data Availability Statement:

The data that support the findings of this study are available from the corresponding author, MB, upon reasonable request.

Keywords

COMT; rs4680; inhibitory control; signal detection theory; childhood development; Go/Nogo task

Executive functioning refers to a set of high-level cognitive processes that support self-control and goal-directed behavior. Inhibitory control (IC), one subcomponent of executive functioning, reflects the ability to inhibit a prepotent response. IC is correlated with, but ultimately separable, from other executive functions like set shifting and working memory (Miyake et al., 2000; Miyake & Friedman, 2012). IC develops throughout childhood (Macdonald, Beauchamp, Crigan, & Anderson, 2014; Williams, Ponesse, Schachar, Logan, & Tannock, 1999), with older children and adolescents demonstrating a stronger abilty to inhibit responses. Previous research has shown that children show significant variability in IC ability (Carlson, Moses, & Claxton, 2004; Gilmore et al., 2013; McDermott, Pérez-Edgar, & Fox, 2007). Individual differences in childhood IC ability have been related to a variety of developmental outcomes, including ADHD (Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; Willcutt et al., 2001), substance use (Gustavson et al., 2017; Ptácek, Kuzelová, & Stefano, 2011), anxiety (Henderson, Pine, & Fox, 2015; Thorell, Bohlin, & Rydell, 2004; Troller-Renfree et al., 2019; White, McDermott, Degnan, Henderson, & Fox, 2011), and physical health problems (Moffitt et al., 2011).

Childhood is marked by vast changes in cognitive abilities, brain structure, and function (Lenroot et al., 2007; Ordaz, Foran, Velanova, & Luna, 2013; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011; Shaw et al., 2008), dynamics missed by cross-sectional research alone. While cross-sectional studies provide useful snapshots of children's ability at a given time point, these approaches do not capture the full picture of development throughout childhood (Karmiloff-Smith, 1998; Karmiloff-Smith, 1997). In contrast, longitudinal studies can leverage data collected at multiple timepoints to build developmental trajectories for each child, quantifying individual differences in rate of change (Barker & Maughan, 2009; Perry, Calkins, Dollar, Keane, & Shanahan, 2017), which has proven useful in prediction of later psychopathology (Dekker et al., 2007; Troller-Renfree et al., 2019). We recently quantified developmental trajectories in IC development across ages 5–10 years, and found individual differences in the rate of IC development across this period (Troller-Renfree et al., 2019). Here, we focus on the role of genetics in determining individual variation in IC development itself.

Heritability estimates garnered from twin studies suggest that differences in IC ability are thought to be largely genetic (with some shared variance due to environment; Friedman et al., 2008). Yet, it remains unclear how specific genetic alleles relate to developmental trajectories of IC. Given that IC is subserved by prefrontal circuits that rely heavily on dopaminergic innervation (Berger, Thierry, Tassin, & Moyne, 1976; Goldman-Rakic, Lidow, Smiley, & Williams, 1992), genetic differences that relate to prefrontal dopamine have been suggested to influence executive functions generally and IC specifically (Barnes, Dean, Nandam, O'Connell, & Bellgrove, 2011; Tunbridge, Harrison, & Weinberger, 2006). Of particular interest is the *COMT* gene, which codes for the catechol-O-methyltransferase enzyme, which catalyzes the breakdown of catecholamines (e.g. dopamine, epinephrine, and

norepinephrine; Haavik et al., 2008). The *COMT* gene is predominantly expressed in prefrontal regions of the brain (Tunbridge et al., 2007), areas vital for top-down control in executive functioning and IC. However, single-nucleotide polymorphisms (SNPs) in the *COMT* gene can affect *COMT* enzyme activity.

The Val158Met SNP (rs4680) is the most commonly studied SNP in the *COMT* gene, at which a change from guanine to adenine results in a methionine (Met) for valine (Val) substitution, allowing for Val/Val, Val/Met, and Met/Met genotypes. The methionine substitution results in a three to fourfold decrease in *COMT* enzyme activity (Chen et al., 2004; Lachman et al., 1996), and consequently a slower rate of catecholine breakdown and more dopamine bioavailability. Increases in dopamine tend to increase prefrontal cortex (PFC) synaptic activity and improve executive functions, including working memory; however, the relation between dopamine and executive function performance follows an inverted U-shape (Egan et al., 2001). Thus, too much or too little dopamine can hinder cognitive performance. Those with the Met/Met genotype, with reduced catecholine breakdown, show increased tonic levels of dopamine and reduced phasic bursts of dopamine in subcortical regions and a higher concentration of dopamine within the PFC. On the other hand, Val allele carries show lower levels of tonic dopamine and increased phasic bursts of dopamine in subcortical regions and a lower concentration of dopamine within the PFC (Bilder, 2012; Bilder, Volavka, Lachman, & Grace, 2004). Elevated tonic dopaminergic activity seen in the Met/Met genotype is thought to sustain task-set maintenance and protect against spontaneous interruption of task-states by irrelevant stimuli, which is suggested as a mechanism explaining why the Met/Met genotype is associated with improved performance on tasks requiring the maintenance of information, such as working memory tasks. Conversely, the increased phasic dopaminergic activity, seen in Val carriers, promotes the updating of task sets with relevant novel information to dynamically adjust behavior, an advantage for set-shifting (Bilder et al., 2004; Durstewitz, Seamans, & Sejnowski, 2000). However, given that inhibitory control tasks also require maintaining a constant set of stimulus-response mappings online throughout the task, it is possible that Met/Met carriers would exhibit improved performance on inhibitory control tasks as well.

Indeed, the relation between *COMT* genotype and executive functions has been studied in both adults and children. As individuals with the Met/Met genotype should exhibit higher levels of tonic dopamine availability, particularly within prefrontal regions of the brain, both adults and children who have the Met/Met genotype display better working memory performance (Bruder et al., 2005; Joober et al., 2002) and more efficient cognitive processing (Egan et al., 2001; Malhotra et al., 2002; Mier, Kirsch, & Meyer-Lindenberg, 2010). Furthermore, although Met/Met homozygotes seem to have the advantage of stability in high levels of some executive functions, Val/Val individuals have improved cognitive flexibility and set-shifting, likely due to increased phasic dopaminergic bursts (Colzato, van den Wildenberg, van Wouwe, Pannebakker, & Hommel, 2009; Moriguchi & Shinohara, 2018). In terms of IC specifically, results in adults have been mixed, as some studies have shown no behavioral differences in IC tasks (Congdon, Constable, Lesch, & Canli, 2009; Winterer et al., 2006), while others show that Val/Val homozygotes are slower to inhibit their responses. (Krämer et al., 2007). In children, there is less evidence for the effect of *COMT* on IC specifically, as only one previous study has investigated these relations, albeit using

self-report measure of IC, finding that Met/Met boys in positive parenting environments have higher levels of parent-reported inhibitory control (Sulik et al., 2015).

It is possible that the mixed findings in regard to the influence of the *COMT* genotype on IC is due to methodological differences across studies. In an attempt to shed light on the mixed findings relating *COMT* to IC, we utilized signal detection theoretic measures (Green & Swets, 1966) to further parse IC into two components, IC performance (d') and response strategy (criterion). IC performance reflects perceptual sensitivity to detect a stimulus (signal) from noise; whereas, response strategy indexes an overall tendency to respond (or not respond). Here, we investigated performance on a Go/No-go task, which typically measures inhibitory control using accuracy on nogo trials, with go trials only present in order to facilitate a prepotent response tendency on nogo trials. However, employing raw nogo accuracy as a measure of IC, without accounting for go accuracy can be problematic, as raw nogo accuracy will not reflect a valid measure of IC for participants that frequently withhold responses to go trials as well (i.e. these participants will not have a preprotent response tendency to override on nogo trials). Using d' to measure IC performance effectively isolates how accurate participants are on nogo trials after accounting for individual differences in go accuracy. On the other hand, criterion (response strategy) reflects the amount of internal evidence needed for an individual to determine the appropriate response, quantifying each child's task strategy. A liberal strategy reflects a tendency to "go" on every trial; whereas, a conservative strategy reflects a propensity to withhold responses. The influence of *COMT* activity on these two separable aspects of IC, IC performance vs response strategy, has also yet to be studied and could provide insight on mixed results surrounding the influence of *COMT* genotype on inhibitory control. In particular, with reduced catecholine breakdown, Met/Met children should exhibit greater tonic dopamine levels within PFC compared to Val/Val and Val/Met children. This increase in tonic dopamine levels is thought to maintain stability in control-related networks, and would presumably impact IC performance, but would not necessarily change a subject's criteria, or bias, which has not been associated with dopaminergic activity (Bilder, 2012; Bilder et al., 2004; Cohen & Servan-Schreiber, 1993; Cools, 2006). Thus, leveraging a signal detection theoretic approach might allow for identifying a more selective effect of *COMT* on IC performance specifically, as opposed to response strategy more generally.

In the present study, we explore the association between the *COMT* Val158Met polymorphism and IC performance and response strategy during childhood using lab-based assessments of IC at multiple timepoints. To this end, we leveraged longitudinal assessments of IC to predict developmental trajectories of IC performance and response strategy as a function of *COMT* genotype. Through the use of latent growth curve modeling, both IC performance and response strategy at age 5, along with the slope of IC performance and response strategy across ages 5, 7, and 10 were estimated. We expected Met/Met homozygotes to have higher levels of IC performance at age 5 and faster development of IC performance from ages 5–10, given the link between elevated dopamine availability and enhanced cognitive performance. However, due to the dearth of research on the relation between *COMT* and response strategy, we had no explicit hypotheses regarding effects of *COMT* genotype on response strategy during this developmental period.

Methods

Participants

Participants included in this sample are part of a longitudinal study examining temperament and its relation to the emergence of later social anxiety. At four months of age, 779 infants completed an in-lab temperament screening, during which emotional and motor reactivity to novel stimuli were observed (Calkins, Fox, & Marshall, 1996; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Hane, Cheah, Rubin, & Fox, 2008). Subsequently, 291 infants (134 male) continued in the study based on in-lab temperament observations, which we coded for positive reactivity (smile and positive vocalizations), negative reactivity (crying and fussing), and motor reactivity (arm and leg movements). Children were subsequently categorized into temperment groups. Infants who were above the median for both positive and motor reactivity were classified as "positive reactive" and those who were above the median for both negative and motor reactivity were classified as "negative reactive." If infants met criteria for both of these groups, they were placed in either the high-positive reactive or high-negative reactive groups depending on their affective bias (i.e., the difference between the standard scores of positive reactivity and negative reactivity). The infants who did not meet these criteria were classified as an "unselected" group. Temperament groups in the sample are as follows: high negative/high motor reactive (n = 116), high-positive/high-motor reactive (n = 106), and an unselected group (n = 69). Our sample consisted of 222 children who completed one or more timepoint of the inhibitory control task.

Demographics

Demographic variables of interest included race, gender, and maternal education. Maternal education was used as a continuous variable with three levels: high school, college, and graduate school. Due to the relatively small percentages of non-Caucasian races represented in the sample, race was coded as Caucasian or not Caucasian. Table 1 details the demographics of the sample included in the latent growth curve (LGC) models. The 222 children included in the study did not differ in gender, $X^2(1, N=291) = .30$, $p = .58$, mother education level, $t(289) = -1.32$, $p = .19$, or in temperament group frequencies, $X^2(1, N=291) = .30$, $p = .86$ from the 69 not included. However, there were significantly more Caucasian children than non-Caucasian children included in the analysis, $X^2(1, N=291) = 4.26$, $p = .04$.

COMT Genotyping

COMT Val158Met (rs4680) was genotyped using the predesigned Assay on Demand C_25746809_50 (Applied Biosystems, Foster City, USA) in a 5'-nuclease assay. Genotyping was performed according to the manufacturer's protocol using 10ng genomic DNA in a 5μl reaction. Amplification was performed using a 9700 thermocycler (Applied Biosystems, Foster City, CA, USA), and genotype determined at end point using SDS software v2.4 in allelic discrimination mode on an ABI 7900HT Sequence Detection System (SDS). Genotyping accuracy was determined empirically by duplicate genotyping of 25% of the samples selected randomly. The error rate was <0.005, and the completion rate was >0.95. Genotyping results for the 116 children who were genotyped for *COMT* were consistent with Hardy-Weinberg equilibrium, $X^2(3, N=116) = .07$, $p = .97$ (36:55:25 Val/

Val:Val/Met:Met/Met). Table 2 details the demographics of the genotype groups and the groups did not differ based on sex, race, maternal education, or temperament group (all $p > .1$). Moreover, as a majority of our sample is classified as high-motor reactive, genotype groups did not differ on a dimensional measure of 4-month motor reactivity, $F(2,114)=1.48, p=.23$.

Go/No-go Task: Zoo Game

Children played a version of a Go/Nogo task called the Zoo Game (Lamm et al., 2014) at 5, 7, and 10 year assessments. During the Zoo Game, children were instructed to help the zookeeper catch animals who had escaped from the zoo. Children were also told that orangutans were the zookeeper's helpers, so they should not catch any orangutans on the screen. At the 5 year visit, the zookeeper's helper was a monkey, while at the 7 and 10 year visits, the helper was an orangutan. Participants were instructed to press a button as quickly as possible when they saw any animal that was not an orangutan (Go trials), but to not press the button when they saw the orangutan (Nogo trials). The Zoo Game had 75% Go trials and 25% No-go trials. The behavioral data were cleaned to remove anticipatory responses (reaction times under 200 ms). All participants had greater than 50% accuracy on go trials at all timepoints. For more detailed information on task specifications, see Troller-Renfree et al. (2018).

Accuracy data for the Zoo Game were decomposed into d' and criterion, commonly used signal detection theoretic measures (Green & Swets, 1966), in order to investigate changes in d' and criterion across the three assessments. Accuracy rates on the Zoo Game are used as a measure of IC ability; however, accuracy rates confound a child's actual IC ability with that of the response strategy they use to perform the task. d' was calculated by subtracting the z-transform of hits from the z-transform of false alarms; therefore, d' quantifies how well a child is able to differentiate "go" trials from "nogo" trials in a Go/Nogo task, creating a measure of *IC performance*, or sensitivity to the different stimuli. Alternatively, criterion was calculated by summing the z-transform of hits and the z-transform of false alarms and dividing by two, and reflects the *response strategy* being used by the child, regardless of trial type. If a child has a liberal strategy, they will be more likely to go on every trial, at the expense of nogo trials. If a child uses a conservative strategy, they would be less likely to go on every trial, allowing for more missed go trials, but more correct nogo trials. Within a go/nogo task, it is imperative to measure both IC performance and response strategy in order to distinguish between these two constructs that together result in raw accuracy. Signal detection theoretic measures create meaningful measures of IC performance and response strategy that can be applied to developmental research (Conners, Epstein, Angold, & Klaric, 2003; Fortenbaugh et al., 2015; Troller-Renfree et al., 2018).

Latent Growth Curve of Inhibitory Control

Consistent with the models used by Troller-Renfree and colleagues (2018), latent growth curve (LGC) models of IC performance and response strategy measures, at ages 5, 7, and 10 were completed separately in Mplus (Muthén & Muthén, 2010) in order to estimate the longitudinal growth (slope and intercept) for each individual. Full information maximum likelihood (FIML) was used to estimate missing data at each timepoint. Slope represents the

change over time in these measures, while the intercept reflects the value at age 5. A linear latent growth curve model was specified by fixed loadings of 0, 2, and 5 for the paths between 5-, 7-, and 10-year assessments and the latent slope factor and fixed loadings of 1 for the paths between 5-, 7-, and 10-year assessments and the latent intercept factor. Next, an unconditional multivariate LGC was specified, allowing the four latent factors (IC performance intercept and slope, response strategy inctercept and slope) to covary. Additionally, modification indices indicated that residuals of 5-year IC performance and 5-year response strategy should also covary. Next, we tested a conditional LGC model with two dummy-coded *COMT* genotype exogenous variables predicting the four latent factors. Val/Met was used as the reference group. Again, FIML was used to estimate data missing on the predictor. Finally, we also tested the conditional LGC model while controlling for race, maternal education, gender, and infant temperament group. Because our sample has a large proportion of children classified as high motor reactive, we also modeled the *COMT* conditional LGC while controlling for race, maternal education, gender, and a continuous measure of 4-month motor reactivity.

Results:

Trajectories from LGC

As reported in Troller Renfree et al. (2018), the LGC model for IC performance (d') alone showed adequate fit, $x^2(1)=.19$, $p=.66$, RMSEA=.00, SRMR=.01 (Hu & Bentler, 1999). Mean initial starting point of IC performance was estimated to be 1.73 and significantly different from zero ($p<.001$, 95% CI=1.61 to 1.86), and mean slope was estimated to be .09 and significantly different from zero ($p<.001$, 95% CI=.06 to .12), suggesting that IC performance improves between the ages of 5 and 10 years in children on the Go/Nogo task.

Similarly, the LGC model for response strategy alone displayed adequate fit, $x^2(1)=1.82$, $p=.17$, RMSEA=0.06, SRMR=0.03. Mean initial starting point of response strategy was estimated to be −.93 and significantly different from zero ($p<.001$, CI=−.98 to −.87) and mean response strategy slope was estimated to be −.004, which was not significantly different from zero ($p=.63$, 95% CI=−.018 to .011). The negative value for the starting point of response strategy suggests that children are more likely to respond (than not) on the Go/Nogo task. This outcome is to be expected given that go trials are the majority of trials in the Go/Nogo task. This pattern was evident at age 5, and there was little average change between the 5 to 10-year assessments.

Finally, the multivariance LGC for both IC performance and response strategy displayed adequate fit, $x^2(6) = 10.61$,p=.10, RMSEA=.06, SRMR=.06. Mean IC performance intercept was 1.77 and significantly different from zero ($p<.001$, CI=1.66 to1.88), and mean IC performance slope was 0.08 and significantly different from zero ($p<.001$, CI=.05 to .11). Mean response strategy intercept was −0.92 and significantly different from zero ($p<.001$, CI=−.98 to −.87), and mean response strategy slope was −.004 and not significanlty different from zero ($p=.56$, CI=−.02 to .01). None of the latent factors were correlated with one another (p's>.2). Estimating the multivariate LGC replicated the results of the separate LGCs for each measure.

COMT and Inhibitory Control

Next, a conditional multivariate LGC with *COMT* genotype predicting intercept and slope of IC performance and response strategy (Figure 1) was performed. Two dummy coded predictors were used to compare Val/Val to Val/Met and Met/Met to Val/Met. The model displayed adequate fit, $x^2(10)=13.17$,p=.21, RMSEA=.04, SRMR=.05. There were no differences between the Val/Val and Val/Met group in relation to IC performance slope or intercept or to response strategy intercept or slope (*p*s>.2). However, the Met/Met group was significantly higher on IC performance slope, Z = .117, *p*=.019, compared to the Val/Met group. This relation remained significant with adequate model fit when controlling for race, maternal education level, gender, and temperament group, or when controlling for race, maternal education level, gender, and 4-month motor reactivity.

Discussion

The present study is the first to investigate the influence of *COMT* genotype on the developmental trajectories of signal detection theoretic measures of inhibitory control (IC) in late childhood. To this end, we examined the influence of the *COMT* Val158Met single-nucleotide polymorphism (SNP) on developmental trajectories of both IC performance and response strategy from age 5 to age 10. Children with the Met/Met genotype, which effectively increases bioavailabity of dopamine within the prefrontal cortex, demonstrated more rapid improvements in IC performance from age 5 to age 10 compared to children with the Val/Met genotype; however, there were no differences between Val/Val and Val/Met children. In contrast, *COMT* genotype was unrelated to baseline levels of IC performance or response strategy at age 5 and to changes in response strategy from age 5 to age 10.

Inhibitory control ability improves throughout early childhood (Bedard et al., 2017; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). Consistent with this developmental trajectory, neuroimaging research demonstrates that children, compared to adults, display increased activation in a fronto-striatal network during a Go/Nogo task (Durston et al., 2002). Increased activation in this context is interpreted as less efficient neural processing associated with inhibitory control, suggesting the efficiency of this network improves with age. Indeed, behavioral improvements in inhibitory control throughout development may be due to increased connectivity between top-down prefrontal areas and subcortical regions (Hwang, Ghuman, Manoach, Jones, & Luna, 2016). Parallel to these developmental changes in activation and connectivity in the prefrontal cortex throughout development, *COMT* expression in the prefrontal cortex increases from infancy to adulthood (Tunbridge et al., 2007). Given that the *COMT* Val158Met SNP is known to modulate prefrontal dopamine levels (Chen et al., 2004; Tunbridge et al., 2007), variation in dopamine bioavailability, as a function of *COMT* genotype, may contribute to individual differences in the development of IC ability. This notion is supported by the finding that *COMT* genotype predicted rates of change in IC performance within the current study.

In the sample of children studied here, individuals with the Met/Met genotype exhibited a greater improvement in IC performance from age 5 to age 10, compared to Val/Met individuals, even after controlling for baseline levels of IC performance. The Met/Met genotype results in lower *COMT* enzyme activity and a reduction in synaptic dopamine

breakdown, leading to increased bioavailability of tonic dopamine within prefrontal cortex. Our finding that children with the Met/Met genotype show accelerated development of IC performance is consistent with prior work in adults showing that Met/Met individuals perform better on executive function tasks (Egan et al., 2001; Malhotra et al., 2002; Mier et al., 2010). Moreover, adults with the Met/Met genotype exhibited greater trial-to-trial adjustments after experiencing negative reinforcement (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). Previous work and our results suggest that *COMT* genotype produces differences in susceptibility or sensitivity to learning from the environment, and the extra prefrontal dopamine affords Met/Met individuals an advantage for cognitive control (Frank et al., 2007; Green, Kraemer, DeYoung, Fossella, & Gray, 2013; Papaleo, Erickson, Liu, Chen, & Weinberger, 2012). Our results differ from work in early childhood (ages 3 – 6) demonstrating that children with the Val/Val genotype show higher levels of executive functioning at age 4 and 5 (Blair et al., 2015; Moriguchi & Shinohara, 2018). However, these studies incorporated tasks that involved set-shifting and cognitive flexibility, two aspects of executive function in which Val/Val individuals typically outperform Met/Met individuals, in line with theories of tonic/phasic dopamine and *COMT* (Bilder, 2012). In other longitudinal studies of working memory, Val/Val children do outperform Met/Met children on working memory tasks until around age 10, when Met/Met children gain the advantage (Dumontheil et al., 2011). Our findings help to reconcile such apparent inconsistencies in prior investigation of *COMT* and executive functions, as we found that Met/Met children did not show baseline differences in IC, but rather, Met/Met children specifically display more rapid development of inhibitory control from ages 5 to 10. Thus, the current results underscore the importance of examining longitudinal change in executive function, as opposed to “snapshots” of executive function ability during a particular developmental period. Nonetheless, inhibitory control is distinct from both set-shifting and working memory (Miyake et al., 2000), and although we suggest that both working memory and IC both benefit from increased levels of tonic dopamine, further research within this domain is warranted.

In contrast to the influence of *COMT* genotype on IC performance, the *COMT* genotype was not associated with response strategy, which reflected an overall bias to respond to go/nogo stimuli. The fact that *COMT* genotype was related to IC performance, but not response strategy, suggests a degree of specificity in the influence of the *COMT* genotype on the development of higher-level cognition. With reduced catecholine breakdown, Met/Met children should exhibit greater tonic dopamine levels within PFC. This increase in tonic dopamine levels is thought to maintain stability in control-related networks, impacting IC, but would not necessarily change a subject’s criteria, or bias, which has not been associated with dopaminergic activity (Bilder, 2012; Bilder et al., 2004; Cohen & Servan-Schreiber, 1993; Cools, 2006). Nonetheless, it is important to note that there was minimal developmental change in response strategy between the ages 5 and 10, potentially limiting the ability to detect a relation between *COMT* genotype and response strategy. It is possible that differences in response strategy on a Go/Nogo task may develop after age 10 and *COMT* genotype could affect the development of response strategy after age 10 or in adolescence.

Additionally, the findings presented here are consistent with the "Warrior/Worrier" hypothesis, a theoretical framework suggesting that individuals with the Val/Val genotype are better able to handle emotional processing and stress (Smolka et al., 2005; Zubieta et al., 2003), while individuals with the Met/Met genotype excel at cognitive processing tasks (Aguilera et al., 2008; Landi et al., 2013). In low stress situations, such as the task presented here, individuals with the Met/Met genotype outperform individuals with the Val/Val genotype. However, the "Warrior/Worrier" hypothesis posits that in high stress situations, individuals with the Val/Val genotype should surpass the performance of individuals with the Met/Met genotype. Future research should explore how *COMT* genotype affects inhibitory control development under stressful situations. It is also important to note that *COMT* genotype only accounted for 3% of the variance in IC performance slope, indicating that other factors influence IC performance trajectories. Previous work has also shown gene-environment interactions between *COMT* genotype and early experience affecting later executive functioning (Blair et al., 2015; Sulik et al., 2015). Notably, Met/Met boys in positive parenting environments had higher levels of parent-reported inhibitory control (Sulik et al., 2015). Future research should explore what environmental influences, such as parenting or early adversity, interact with *COMT* genotype to predict unexplained variance in trajectories of IC development (Amicarelli, Kotelnikova, Smith, Kryski, & Hayden, 2018; Moilanen, Shaw, Dishion, Gardner, & Wilson, 2010). Similarly, initial work has also demonstrated a link between *COMT*, IC, and internalizing psychopathology (Sulik et al., 2015), in line with other work linking temperament, IC development, and anxiety specifically (Troller-Renfree et al., 2018). Future research should also examine how *COMT* genotype and inhibitory control development interact to influence externalizing psychopathology within a larger and more diverse sample.

One limitation of the current study is the relatively small sample size that was studied. Therefore, the current results can be considered exploratory and require replication. However, it should be stressed that the results of this study remain valuable, as individualized, longitudinal trajectories of inhibitory control—assessed using signal detection theoretic measures of lab- based tasks—are rare. Thus, the current study provides an important first step in investigating the relations between the *COMT* genotype and longitudinal development in inhibitory control performance in childhood. Another limitation of the current study is that we employed a sample that was selected based on temperament classifications, with most children being classified as high in motor reactivity. Therefore, the results should be interpretated carefully and replicated within a normative sample.

In conclusion, the current study suggests that *COMT* genotype influences the development of IC performance in childhood. Homozygous Met individuals for the *COMT* gene have a faster rate of development of IC performance, presumably due to the influence of dopamine availability within prefrontal cortex. These findings improve the current understanding of IC development by pointing to a genetic explanation for individual differences in the typical development of inhibitory control.

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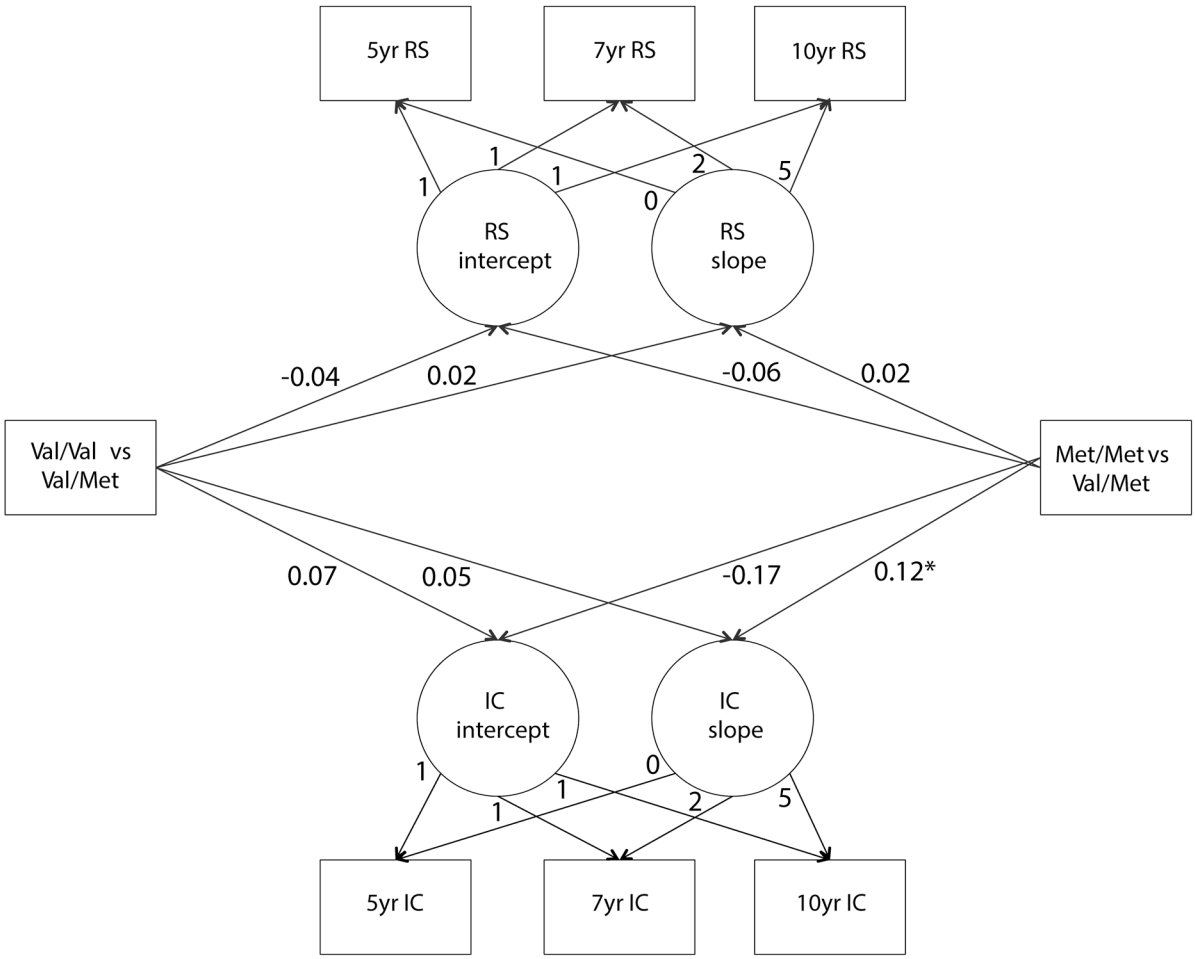

Figure 1.

Conditional latent growth curve model predicting intercept and slope of IC performance and response strategy from COMT genotype. COMT genotype is dummy coded with Val/Met as the reference group. Unstandardized betas are presented. Paths not pictured: covariances between latent variables and between errors of 5 yr IC and 5 yr RS. *$p < .05$.

Table 1.

Statistics at Each Assessment for Children Included in Growth Models of Inhibitory Control.

	5 Year	7 Year	10 Year
Participants (N)	209	169	144
Age (Years)	5.21 (0.30)	7.63 (0.22)	10.27 (0.34)
Sex (Female)	115 (55%)	93 (55%)	78 (54.2%)
Mother's Education Level			
High School Graduate	34 (16.4%)	25 (15.0%)	23 (16.2%)
College Graduate	88 (42.5%)	77 (46.1%)	65 (45.6%)
Graduate Degree	77 (37.2%)	60 (35.9%)	47 (33.1%)
Other	8 (3.9%)	5 (3.0%)	7 (4.9%)
Race			
Caucasian	99 (66.4%)	83 (64.8%)	78 (65.5%)

Note. Data presented as Frequency (%) or Mean (SD). Additionally, it is important to note that FIML estimation was used to account for missing data in the latent growth model.

Table 2.

Demographics for each genotype

	Val/Val N = 36	Val/Met N = 55	Met/Met N = 25
Sex			
Male	16 (13.8%)	22 (19.0%)	12 (10.3%)
Female	20 (17.2%)	33 (28.4%)	13 (11.2%)
Race			
Caucasian	22 (18.9%)	40 (34.5%)	21 (18.1%)
Non-Caucasian	14 (12.1%)	15 (12.9%)	4 (3.4%)
Maternal Education			
High School	6 (5.4%)	7 (6.0%)	4 (3.4%)
College	19 (16.4%)	27 (23.3%)	7 (6.0%)
Graduate School	11 (9.4%)	18 (15.5%)	11 (9.5%)
Unknown	0 (0.0%)	3 (2.6%)	3 (2.6%)

Note. Data presented as Frequency (% of total sample).