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Contributions of COMT Val¹⁵⁸Met to cognitive stability and flexibility in infancy

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Abstract

Adaptive behavior requires focusing on relevant tasks while remaining sensitive to novel information. In adult studies of cognitive control, cognitive stability involves maintaining robust cognitive representations while cognitive flexibility involves updating of representations in response to novel information. Previous adult research has shown that the Met allele of the *COMT* Val¹⁵⁸Met gene is associated with enhanced cognitive stability whereas the Val allele is associated with enhanced cognitive flexibility. Here we propose that the stability/flexibility framework can also be applied to infant research, with stability mapping onto early indices of behavioral regulation and flexibility mapping onto indices of behavioral reactivity. From this perspective, the present study examined whether *COMT* genotype was related to 7-month-old infants' reactivity to novel stimuli and behavioral regulation. Cognitive stability and flexibility were assessed using (1) a motor approach task, (2) a habituation task, and (3) a parental-report measure of temperament. Val carriers were faster to reach for novel toys during the motor approach task and received higher scores on the temperament measure of approach to novelty. Met carriers showed enhanced dishabituation to the novel stimulus during the habituation task and received higher scores on the temperament measures of sustained attention and behavioral regulation. Overall, these results are consistent with adult research suggesting that the Met and Val alleles are associated with increased cognitive stability and flexibility, respectively, and thus suggest that *COMT* genotype may similarly affect cognitive function in infancy.

Introduction

Adaptive behavior requires the ability to maintain stable cognitive representations while remaining sensitive to novel information in order to modify behavior based on changing task contexts (Bilder, Volavka, Lachman & Grace, 2004; Ettinger, Kumari, Collier, Powell, Luzi, Michel, Zedoni & Williams, 2008). These complementary mechanisms, referred to as cognitive stability and flexibility, form the core of cognitive control (Colzato, Waszak, Nieuwenhuis, Posthuma & Hommel, 2010). A balance of stability and flexibility is critical; inflexible cognitive representations and excessive focus contribute to perseverative behaviors, while extreme sensitivity to novel information can lead to distractibility.

impulsivity (Goschke, 2003; Marco-Pallarés, Nager, Krämer, Cunillera, Càmara, Cucurell, Schüle, Schöls, Rodríguez-Fornells & Münte, 2010). Piaget was among the first developmental researchers to recognize that this balance between stability and flexibility is especially important during early development, as infants are faced with a massive amount of novel information that must be integrated to form stable representations of the world. In his terms, stable cognitive structures develop via continual adaptation following novel experiences with the world (Flavell, 1996; Piaget, 1952). Moreover, the availability of basic cognitive processes early in life that allow for both stable goal/task representations as well as flexible responding to novel information provides a foundation for subsequent development of more complex aspects of cognitive control (Mandell & Ward, 2011).

Although the stability/flexibility framework is not typically applied to infant research, doing so may provide a link between the components of cognitive stability and flexibility that are available early in life and more complex cognitive control processes observed among older children and adults. Among adults, cognitive stability has been studied using working memory, response inhibition, sustained attention, and stimulus–response conflict tasks. Conversely, cognitive flexibility has typically been studied using novelty detection, reversal learning, and task-switching paradigms. Developmental studies have utilized similar tasks to assess cognitive stability and flexibility among children and adolescents ranging from ages 2 to 17 (Best & Miller, 2010; Carlson, 2005; M.C. Davidson, Amso, Anderson & Diamond, 2006). Numerous studies have further indicated that these diverse skills comprising cognitive control are mediated by dopamine signaling within frontostriatal networks (Casey, Durston & Fossella, 2001; Casey, Tottenham & Fossella, 2002; Kehagia, Murray & Robbins, 2010; Levy & Wagner, 2011; Robbins & Arnsten, 2009). These studies have shown that prefrontal dopamine signaling is differentially related to cognitive stability and flexibility, with elevated dopamine levels associated with improved performance on measures of stability (Luciana, Depue, Arbisi & Leon, 1992; Müller, von Cramon & Pollmann, 1998; Sawaguchi & Goldman-Rakic, 1991; Watanabe, Kodama & Hikosaka, 1997) and reduced prefrontal dopamine levels linked to improved performance on measures of flexibility (Crofts, Dalley, Collins, Van Denderen, Everitt, Robbins & Roberts, 2001; Kähkönen, Ahveninen, Pekkonen, Kaakkola, Huttunen, Ilmoniemi & Jääskeläinen, 2002; Robbins, 2005; Roberts, De Salvia, Wilkinson, Collins, Muir, Everitt & Robbins, 1994). Together these studies indicate that frontostriatal dopamine signaling contributes to individual differences in cognitive stability and flexibility among children, adolescents, and adults.

Infant researchers have developed tasks to similarly examine components of cognitive control in early development, such as short-term memory and attention/ oculomotor control (e.g. A-not-B and orienting tasks) (Diamond, 1988; Holmboe, Fearon, Csibra, Tucker & Johnson, 2008; Sheese, Rothbart, Posner, White & Fraundorf, 2008). In addition, there is a second body of research that construes early cognitive control as a dynamic balance between reactivity and regulation, based on relatively stable behaviors that reflect both affective responses to novel stimuli and developing regulatory systems that modulate those affective responses (Hane, Fox, Henderson & Marshall, 2008). The cognitive stability/flexibility framework can also be applied to this work, with cognitive flexibility manifested as behavioral reactivity in response to novel stimuli and cognitive stability manifested as the

processes that regulate these behavioral reactions. For example, Rothbart's model of temperament (Rothbart & Derryberry, 1981; Rothbart, Derryberry & Posner, 1994) includes reactivity dimensions based on infants' responses to sensory stimulation, as well as a regulatory dimension that reflects the development of executive attention and inhibitory skills (Derryberry & Rothbart, 1997; Rothbart, 2007). Though this temperament model is not typically described in terms of cognitive stability and flexibility, it incorporates many of the same component processes that are believed to reflect cognitive stability (e.g. executive attention, inhibitory control) and flexibility (e.g. sensitivity to changing sensory stimuli) among adults. Previous work has linked individual differences in infants' and toddlers' reactivity to novel stimuli and subsequent development of inhibitory control and executive attention skills that are typically assessed among adults (Aksan & Kochanska, 2004; Sheese *et al.*, 2008). Similarly, Mandell and Ward (2011) identified response to novelty as a fundamental cognitive process that supports subsequent development of cognitive control. Furthermore, studies of the neural bases of reactivity and behavioral regulation have implicated frontal, striatal, and limbic regions that correspond to those identified in studies of cognitive stability and flexibility in adulthood (R.J. Davidson, 1992; Dawson, 1994; LoBue, Coan, Thrasher & DeLoache, 2011; Posner & Rothbart, 2009; Rothbart, Sheese & Posner, 2007; Whittle, Allen, Lubman & Yucel, 2006; Wolfe & Bell, 2007). This convergence suggests that reactivity and behavioral regulation in infancy may be tightly linked to cognitive stability and flexibility.

Most studies linking cognitive control to frontostriatal dopamine function have utilized animal models, pharmacological studies, or neuroimaging studies. More recently, researchers have utilized genetic methods to examine links between individual differences in adults' cognitive control and normative genetic polymorphisms that affect frontostriatal dopamine signaling. Given that neuroimaging and pharmacological methods are not easily applied to infant research, these genetic methods may be useful in clarifying the relationship between dopamine function and cognitive control in early development. One of the most extensively studied dopaminergic polymorphisms is the *COMT* Val¹⁵⁸Met single nucleotide polymorphism (Dickinson & Elvevag, 2009). This polymorphism affects expression of the COMT enzyme, which catalyzes degradation of dopamine in prefrontal cortex (Mannisto & Kaakkola, 1999). Reduced COMT thus leads to increased levels of synaptic dopamine and corresponding increases in dopamine signaling. For the *COMT* Val¹⁵⁸Met polymorphism, the Met allele is associated with lower levels of enzyme activity and an increase in baseline dopamine levels, whereas the Val allele is associated with increased degradation of dopamine by COMT and reduced baseline levels of dopamine (Chen, Lipska, Halim, Ma, Matsumoto, Melhem, Kolachana, Hyde, Herman, Apud, Egan, Kleinman & Weinberger, 2004; Lachman, Papolos, Saito, Yu, Szumlanski & Weinshilboum, 1996; Weinshilboum, Otterness & Szumlanski, 1999).

Just as dopamine signaling has inverse effects on cognitive stability and flexibility, the Met and Val alleles of the *COMT* polymorphism are differentially linked to cognitive stability and flexibility among adults. Individuals with the Met allele tend to perform better on tasks requiring cognitive stability, demonstrating enhanced working memory and executive attention performance (Barnett, Robbins & Muller, 2007; Bertolino, Blasi, Latorre, Rubino,

Rampino, Sinibaldi, Caforio, Petruzzella, Pizzuti, Scarabino, Nardini, Weinberger & Dallapiccola, 2006; G. Blasi, Mattay, Bertolino, Elvevag, Callicott, Das, Kolachana, Egan, Goldberg & Weinberger, 2005; Caldu, Vendrell, Bartres-Faz, Clemente, Bargallo, Jurado, Serra-Grabulosa & Junque, 2007; Diaz-Asper, Goldberg, Kolachana, Straub, Egan & Weinberger, 2008; Egan, Goldberg, Kolachana, Callicott, Mazzanti, Straub, Goldman & Weinberger, 2001; Fossella, Sommer, Fan, Wu, Swanson, Pfaff & Posner, 2002; Stefanis, van Os, Avramopoulos, Smyrnis, Evdokimidis & Stefanis, 2005). Individuals with the Val allele instead demonstrate enhanced cognitive flexibility, with improved performance on updating tasks, fewer task-switching costs, and augmented neurophysiological responses to novel stimuli (Colzato *et al.*, 2010; Haraldsson, Ettinger, Magnusdottir, Sigmundsson, Sigurdsson, Ingason & Petursson, 2010; Marco-Pallarés *et al.*, 2010; Nolan, Bilder, Lachman & Volavka, 2004). Developmental studies have found similar results among children at 6–18 years of age, with the Met allele and/ or reduced COMT function associated with enhanced performance on working memory, verbal inhibition, and response conflict tasks (Barnett, Herson, Goldman, Jones & Xu, 2009; Diamond, Briand, Fossella & Gehlbach, 2004; Dumontheil, Roggeman, Ziermans, Peyrard-Janvid, Matsson, Kere & Klingberg, 2011). These studies thus provide convergent evidence for a relationship between the *COMT* Val¹⁵⁸Met polymorphisms and individual differences in cognitive control at multiple developmental time points.

Despite this evidence for a role of *COMT* polymorphisms in adult cognitive control, it remains unclear whether *COMT* similarly impacts cognitive stability and flexibility in early development. *COMT* is primarily expressed in prefrontal regions (Sesack, Hawrylak, Matus, Guido & Levey, 1998) and is believed to have a greater impact on cognitive processes mediated by these regions (Diamond *et al.*, 2004). Given that prefrontal cortex follows a protracted developmental course (Gogtay, Giedd, Lusk, Hayashi, Greenstein, Vaituzis, Nugent, Herman, Clasen, Toga, Rapoport & Thompson, 2004), it is possible that *COMT* polymorphisms will have less influence on cognitive processing during infancy. To date, only a handful of studies have addressed this question. All of these studies have identified a relationship between *COMT* and early cognitive processes; however, the direction of effects varies across studies. For example, one study found that 9-month-old infants with the Met/Met genotype showed greater focused attention and reduced distractibility (Holmboe, Fearon, Csibra, Tucker & Johnson, 2010), whereas a second study found that the Val allele was associated with enhanced executive attention among 18–20-month-olds (Voelker, Sheese, Rothbart & Posner, 2009). Studies have also linked *COMT* to measures of cognitive flexibility/ behavioral reactivity, including positive affect (Sheese, Voelker, Posner & Rothbart, 2009) and updating of attention to novel locations (Markant, Cicchetti, Hetzel & Thomas, 2013). Taken together, these results show some consistency with the adult literature, with the Val allele associated with updating and behavioral reactivity and the Met allele associated with executive attention. Nonetheless, the small number of existing studies and their mixed results necessitate further investigation of the relationship between *COMT* genotype and behavioral and temperament measures of early cognitive control.

The present study adopts the cognitive stability/flexibility framework to examine potential links between the *COMT* Val¹⁵⁸Met polymorphism and behavioral reactivity and regulation

among 7-month-old infants. Within the adult literature, novelty detection, responses to novel stimuli, and updating based on novel information are considered indices of cognitive flexibility. Conversely, working memory, sustained attention, and executive attention are considered indices of cognitive stability. We propose that behavioral reactivity in infancy can be viewed as an early index of cognitive flexibility, while behavioral regulation can be viewed as an early index of cognitive stability. In the current study, early cognitive stability and flexibility were examined using multiple measures, including: (1) a motor approach task modeled after Rothbart, Derryberry and Hershey (2000) that measures infants' motor reactivity to novel toys, and (2) the Infant Behavior Questionnaire (IBQ; Gartstein & Rothbart, 2003) which provided parental ratings of infants' sustained attention (behavioral regulation) and their propensity to approach novel and/or exciting stimuli (behavioral reactivity).

In addition to these measures, we included a classic measure of learning and memory during infancy, the habituation–dishabituation task. In standard habituation tasks, infants view repeated presentations of a single stimulus, followed by presentation of the same habituation stimulus and a novel stimulus. Infants typically show recovery of interest/attention to the novel stimulus (i.e. dishabituation). Many models of infant habituation conceptualize the underlying mechanism as a comparative process in which the novel stimulus is compared to the existing representation of the familiar habituation stimulus, with a greater discrepancy leading to a stronger dishabituation response (see Kavšek, 2012, for review). Thus, based on these models, the ability to develop and maintain a representation of the familiarized stimulus is critical to evoke subsequent dishabituation to novel stimuli. Among adults, the ability to maintain and/or manipulate cognitive representations over time (i.e. working memory) is an index of cognitive stability (Bertolino *et al.*, 2006; Diaz-Asper *et al.*, 2008; Egan *et al.*, 2001). Thus, it is possible that the habituation–dishabituation task may similarly reflect early cognitive stability during infancy. Alternatively, it is possible that infants' responses on this task may reflect individual differences in sensitivity to novelty, with stronger dishabituation responses among infants who are more attuned to novel stimuli.

In sum, the present study comprises two primary measures of early cognitive flexibility (motor approach to novel toys and parental ratings of infants' propensity to approach novel stimuli in daily life), one primary measure of early cognitive stability (parental ratings of sustained attention and behavioral regulation) and a traditional measure of basic learning during infancy (habituation–dishabituation responses). As discussed earlier, the adult literature has consistently linked the Met allele to greater stability of cognitive representations and the Val allele to increased updating in response to novelty. To preview, the present results show a high degree of consistency with the adult literature, as infants with the Met/Met genotype show stronger dishabituation responses and higher parental ratings of sustained attention and behavioral regulation, whereas Val carriers show greater reactivity to novel toys in the motor approach task and higher parental ratings of reactivity to novelty in daily life.

General methods

Participants

Ninety-seven 7-month-old infants (48 M, 49 F; $M_{Age} = 7$ months, 1 day; range = 6 months, 23 days–7 months, 9 days) participated in a single test session as part of a larger study of attention development. Based on parental report, 89.47% of participants were Caucasian, 1.05% were African-American, 5.26% were Asian, and 4.21% were Other/Unknown. Infants were excluded from the study if they had been born early (< 37 weeks gestation), had low birth weight (< 5 lb), or had any history of serious health problems. All families received an infant T-shirt as a thank-you for participating.

Behavioral measures

The test session included three behavioral tasks: a spatial cueing task, a motor approach task, and a habituation–dishabituation task. Each infant completed the behavioral tasks in a fixed order, with the spatial cueing task first, the motor approach task second, and the habituation–dishabituation task last. The tasks were presented in a fixed order because analyses for the spatial cueing task required the greatest number of trials and we anticipated that infants' energy/interest would decline over the entire test session. Main findings from the spatial cueing task have been reported in a separate manuscript (Markant, Cicchetti, Hetzel & Thomas, 2013) and will not be discussed here. However, infants' reaction times from this task were used as a baseline measure of reaction time for analyses of the two subsequent behavioral tasks (the motor approach and habituation–dishabituation tasks) in order to control for individual differences in reaction time. In addition to these behavioral tasks, parents completed the revised version of the Infant Behavior Questionnaire (Gartstein & Rothbart, 2003).

Materials—The spatial cueing and habituation–dishabituation tasks were presented on a 42" Magnavox LCD screen. Computerized stimuli were presented using Macromedia Director MX 2004. Infants sat on their parent's lap about 122 cm from the screen. A digital video camera with infrared night vision (Sony DCR-SR45) was placed on the table below the screen to record infants' head and eye movement responses. The video camera provided live feed to the experimenter's monitor, which was used for online data coding. The video output was also burned to DVD using a Sony Video Cassette/DVD recorder (RDR-VX560) for subsequent offline coding.

Spatial cueing task

A more detailed description of the design and procedure for the spatial cueing task can be found in Markant *et al.*, 2013. In this task, infants oriented from a central fixation stimulus to one of two peripheral targets, yielding a measure of overall orienting reaction time.

Materials—Task stimuli included a central fixation, a peripheral cue, and a target shape. The central fixation was a blue cross that loomed in and out to maintain infants' interest. The cue was a yellow ring and the targets were identical green hearts presented as static images. Cue and target stimuli were presented 18° to the left or right of the fixation.

Procedure—Each trial began with presentation of the central fixation. After 1000 ms, the cue appeared on the left or right side for 100 ms. Following a variable delay (33 or 600 ms), the targets simultaneously appeared on both the left and right sides. The fixation remained visible through the cue presentation and subsequent delay and disappeared at target onset. The targets remained visible up to 1500 ms or until the infant looked away for more than 500 ms.

The experimenter monitored the infant's eye movements and indicated when the infant was looking center, left, right, or away from the screen. The experimenter was kept blind to all stimuli. Trials were scored as invalid if the infant looked away before target onset or if the infant failed to look at a target within the 1500 ms time window. Invalid trials were replaced to maximize the amount of usable data from each infant. Trials continued until the infant became too fussy to continue or completed a maximum of 48 valid trials.

Data Processing—Videos were coded offline for the timing and direction (e.g. center, left, right, or away) of each eye movement. These coded data were used to compute the latency of the infant's first look following target onset. In most cases, additional trials were excluded after this more accurate offline coding. Individual trials were discarded if the infant looked away before looking at a target ($M = 28\%$, $SD = 13.4\%$), if the infant looked at the cue/broke fixation from the central fixation prior to target onset ($M = 8.6\%$, $SD = 7.8\%$), or if the infant never oriented to a target ($M = 1.1\%$, $SD = 2.7\%$). Trials were further filtered to exclude those with latencies that were less than 200 ms or greater than 2 SD above the individual mean. Latency values were averaged to determine each infant's mean reaction time to the peripheral targets. Approximately half of the videos were coded for reliability; all latency measures were highly reliable ($r = .95$, $p < .001$).

Motor approach task

Materials—Infants were seated in a highchair with an attached 12" × 24" tray. Parents sat behind the highchair and were asked to avoid interacting with their child. An opaque curtain separated the infant and the experimenter and the surrounding walls were covered in the same opaque fabric to limit distraction. The experimenter presented toys through a small opening (12" × 18") in the curtain. Infants' responses were recorded using the digital video camera placed on a table in front of the highchair. The video camera output was burned to DVD for subsequent offline coding.

Stimuli consisted of the four toys presented in Figure 1. Two of these toys were considered typical toys, as we assumed that they would likely be relatively familiar to the infants. Two additional toys were constructed in the lab to be relatively novel to the infants. All four toys made a rattling or clanking noise when shaken.

Procedure—The task consisted of four trials, with one toy presented on each trial. The two typical toys were always presented first to allow the infants a 'warm-up' period before interacting with the novel toys. Thus the typical toys were presented in the first two trials and the novel toys were presented in the last two trials. Within these categories, presentation order for the specific toy was counterbalanced. At the beginning of each trial, the experimenter shook the toy to attract the infants' attention and placed it in the center of the

tray. Infants were given one minute to reach for and examine each toy. Infants did not have any interaction with the experimenter or their caregiver before they touched the toy for the first time.

Data coding and processing—The first 30 seconds of each toy presentation were coded offline to determine infants' latencies to grasp the toy for the first time. The beginning of each trial was identified as the time at which the toy made contact with the tray. Trained coders scored the time at which the infant made his/her first contact with the toy and computed the infant's latency to approach each toy. Latencies to approach each toy were standardized based on individual infants' overall mean approach latency. Mean standardized latencies were computed for the typical and novel toy categories.

Habituation–dishabituation task

Materials—Two smiling, Caucasian female faces were selected from the MacBrain Face Stimulus Set (Tottenham, 1998). The two faces were selected to be as dissimilar as possible. One face (MacBrain Stimulus #07_HA_O) had short brown hair, brown eyes, a round face, and a rosy complexion. The second face (MacBrain Stimulus #10_HA_O) had long blond hair, hazel eyes, an oval face, and a fair complexion. The faces were 30 cm² and were presented on a black background. One face served as the habituation stimulus and the second face served as the novel stimulus during the subsequent test phase. Habituation and test faces were counterbalanced across infants.

Procedure

Habituation: During habituation trials, the habituation face was presented for up to 15 seconds or until the infant looked away for more than 1000 ms. An attention-getter stimulus was presented between trials to reorient infant's attention to the center of the screen. Throughout the task, the experimenter viewed the live video-feed and used key presses to indicate when the infant was looking at or away from the screen. The experimenter was blind to all stimulus presentations. The computer program used the experimenter's key presses to calculate the cumulative duration of time the infant looked at the screen and away from the screen.

The habituation criterion was based on a sliding window design. Habituation was achieved when the infant's average look duration over three consecutive trials was less than 50% of the average look duration for the first three trials of the experiment. Infants were allowed a maximum of 21 trials to reach habituation.

Dishabituation: The test phase began when the infant reached the habituation criterion. During the test phase there were three familiar test trials in which the now-familiar habituation face was presented and three novel test trials in which the novel face was presented. Trial order (familiar vs. novel) was randomized across infants. Trials lasted up to 10 seconds or until the infant looked away for more than 1000 ms. As before, the experimenter (blind to all stimuli) indicated when the infant was looking at the screen and the computer program calculated the cumulative looking time to each test face.

Data coding and processing—Videos were coded offline to confirm the infants' cumulative look durations for every habituation and test trial. All measures of look duration were highly reliable across the raw data output and the coded data ($r = .97, p < .001$). The coded data were used to determine each infant's mean looking time during habituation trials as well as their total cumulative looking time across the habituation phase. For the test phase, total cumulative looking times were computed separately for the novel and familiar test faces.

Infant Behavior Questionnaire—The revised version of the Infant Behavior Questionnaire (Gartstein & Rothbart, 2003) was sent to parents at the time of recruitment (typically 1–2 weeks prior to their appointment). Parents completed the questionnaire and returned it at the test session. The questionnaire asks parents to rate the frequency of specific behaviors displayed by their infant over the week prior to the time the questionnaire was completed. Three temperament factors were examined, Surgency/Extraversion, Negative Affect, and Orientation/Regulation. These scores were obtained by averaging scores for the subscales that load most heavily on that factor, as determined by Gartstein and Rothbart (2003). The Surgency/Extraversion factor was based on the Approach, Vocal Reactivity, High Intensity Pleasure, Smiling and Laughter, Activity, and Perceptual Sensitivity scales. The Negative Affect factor was based on the Sadness, Distress to Limitations, Fear, and Falling Reactivity (reverse scored) scales. Finally, the Orientation/Regulation factor was based on the Low Intensity Pleasure, Cuddliness, Duration of Orienting, and Soothability scales. In addition to these three factors, we also examined the Duration of Orienting and Approach subscales, based on a priori hypotheses that these dimensions may be related to cognitive control and/or processing of novel information.

Genotyping

Procedure—DNA samples were collected from participants using the BuccalAmp DNA Extraction Kit (BQ0901SCR, EpiCentre) per kit instructions. The DNA containing solution was then diluted to a working concentration for genotype testing. The *COMT* Val¹⁵⁸Met (rs4680) SNP was genotyped using the TaqMan SNP Genotyping Assay C__25746809_50 (Applied Biosystems). Assay specific reagents were combined with TaqMan Genotyping Master Mix (4371353, Applied Biosystems) and amplified per kit instructions followed by end-point fluorescence detection on a Tecan M200 with allelic determinations made using JMP 8.0 (SAS). All DNA samples were genotyped in duplicate for quality control. DNA from cell lines was purchased from Coriell Cell Repositories for all representative genotypes in duplicate. Genotypes were confirmed by sequencing using DTCS chemistry on an ABI 3130x1.

Results

Distribution of genetic variants

Seven of the buccal cell samples became contaminated before genotyping was complete; five of these samples were re-collected when the infants were approximately 12 months old. Thus, genetic data were obtained from a final sample of 95 infants. All 95 samples were successfully genotyped for the *COMT* Val¹⁵⁸Met SNP; 23 infants (24.2%) had the Met/Met

genotype, 49 infants (51.6%) had the Val/Met genotype, and 23 infants (24.2%) had the Val/Val genotype. This allele distribution was consistent with expected frequencies derived from the Hardy-Weinberg equilibrium ($\chi^2(2) = 0.095, p = .954$).

Spatial cueing task

Primary results from the spatial cueing task have been reported in a separate manuscript (Markant *et al.*, 2013) and will not be detailed here. However, one result relevant to the present study was a main effect of *COMT* genotype on mean orienting reaction time (RT). Specifically, Met/Met infants showed slower orienting reaction times ($M = 584.39$ ms, $SD = 97.98$ ms) compared to infants with the Met/Val ($M = 529.27$ ms, $SD = 529.27$ ms) and Val/Val genotypes ($M = 554.26$ ms; $SD = 71.64$ ms). This difference in orienting RT may reflect basic differences in speed of processing. As such, this orienting RT measure was utilized as a covariate in analyses of the subsequent behavioral tasks in order to control for individual differences in baseline reaction time.

Motor approach task

The motor approach task examined whether infants with the Val allele showed increased motor reactivity to novel toys relative to typical toys. One infant (Val/Val) was excluded because she became fussy and did not complete all trials; data from three infants (Met/Val = 2, Val/Val = 1) could not be coded due to technical errors. One infant (Met/Val) was also excluded because his mean latency was greater than 3 *SD* above the group mean and two additional infants (Met/Val, Val/Val) were residual outliers and were excluded to preserve model assumptions. These attrition rates were not related to any of the IBQ measures of temperament. All analyses of approach latencies were based on the remaining sample of 88 infants (Met/Met = 23, Met/Val = 45, Val/Val = 20).

Genetic effects—We first examined whether the genotype groups showed differences in approach latencies to the toy that was presented on the first trial. Standardized approach latencies to the first toy were entered into an ANCOVA with genotype as a between-subjects factor and mean orienting RT as the covariate. Results indicated a trend-level difference in initial approach latencies across genotypes ($F(2, 80) = 2.21, p = .116$); however, follow-up paired comparisons indicated no reliable differences in approach latencies to the first toy ($M_{Met/Met} = 2.28$ s, $SD = 1.96$ s, $M_{Met/Val} = 3.73$ s, $SD = 6.18$ s, $M_{Val/Val} = 3.71$ s, $SD = 4.77$ s).

We next examined whether approach latencies to the typical versus novel toys differed across genotype groups. Standardized approach latencies to the typical and novel toys were entered into a 2 (typical vs. novel toys) $\times$ 3 (*COMT* genotype) ANCOVA with mean orienting RT as the covariate. Results indicated a significant Toy category $\times$ Genotype interaction ($F(2, 82) = 3.32, p = .041$; Figure 1). Follow-up analyses indicated that the Val/Val group showed a significant approach bias for the novel toys ($M_{Typical} = 3.03$ s, $SD = 2.54$ s, $M_{Novel} = 1.77$ s, $SD = 0.98$ s; $t(19) = 2.93, p = .009$). A similar novelty preference was also evident within the Met/Val genotype ($M_{Typical} = 3.10$ s, $SD = 3.43$ s, $M_{Novel} = 2.18$ s, $SD = 4.58$ s; $t(44) = 2.48, p = .017$). In contrast, within the Met/Met group there was no

difference in response times to the novel ($M = 2.55$ s, $SD = 2.76$ s) versus typical toys ($M = 2.17$ s, $SD = 1.42$ s; $t(22) = -0.30$, $p = .767$).

Additional analyses indicated a significant effect of genotype on standardized approach latencies to the typical toys ($F(2, 82) = 3.62$, $p = .031$). Met/Val infants showed slower responses to the typical toys ($M = 3.10$ s, $SD = 3.43$ s) compared to infants with the Met/Met genotype ($M = 2.55$ s, $SD = 2.76$ s; $F(1, 63) = 4.74$, $p = .033$). Infants with the Val/Val genotype were similarly slower to approach the typical toys ($M = 3.03$ s, $SD = 2.54$ s) relative to the Met/Met infants ($F(1, 40) = 6.46$, $p = .015$). There was also a marginally significant effect of genotype on standardized approach latencies to the novel toys ($F(2, 82) = 2.94$, $p = .059$). However, in this case, infants with the Met/Val and Val/Val genotypes were faster to approach the novel toys ($M_{Met/Val} = 2.18$ s, $SD = 2.58$ s; $M_{Val/Val} = 1.77$ s, $SD = 0.98$ s) relative to the Met/Met infants ($M = 2.17$ s, $SD = 1.42$ s; $F_{Met/Val}(1, 63) = 4.18$, $p = .045$; $F_{Val/Val}(1, 40) = 5.28$, $p = .027$).

These parametric analyses were confirmed by examining the proportion of infants who showed faster responses to the novel toys relative to the typical toys. Within the Met/Val group, the proportion of infants who showed faster responses to the novel toys ($N = 31$, 68.9%) was significantly above chance (i.e. 50%; $\chi^2(1) = 6.42$, $p = .011$; Figure 2B). A similar pattern was evident within the Val/Val group, with 15 infants (75%) showing faster responses to the novel toys ($\chi^2(1) = 5.0$, $p = .025$). In contrast, the proportion of infants in the Met/Met group who showed faster responses to the novel toys ($N = 13$, 56.5%) was at chance ($\chi^2(1) = 0.39$, $p = .532$). Thus, Val carriers showed faster approach latencies to the novel toys relative to the typical toys, whereas the Met/Met infants did not show a response bias to either the novel or typical toys.

Habituation–dishabituation task

The habituation–dishabituation task examined whether the Met and Val alleles were associated with differential discrimination between the novel and familiar stimuli. Thirteen infants (Met/Met = 5, Met/Val = 6, Val/Val = 2) became fussy during testing and did not complete the entire task. Of the remaining sample, 10 infants (Met/Met = 1, Met/Val = 5, Val/Val = 4) were excluded because they failed to habituate within the criterion of 21 trials. These attrition rates were not related to any of the IBQ measures of temperament. An additional four infants (Met/Met = 1, Met/Val = 2, Val/Val = 1) were excluded due to technical errors and one infant (Met/Val) did not complete the task because her mother became ill during testing. All analyses involving data from this task were based on the remaining sample of 67 infants (Met/Met = 16, Met/Val = 35, Val/Val = 16).

On average, infants required 11.6 trials ($SD = 4.8$ trials) and a total cumulative looking time of 79.78 s ($SD = 46.84$ s) to reach the habituation criterion. The number of trials needed to reach habituation criterion and total cumulative looking time during habituation were correlated with infants' total looking times at test ($r_{Trials} = 0.31$, $p = .01$; $r_{Total\ Hab\ Time} = 0.41$, $p = .001$). Thus, infants who experienced a more prolonged habituation phase showed longer looks at test. However, these habituation variables were not related to the extent to which infants dishabituated at test.

Genetic effects—Results of a one-way MANCOVA with genotype as the between-subjects factor and mean orienting RT as the covariate showed no differences in average or total looking times during habituation. There was a numerical trend for Val carriers to require fewer habituation trials ($M_{Met/Met} = 13.7$ trials, $SD = 5.5$; $M_{Met/Val} = 11.1$ trials, $SD = 4.5$; $M_{Val/Val} = 10.9$ trials, $SD = 3.9$); however, this difference was not significant ($F(2, 66) = 1.99, p = .145$).

COMT effects on the extent of infants' dishabituation to the novel test face were examined by entering total looking times at test into a 2 (trial type: novel vs. familiar face) $\times$ 3 (genotype) ANCOVA with mean orienting RT as a covariate. Results indicated a main effect of trial type ($F(1, 61) = 4.18, p = .045$), indicating that infants spent more time looking at the novel face ($M = 14.79$ s, $SD = 5.86$ s) compared to the familiar face ($M = 12.61$ s, $SD = 5.69$ s). In addition, there was a significant trial type $\times$ genotype interaction ($F(2, 62) = 3.31, p = .043$; Figure 3A). Follow-up comparisons indicated that the Met/Met group showed a significant preference for the novel face ($M_{Familiar} = 11.17$ s, $SD = 3.84$ s, $M_{Novel} = 15.46$ s, $SD = 5.12$ s; $t(15) = 3.58, p = .003$). A similar novelty preference was also evident within the Met/Val genotype ($M_{Familiar} = 11.82$ s, $SD = 5.89$ s, $M_{Novel} = 14.14$ s, $SD = 6.01$ s; $t(34) = 2.6, p = .014$). However, the Val/Val group showed no difference in total looking times to the familiar ($M = 15.29$ s; $SD = 6.3$ s) and novel test items ($M = 15.34$ s, $SD = 6.29$ s; $t(15) = 0.04, p = .966$).

These parametric analyses were again confirmed by determining the proportion of infants in each genotype group who showed preferential looking to the novel face (Figure 3B). The proportion of infants who showed preferential looking to the novel face was above chance in both the Met/Met ($N = 12, 75\%$; $\chi^2(1) = 4.0, p = .046$) and the Met/Val group ($N = 23, 65.7\%$; $\chi^2(1) = 3.46, p = .063$). In contrast, the proportion of Val/Val infants who showed preferential looking to the novel face was at chance ($N = 8, 50\%$; $\chi^2(1) < 0.001, p = 1.0$). Thus, while Met carriers showed dishabituation in response to the novel test item, infants with the Val/Val genotype did not show preferential looking to the novel face.

While there was no difference in overall looking times at test across genotype groups, there was a trend level main effect of genotype on looking times to the familiar face ($F(1, 62) = 2.78, p = .067$), with the Val/Val group ($M = 15.29$ s; $SD = 6.3$ s) showing longer looking times to the familiar face relative to both the Met/Met ($M = 11.17$ s, $SD = 3.84$ s; $t(30) = 2.23, p = .033$) and the Met/Val genotype groups ($M = 12.03$ s, $SD = 5.85$ s; $t(49) = 1.91, p = .062$). In contrast, there were no differences in looking times to the novel face across genotype groups. Taken together, these results suggest that the lack of dishabituation among infants with the Val/Val genotype reflected their maintained interest in the familiar test item.

Infant Behavior Questionnaire

The IBQ measures were examined to determine whether *COMT* genotype was differentially related to measures of behavioral regulation (i.e. Orientation/Regulation, Duration of Orienting) versus measures of behavioral reactivity (i.e. Surgency/Extraversion, Approach). IBQ scores were not available for seven infants (Met/Met = 1, Met/Val = 5, Val/Val = 1) because their parents did not return the questionnaire. All analyses involving IBQ scores were based on a sample of 88 infants (Met/Met = 22, Met/Val = 44, Val/Val = 22).

Genetic effects—Scores for each of the three primary factors (Surgency/ Extraversion, Negative Affect, and Orientation/Regulation) were entered into a one-way MANOVA with genotype as the between-subjects factor. There were no effects of *COMT* on Surgency or Negative Affect. However, there was a marginal effect of genotype on the Orientation/Regulation factor ($F(2, 85) = 2.98, p = .056$; Figure 4). Follow-up analyses showed that the Val/ Val genotype group received lower scores for Orientation/Regulation ($M = 4.24, SD = 0.47$) compared to the Met/Met ($M = 4.56, SD = 0.4; t(42) = 2.41, p = .02$) or Met/Val groups ($M = 4.50, SD = .50; t(64) = 2.0, p = .05$). Orientation/Regulation scores did not differ across the Met/Met and Met/Val groups.

A second one-way MANOVA was conducted with scores from the Duration of Orienting and Approach subscales. Results indicated a significant main effect of genotype on Duration of Orienting scores ($F(2, 85) = 4.91, p = .01$; Figure 5A). There was no difference in Duration of Orienting scores across the Met/Met ($M = 4.01, SD = .59$) and the Met/Val groups ($M = 3.71, SD = .92; t(59) = 1.57, p = .12$). However, the Val/Val group received lower scores on the Duration of Orienting scale ($M = 3.25, SD = 0.77$) compared to both the Met/Met ($t(42) = 3.65, p = .001$) and the Met/Val groups ($t(64) = 2.03, p = .046$). There was no significant main effect of genotype on Approach scores ($F(2, 85) = 2.06, p = .134$; Figure 5B); however, paired comparisons indicated that Met/Met infants received significantly lower Approach scores ($M = 4.18, SD = 0.45$) compared to Met/Val infants ($M = 4.43, SD = 0.43; t(64) = 7\text{minus}; 2.17, p = .034$). There was no difference in Approach scores across infants with the Val/Val group ($M = 4.40, SD = 0.58$) and those with the Met/Met ($t(42) = -1.35, p = .185$) or Met/ Val genotypes ($t(64) = 0.29, p = .769$).

Correlations across behavioral measures

For the purpose of examining possible correlations across the behavioral measures used in this study, we limited the sample to include only infants who provided usable data for all three measures ($n = 58$). There were no significant correlations between the motor approach task and the habituation/dishabituation task. There was a significant correlation between infants' latency to approach the typical toys and their scores on the Negative Affect factor of the IBQ ($r(58) = .26, p = .046$), indicating that infants who were slowest to approach the typical toys tended to score higher on Negative Affect. The Negative Affect factor was also correlated with infants' looking times to the novel face during the habituation/dishabituation task ($r(58) = .26, p = .049$). In addition, infants' scores on the Approach subscale of the IBQ were positively correlated with their looking times to the familiar face during the test phase of the dishabituation task ($r(53) = .25, p = .067$). However, IBQ scores were not related to differential responding to familiar versus novel items on either the motor approach or dishabituation tasks.

Discussion

In the present study, the *COMT* Val¹⁵⁸Met polymorphism was related to individual differences in 7-month-old infants' responses across multiple measures of cognitive flexibility/ behavioral reactivity and cognitive stability/behavioral regulation. Specifically, the Val allele was associated with measures of cognitive flexibility/ reactivity, including

more rapid approach to novel toys and higher scores on the Approach temperament dimension, which indexes rapid approach and/or positive anticipation of novel or enjoyable activities. Conversely, the Met allele was associated with measures of cognitive stability/regulation, including stronger dishabituation responses, higher scores on the Duration of Orienting temperament dimension, which indexes infants' sustained attention to a single stimulus, and higher scores on the Orientation/Regulation temperament factor, which is believed to be a precursor to later-developing self-regulation and executive control (Rothbart *et al.*, 2007). Together, these results suggest that the Val allele is associated with an enhanced tendency to readily respond to and approach novel information whereas the Met allele is associated with enhanced sustained attention and behavioral regulation. As noted, the adult literature has similarly related the Met allele to measures of cognitive stability (e.g. sustained attention, working memory, and response inhibition) and the Val allele to measures of cognitive flexibility (e.g. updating based on novel information). The present results thus suggest that *COMT* genotype may be similarly related to early indices of cognitive stability and flexibility even at 7 months of age.

Although the Val allele was linked to more robust responses to novelty in all other measures, infants with the Val/Val genotype showed the weakest dishabituation in the habituation task. This lack of dishabituation may reflect reduced efficacy in maintaining a robust representation of the familiar stimulus over time. Habituation involves mechanisms that construct and maintain a representation of the habituation stimulus over the course of repeated exposures. As this representation becomes more detailed, the discrepancy between these familiar and novel stimulus features becomes more apparent, allowing for a strong dishabituation response when the novel stimulus is introduced (Colombo & Mitchell, 2009; Sokolov, 1963). Maintaining a robust representation of the familiar stimulus is thus crucial to elicit dishabituation to novel stimuli. Among adults, this ability (i.e. working memory) has consistently been linked to the Met allele (Bertolino *et al.*, 2006; Diaz-Asper *et al.*, 2008; Egan *et al.*, 2001). In the present study the Met/Met infants may have more effectively maintained a robust representation of the familiar face, which in turn supported enhanced discrimination of the novel and familiar items at test. Conversely, Val/Val infants may have engaged in more frequent updating of the face representation. Recent adult studies suggest that individuals with reduced or imbalanced prefrontal dopamine signaling update working memory representations after any sensory change, regardless of its task relevance (Garcia-Garcia, Barcelo, Clemente & Escera, 2010, 2011). In other words, robust cognitive flexibility may contribute to frequent updating of representations even when updating is not necessary. Extending this to the present data, it is possible that the Val/Val infants updated the face representation each time the face changed, resulting in reduced discrimination between the novel and familiar faces.

The present results are consistent with the existing adult literature linking the Met allele to a bias towards cognitive stability and the Val allele to a bias towards cognitive flexibility. Nonetheless, it is important to consider alternative interpretations of the data. For example, the robust dishabituation among the Met/Met infants may reflect a greater sensitivity to novelty among those infants relative to Val carriers. This seems less likely given that the differential dishabituation across genotype groups was driven by the looking times to the

familiar face while looking times to the novel face were the same across groups; however, this ‘novelty-seeking’ interpretation cannot be fully ruled out. Similarly, in the motor approach task, it is possible that the Met/Met infants approached the toys more readily at the beginning of the task than the Val carriers, leading to a greater differential between the typical and novel toys within the Val genotype groups. Nonetheless, the Met/Met response times in the task were remarkably consistent across all four trials relative to Val carriers. Given that this study is among the first to relate *COMT* genotype to cognitive stability and flexibility in infancy, additional work will be necessary to definitively tease apart these possible interpretations.

Interestingly, the behavioral and parental report measures used in this study were not strongly correlated, suggesting that *COMT* may be broadly related to early indices of cognitive control even though the specific measures used to assess early cognitive stability/flexibility may not be tightly linked. Furthermore, though the behavioral measures were not correlated in this study, the direction of *COMT* effects provides a coherent picture in which the Val allele is associated with an increased readiness to approach novel information, while the Met allele is associated with robust sustained attention, and potentially with a more robust representation of the familiar stimulus during the dishabituation task. These results suggest that it will be important for future studies to utilize a wide range of measures in order to develop a complete understanding of the relationships between *COMT* genotype and specific mechanisms involved in cognitive stability and flexibility early in development.

More broadly, the present results have important implications for our understanding of the development of prefrontal cortex. *COMT* polymorphisms typically have a greater selective effect on activity in prefrontal cortex (Diamond *et al.*, 2004) since the COMT enzyme serves as the primary mechanism for dopamine degradation in this region (Sesack *et al.*, 1998). In addition, many components of cognitive stability/behavioral regulation and cognitive flexibility/behavioral reactivity are mediated by frontostriatal networks (Casey *et al.*, 2001; Guyer, Nelson, Perez-Edgar, Hardin, Roberson-Nay, Monk, Bjork, Henderson, Pine, Fox & Ernst, 2006; Kehagia *et al.*, 2010; Levy & Wagner, 2011; LoBue *et al.*, 2011; Posner & Rothbart, 2009). The present evidence linking *COMT* to early indices of cognitive stability and flexibility among 7-month-old infants suggests that prefrontal regions may be more functional at this early age than previously thought. This is consistent with physiological studies showing behaviorally relevant activity in prefrontal regions during infancy (A. Blasi, Mercure, Lloyd-Fox, Thomson, Brammer, Sauter, Deeley, Barker, Renvall, Deoni, Gasston, Williams, Johnson, Simmons & Murphy, 2011; Grossmann & Johnson, 2010; Grossmann, Parise & Friederici, 2010; Nakano, Watanabe, Homae & Taga, 2009). Of course, the tasks used with infants are quite different from the more nuanced tasks used with adults. While adult tasks target specific components of cognitive control, the measures utilized in the present study may index more general aspects of cognitive stability and flexibility that provide a foundation for subsequent development of complex cognitive control. Thus, while the present results implicate *COMT* and prefrontal cortex activity in cognitive stability and flexibility, the prolonged development of prefrontal cortex no doubt contributes to the emergence of much more complex aspects of cognitive control.

The present results are consistent with some of the previous studies that have examined the *COMT* genotype in infancy. Similar to the present study, Holmboe *et al.* (2010) found that 9-month-olds with a Met allele showed greater sustained attention and reduced distractibility. In addition, Markant *et al.* (2013) found that the Val allele was associated with more rapid orienting and increased attention updating to novel locations, which is consistent with the increased reactivity observed in the present study. However, the present results diverge from other studies that found a relationship between *COMT* and positive reactivity (Sheese *et al.*, 2009) and a relationship between the Val allele and early executive attention among 18–20-month-olds (Voelker *et al.*, 2009). These differences may be due to the older age group and specific task used in Voelker *et al.* (2009) and the relatively small sample size available in the Sheese *et al.* (2009) study ($N_{Met/Met} = 10$; $N_{Met/Val} = 19$; $N_{Val/Val} = 7$). Despite these differences, all of these studies collectively highlight a role of *COMT* in individual differences in cognitive processing during infancy.

Given the small number of existing studies examining genetic polymorphisms in infancy, it will be critical to further examine the impact of *COMT* genotype on behavioral reactivity/regulation and early indices of cognitive stability/flexibility. In particular, it will be important to utilize a wider range of measures that further target the multiple cognitive processes contributing to cognitive stability and flexibility. For example, the results of the habituation task in the present study suggest that *COMT* may be related to individual differences in infants' ability to maintain representations of familiar stimuli, which is akin to working memory. In future studies it may be possible to more specifically target links between *COMT* and early working memory processes using a change detection paradigm (Ross-Sheehy, Oakes & Luck, 2003). Similarly, there are several behavioral tasks developed to assess early temperamental reactivity and regulation, such as the Lab-TAB assessment tool (Gagne, Van Hulle, Aksan, Essex & Goldsmith, 2011). In addition to using a broader range of behavioral measures, it will also be revealing to examine interactions between *COMT* and other genetic polymorphisms. Given the role of frontostriatal networks in cognitive control, it will likely be especially fruitful to examine genetic polymorphisms that affect dopamine signaling within these networks. Several recent studies have highlighted the potential importance of these interactions for cognitive control in adulthood (Cools & D'Esposito, 2011; Cools, Miyakawa, Sheridan & D'Esposito, 2010; Garcia-Garcia *et al.*, 2011), suggesting that these gene-gene interactions may similarly play a role in driving cognitive stability and flexibility early in development.

Despite the mixed results across studies of *COMT* effects in infancy, the present results are quite consistent with the existing adult literature. As in adults, the Val allele of the *COMT* Val¹⁵⁸Met polymorphism was related to greater cognitive flexibility (i.e. motor reactivity/approach behaviors), whereas the Met allele was associated with enhanced cognitive stability (i.e. robust dishabituation, sustained attention, and behavioral regulation). Though cognitive control clearly undergoes substantial development over time, this convergence across infancy and adulthood suggests the intriguing possibility that core processes mediating cognitive stability and flexibility may be available as early as 7 months of age. Future studies in this vein will clarify the mixed results that are currently available, allow for a more meaningful comparison of *COMT* effects during infancy and adulthood, and provide

a foundation to investigate how changes in the dopamine system early in life affect the development of cognitive control.

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Figure 1.
Pictures of the typical (A) and novel (B) toys used in the motor approach task.

Figure 2.

(A) Latency to approach typical vs. novel toys based on COMT genotype. (B) Proportion of infants who were faster to approach the novel toys relative to the typical toys.

Figure 3.

(A) Total looking time to the familiar and novel test items based on COMT genotype. (B) Proportion of infants who showed preferential looking to the novel face.

Figure 4.
Mean parental rating on the Orientation/Regulation factor of the Infant Behavior Questionnaire – R.

Figure 5.
Mean parental rating on the Duration of Orienting (A) and Approach (B) subscales of the Infant Behavior Questionnaire – R.