Catechol *O*-Methyltransferase Val[158]Met Polymorphism is Associated with Cognitive Performance in Nondemented Adults

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Abstract

■ The catechol *O*-methyltransferase (COMT) gene is essential in the metabolic degradation of dopamine in the prefrontal cortex. In the present study, we examined the effect of a Val[158]Met polymorphism in the COMT gene on individual differences and changes in cognition (executive functions and visuospatial ability) in adulthood and old age. The participants were 292 nondemented men (initially aged 35–85 years) from a random sample of the population (i.e., the Betula study) tested at two occasions with a 5-year interval. Confirmatory factor analyses were used to test the underlying structure of three indicators of executive functions (verbal fluency, working memory, and Tower of Hanoi). Associations between COMT, age, executive functioning, and visuospatial (block design) tasks were examined using repeated-measures analyses of variance. Carriers of the Val allele (with higher enzyme activity) compared with carriers of the Met/Met genotype (with low enzyme activity) performed worse on executive functioning and visuospatial tasks. Individuals with the Val/Val genotype declined in executive functioning over the 5-year period, whereas carriers of the Met allele remained stable in performance. An Age × COMT interaction for visuospatial ability located the effect for middle-aged men only. This COMT polymorphism is a plausible candidate gene for executive functioning and fluid intelligence in nondemented middle-aged and older adults. ■

INTRODUCTION

The neurotransmitter dopamine plays an important role in the regulation of cognitive functions in the prefrontal cortex. Catechol *O*-methyltransferase (COMT) is an important enzyme responsible for the degradation of released dopamine. A single nucleotide polymorphism (SNP), leading to a Val to Met substitution (Val[158]Met), in the coding region of the COMT gene has gained recent attention because of its tentative importance for frontal lobe functions. This SNP has been shown to influence the activity and thermal stability of the enzyme (Lachman et al., 1996; Lotta et al., 1995) in vitro, and determines low or high enzyme activity with the Met allele having one quarter of the enzyme activity of the Val allele at body temperature (Lachman et al., 1996). Individuals with the Met/Met genotype would be expected to have better prefrontal functioning than Met/Val or Val/Val genotypes because of their greater availability of catecholamine neurotransmitters (Malhotra et al., 2002; Egan et al., 2001; Weinberger et al., 2001). Brain imaging studies also provide support for the influence of the Val[158]Met polymorphism on brain functions (Akil et al., 2003; Gallinat et al., 2003; Mattay et al., 2003; Tsai et al., 2003; Egan et al., 2001), indicating that Met allele carriers have more efficient prefrontal functioning than Val allele carriers.

COMT is a recently studied gene in the understanding of cognitive functioning in schizophrenia and Parkinson's disease (e.g., Nolan, Bilder, Lachman, & Volavka, 2004; Goldberg et al., 2003; Bilder et al., 2002; Egan et al., 2001; Meco & Alessandri, 2000), and cognitive functioning in healthy adults (de Frias et al., 2004; Joober et al., 2002; Malhotra et al., 2002) and children (Diamond, Briand, Fossella, & Gehlbach, 2004). The COMT Val[158]Met polymorphism was related to variation in working memory (an executive function) in three samples: schizophrenic patients, healthy siblings, and normal controls (Goldberg et al., 2003). In a sample of healthy volunteers, Malhotra et al. (2002) reported that carriers of the Met allele made fewer perseverative errors on the Wisconsin Card Sorting Test (WCST) as compared to carriers of the Val allele. Similarly, Joober et al. (2002) reported a trend for a genotype-related variation on the WCST in a mixed sample of patients with schizophrenia and healthy controls; Met allele carriers performed better than Val carriers. However, Tsai et al. (2003) found no association between COMT genotypes and executive functioning in

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a sample of young healthy Chinese women. In a recent study from the Betula project derived from the same parent sample (the present study excluded participants with incident dementia), we reported an association between the COMT polymorphism and episodic and semantic memory in middle-aged and older adult men (de Frias et al., 2004). Specifically, carriers of the Met/Met genotype performed better than carriers of the Val allele on episodic memory (on recall, but not on recognition) and semantic memory (knowledge and fluency). These studies alert to the influence of the COMT gene on frontally mediated cognitive tasks (episodic and semantic memory, executive functioning) possibly because of its effect on the dopamine system.

The organization of executive functions has been examined in various populations (e.g., Salthouse, Atkinson, & Berish, 2003; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; Robbins et al., 1998). Several definitions of executive functions have been proposed. Salthouse et al. (2003) defines executive functions as control processes responsible for planning, coordinating, and monitoring other cognitive operations. Rabbitt (1997) stated that executive functions are a group of cognitive actions dealing with novelty, planning, monitoring performance, and inhibiting task-irrelevant information. Generally, executive functions refer to a set of processes used to control and monitor behavior in novel situations. Tasks that do not demand preexisting knowledge structures, but rather require processing in novel situations, are more sensitive to age-related decline. Fluid intelligence tests also involve relatively unfamiliar material and demand efficient solutions to novel problems. Tests assessing fluid aspects of intelligence show robust decline across the adult age span (Baltes, Lindenberger, & Staudinger, 1998).

Age-related reductions in volume and activation of the prefrontal cortex are linked to age-related cognitive deficits (e.g., errors in the executive control of cognitive performance; Raz, 2004), and executive tasks have been associated with prefrontal regions in functional imaging studies (Anderson & Tranel, 2002; Cabeza & Nyberg, 2000). Several cognitive functions relevant to the present study are dependent on the neural circuitry of the prefrontal cortex (Raz, 2004; Anderson & Tranel, 2002). The dorsolateral prefrontal (DLP) cortex and posterior parietal cortices function coordinately in the performance of visuospatial tasks (e.g., block design; Anderson & Tranel, 2002; Raz, Briggs, Marks, & Acker, 1999). The DLP cortex has also been linked to impairments in executive functions (Anderson & Tranel, 2002). Working memory and divided attention are important cognitive operations of executive functioning and both PET studies (Iidaka, Anderson, Kapur, Cabeza, & Craik, 2000) and functional MRI studies (Kensinger, Clarke, & Corkin, 2003) have demonstrated activation of the prefrontal cortex for working memory tasks (i.e., memory tasks with divided attention). A widely used measure of executive function is the WCST and studies have shown activation of the DLP cortex during task performance (Anderson & Tranel, 2002). In addition, Val allele carriers show less efficient frontal processing during card sorting than Met carriers (Mattay et al., 2003; Egan et al., 2001). Other cognitive functions that are sensitive to prefrontal functioning are verbal fluency (Phelps, Hyder, Blamire, & Shulman, 1997) and planning (e.g., using Tower of Hanoi [TOH] or London tasks; Anderson & Tranel, 2002; Dagher, Owen, Boecker, & Brooks, 1999). These studies alert to the possible sensitivity of such cognitive operations, and relevant tasks, to assess the effect of COMT genotype variation on cognitive performance.

Age-related deficits in cognitive functioning are partly affected by the availability of dopamine (for review, see Bäckman & Farde, 2004). Although no studies to date have examined whether decline in cognitive functioning is accounted for by decline in dopamine, and especially independent of decline in other neurotransmitter systems (e.g., acetylcholine) or cerebral blood flow, some evidence for the association between cognition and dopamine is available. PET studies have shown that D_1- and D_2-receptor binding (Bäckman et al., 2000; Volkow et al., 1998; Wang et al., 1998) in the neostriatum decreases with advancing age. Although dopamine levels decline with age, there is also evidence that dopamine receptors predict cognitive performance independent of chronological age (Bäckman et al., 2000). Evidence from animal studies has also shown associations between dopamine loss and cognitive deficits (Baunez & Robbins, 1999).

Based on prior association studies in humans supporting the effect of COMT on executive functions and both episodic and semantic memory in healthy adults, and some evidence for a triad association between age, dopamine, and cognition (Bäckman & Farde, 2004; Volkow et al., 1998), we expected that variation in COMT genotype would also be related to performance on executive cognition and visuospatial tasks in healthy middle-aged and older adults. The goals of the present study were to examine the association between the COMT polymorphism and cognitive performance over a 5-year period in a similar sample of middle-aged and older adult men. Specifically, our hypotheses were that (a) the Met/Met genotype group will perform better on cognitive tasks than Val allele variants, (b) the effect of this COMT polymorphism on cognitive functioning will be greater for older age groups, and (c) the Val variant carriers will show greater decline in cognitive functioning over the 5-year period than the Met/Met genotype group.

RESULTS

Confirmatory Factor Analyses

Confirmatory factor analyses were used to test the structure of the three indicators of executive functions

Table 1. Standardized Factor Loadings for Executive Function Tests

	Executive Function Factor	
Indicators	*Wave 1*	*Wave 2*
Verbal fluency	.60	.52
Working memory	.44	.67
Tower of Hanoi	.50	.50

All factor loadings were significantly different from zero.

at Waves 1 and 2, separately. A single-factor model of executive functioning was a good fit to the data at both Wave 1 ($\chi^2 = 0.41$, $df = 1$, $p = .52$, RMSEA = .00, CFI = 1.00, GFI = 1.00), and Wave 2 ($\chi^2 = 0.04$, $df = 1$, $p = .84$, RMSEA = .00, CFI = 1.00, GFI = 1.00). Factor loadings are presented in Table 1. The single factor was used to assess executive functioning (i.e., the ability to control cognitive operations) using three executive tasks that are sensitive to frontal lobe functioning.

The factor regression weights at each wave were as follows: Executive Function factor at Wave 1 = (verbal fluency × .26) + (working memory × .16) + (TOH × .21); Executive Function factor at Wave 2 = (verbal fluency × .14) + (working memory × .25) + (TOH × .10). The factor scores were created in two ways: (a) using the average of the regression weights from Waves 1 and 2, and (b) using unit weighting (summing across raw variables). These factor scores were used as dependent variables in subsequent repeated-measures analyses of variance (ANOVA) models. Both methods of creating factor scores resulted in similar results, and because the latter is more generalizable across datasets, we report analyses with unit-weighted factor score composites.

Repeated-Measures ANOVAs

Using the combined S2 and S3 longitudinal sample, 3 (COMT) × 3 (age group) × 2 (time) repeated-measures ANOVAs were conducted for each dependent variable (i.e., the executive function factor and block design). Only main effects of COMT and related interactions (i.e., COMT × Age, COMT × Time, or COMT × Age × Time) are presented. The COMT genotype distributions were as follows: Val/Val ($n = 55$; 18.8%), Val/Met ($n = 151$; 51.7%), and Met/Met ($n = 86$; 29.5%). (The COMT genotype distributions for this sample are not identical to our previous study because this sample excluded participants with incident dementia.)

Main Effect of COMT

The main effect of COMT (using the additive model: comparing all 3 genotypes) was significant for executive function [$F(2,269) = 3.03$, $p = .05$, $\eta^2 = .02$], but not for block design [$F(2,282) = 2.28$, $p = .11$, $\eta^2 = .02$]. A Val allele dominant model was tested (as supported in de Frias et al., 2004) by comparing the Met/Met group with a combined Met/Val + Val/Val group. The main effect of COMT was significant for executive function [$F(1,272) = 6.20$, $p = .01$, $\eta^2 = .02$] and block design [$F(1,285) = 4.59$, $p = .03$, $\eta^2 = .02$]. The Met/Met group performed better than the Val variants on executive function (M = 0.55, −0.06; SE = 0.20, 0.13), and block design (M = 0.16, −0.07; SE = 0.09, 0.06).

COMT Interactions

The COMT × Age interaction was significant for block design [$F(4,282) = 2.39$, $p = .05$, $\eta^2 = .03$], but not for executive function [$F(4,269) = .94$, $p = .44$, $\eta^2 = .01$]. As shown in Figure 1, the Met/Met (M = 1.04; SE = 0.19) group performed better on block design than the Val/Met (M = 0.35; SE = 0.14) and Val/Val (M = 0.25; SE = 0.20) genotypes among the middle-aged men. No differences between COMT genotypes within the young-old and old-old age groups were reliable. Testing the Val allele dominant model also resulted in a similar significant COMT × Age interaction for block design [$F(2,285) = 4.74$, $p = .01$, $\eta^2 = .03$].

The COMT × Time interaction was significant for executive function [$F(2,269) = 3.78$, $p = .02$, $\eta^2 = .03$], but not for block design [$F(2,282) = .80$, $p = .45$, $\eta^2 = .01$], for the additive model. As shown in Figure 2, carriers of the Val/Val genotype declined in executive functioning over the 5-year period, whereas homozygotes, and especially the heterozygotes, for the Met allele maintained their performance over the same period.

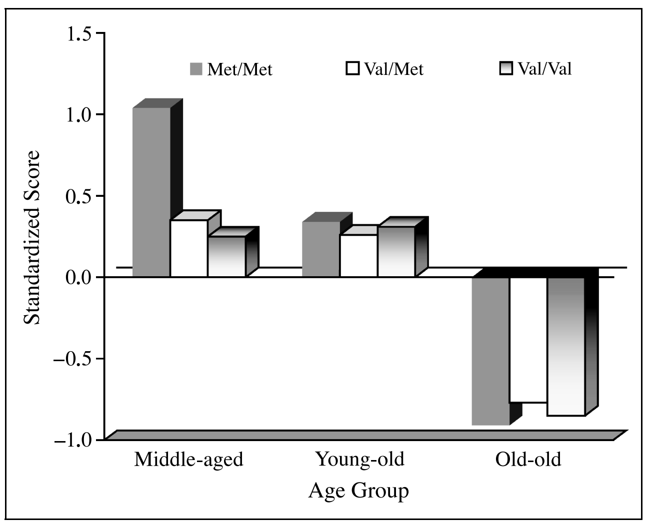

Figure 1. COMT gene by Age interaction for block design. Middle-aged men who were Met/Met carriers performed better than Val variants on block design, but no effect of COMT for young-old and old-old adults.

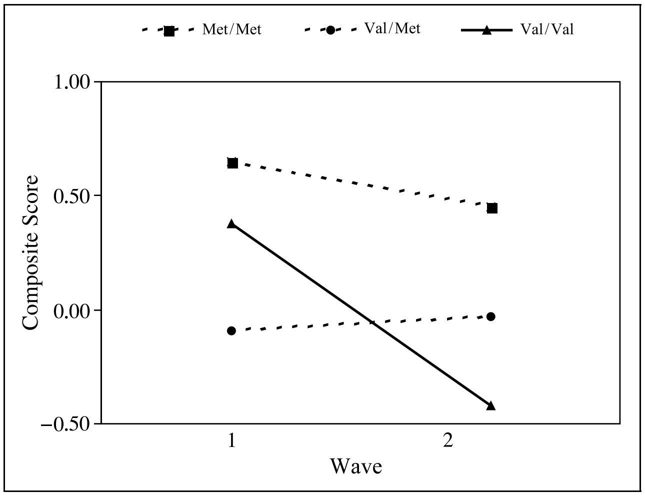

Figure 2. Individuals with the Val/Val genotype declined in executive functioning over a 5-year period.

The three-way COMT × Age × Time interaction was not significant for executive function or block design.

DISCUSSION

The present study tested the association between COMT genotype, age, and individual differences and changes in executive functioning and visuospatial ability. In a random population of adults, carriers of the Met/Met genotype performed significantly better than Val variants on a composite index of executive tasks and visuospatial ability (a component of fluid intelligence). These data are consistent with the results of other studies examining the role of the COMT gene on executive functions (e.g., Goldberg et al., 2003; Egan et al., 2001) and our study on declarative memory performance (de Frias et al., 2004). The superior performance of Met allele carriers has also been noted for a working memory task (i.e., *n*-back) in schizophrenic patients (Goldberg et al., 2003; Weinberger et al., 2001), and a shifting task also in schizophrenic patients and healthy young adults (Joober et al., 2002; Malhotra et al., 2002; Egan et al., 2001).

The results from confirmatory factor analyses indicated that a single factor captured the underlying organization among three different executive tests (i.e., verbal fluency, working memory, and TOH). A single-factor solution of executive functions has also been reported in other healthy samples of adults (e.g., de Frias, Dixon, & Strauss, submitted; Salthouse et al., 2003). The single executive composite score in our study was a broad marker for executive functioning. Given the diversity of executive functions, using a confirmatory factor analysis approach allowed for the evaluation of shared variance among the tests. Because executive tasks may also have unique components, it is important to use statistical analyses to partial out unique variance in the tasks (e.g., confirmatory factor analysis), or to aggregate the tasks (Miyake, Emerson, & Friedman, 2000).

Age was a significant moderator of the effect of COMT on average visuospatial ability (an indicator of fluid intelligence), but not executive functions. The Met/Met group performed better than the Val allele groups in middle-aged men only. No significant differences were noted between COMT genotypes within young-old and old-old adult age groups. The moderating effect of age was observed when an additive model of COMT and a Val dominant model were tested. The early onset and gradual nature of age-related cognitive decline may be determined by biological factors with a similar trajectory. One limitation of this study was that only a single component of fluid intelligence was available. Future research needs to examine the relation between COMT and other cognitive processes (other than visuospatial ability) that reflect fluid intelligence. The Val/Val genotype group declined in executive functioning over the 5-year period, whereas Met allele variants maintained their performance over the same period. Our results indirectly support the claim that age-related deficits in executive functioning may be affected by the availability of dopamine (Bäckman & Farde, 2004).

Altering dopaminergic transmission (as in the case with COMT) could contribute to cognitive deficits (Nieoullon, 2002). Tasks that require working memory (i.e., demand executive control) are sensitive to dopamine levels in the DLP cortex (Diamond et al., 2004; Luciana & Collins, 1997), and studies have reported an association between D_1 and D_2 receptor activation and optimal working memory performance (Durstewitz & Seamans, 2002; Luciana, Depue, Arbisi, & Leon, 1992). Based on a theory of tonic and phasic modes of dopamine modulation (Bilder, Volavka, Lachman, & Grace, 2004; Dreher & Burnod, 2002), Nolan et al. (2004) postulated that the Met allele would have differential effects of dopamine manipulation depending on whether the cognitive task requires tonic dopamine (cognitive stability; beneficial effect) or phasic dopamine (cognitive flexibility; detrimental effect). The effect of dopamine on prefrontal functioning has been expressed as an inverted U-shaped dose–response curve, such that individuals with too much dopamine (e.g., individuals with Huntington's disease, schizophrenia), or too little dopamine (e.g., individuals with Parkinson's disease) have poorer prefrontal functioning compared with those with moderate levels (Mattay et al., 2003; Williams & Goldman-Rakic, 1995). Mattay et al. (2003) reported that Val/Val individuals on amphetamines performed similar to Met/Met individuals at baseline on a working memory task (1-back, 2-back, 3-back), but that the Met/Met individuals on amphetamines performed more poorly than Val homozygotes at baseline only when working memory load was greatest (i.e., 3-back condition). Our sample consisted of nondemented adults without known

psychiatric disorders that may alter the dopamine system, therefore, dopamine levels are expected to be in the mid- (optimal) range. Consequently, we suspected the effect of the Met/Met genotype on dopamine function to be moderate as compared to that obtained by drugs such as amphetamine. The moderating effects of task difficulty and use of psychostimulants on COMT activity is an important line of future research.

Interindividual variability in cognitive aging may be partly accounted for by the COMT gene. The neurochemical mechanism responsible for the effect of COMT on executive functioning and fluid intelligence is likely dopamine, but noradrenaline is also a possible mediator. COMT, with its effect on neurotransmitter systems, may inform about how neurochemical modulation in the prefrontal cortex affects age-sensitive cognitive domains (e.g., executive functions, fluid intelligence).

METHODS

Participants

The participants in the present study were taken from two samples of community-dwelling adults from the Betula project (Nilsson, Adolfsson, et al., 2004; Nilsson, Bäckman, et al., 1997, for review), an ongoing sequential study of memory, health, and aging. The data used for this study were from Samples 2 and 3, for both available occasions of measurement. The first wave of testing was in 1993–1995, and the second wave was in 1998–2000. The interval between the two testing periods was 5 years. The participants were recruited by random selection of names from the population registry. The overall sample was composed of 299 men. Seven participants were excluded from the study because they were diagnosed with incident dementia at the second wave. The present sample was composed of 292 nondemented men between the ages of 35 and 85 years (*M* age = 58.01 years, *SD* = 12.86). Participants were divided into three age groups based on age at Wave 1. The middle-aged group (MA; n = 61) ranged from 35 to 45 years (*M* = 40.98; *SD* = 3.63). The young-old age group (YO; n = 119) ranged from 50 to 60 years (*M* = 53.49; *SD* = 3.71). The old-old age group (OO; n = 112) ranged from 65 to 85 years (*M* = 72.10; *SD* = 5.52).

After complete description of the study to the participants, written informed consent was obtained.

Cognitive Measures

The cognitive tasks were administered during two test sessions, both of which lasted between 1.5 and 2 hr for each participant. Three tests (i.e., verbal fluency, working memory, and TOH) were used to measure executive functions, and one test measured visuospatial ability (block design).

Verbal Fluency

Participants were instructed to generate aloud as many words as possible beginning with the letter A in 1 min.

Working Memory

In the working memory task (Baddeley, Lewis, Eldridge, & Thomson, 1984), participants were presented auditorily with one word list containing 12 items. A card-sorting task was provided simultaneously at both encoding and retrieval. The card-sorting task consisted of sorting a deck of playing cards into two piles, one red pile and one black pile. At encoding, the participant was instructed to sort one card after each word was presented from the list. At retrieval, the participant was asked to recall the words from the list and to simultaneously sort a card after the sound of a tone (at 2-sec intervals). The performance score for this study was the number of correctly recalled words.

Tower of Hanoi

The TOH puzzle is a test of executive functioning (i.e., planning; Lezak, 1995), which requires movement of a set of pegs to a goal position. Three pegs are mounted on a block with five disks of varying sizes placed on the leftmost peg. The largest disk is placed at the bottom and smallest at the top of the disk pile. The experimenter instructs the participant to duplicate this formation on either the middle or rightmost peg. The disks could be moved to any peg with three restrictions: (a) only one disk could be moved at a time, (b) a larger disk could not be placed over a smaller disk, and (c) a disk that was moved had to be placed on another peg. Participants were instructed to move the disks as quickly as possible and to solve the task with as few moves as possible. Two scores were calculated for this study: number of moves and time to complete task (latency). A ratio measure was computed: time/total number of moves. The performance score was time to task completion (latency), controlling for number of moves (Rönnlund, Lövdén, & Nilsson, 2001).

Block Design

Block design is a standardized test of visuospatial ability from the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1991). This task involves putting sets of colored blocks together to match patterns on cards.

Molecular Genetics

Genomic DNA was isolated from whole blood by Qiagen Genomic DNA Purification Kit (Qiagen, Chatsworth, CA, USA). Polymerase chain reactions were carried out using

Table 2. Unstandardized Means for All Cognitive Tasks

Tasks	*Wave 1*	*Wave 2*
Letter fluency	10.92 (4.3)	10.65 (4.48)
Working memory	3.58 (1.22)	3.31 (1.28)
Tower of Hanoi	6.40 (4.87)	6.72 (6.98)
Block design	28.09 (10.48)	26.06 (10.99)

Values for standard deviations are in parentheses.

HotstarTaq polymerase (Qiagen) in a total volume of 20 μl containing 1.5 mM $MgCl_2$, 0.15 μM primers (fw: 5′-TCA CCA TCG AGA TCA ACC CC-3′, rev: 5′-ACA ACG GGT CAG GCA TGC A-3′), and approximately 50 ng genomic DNA. After an initial 15 min denaturation step at 95°C, 45 cycles were performed including 30 sec at 94°C, 30 sec at 62°C, and 30 sec at 72°C. PCR products were genotyped with a Pyrosequencer PSQ 96 and the PSQ 96 SNP Reagent Kit (Pyrosequencing, Uppsala, Sweden; Nordfors et al., 2002), using the sequence primer 5′-TGG TGG ATT TCG CTG-3′.

Statistical Analyses

All measures were converted to *z*-score units. Means and standard deviations for *z*-scores at Wave 2 were based on the descriptives from Wave 1 (to preserve longitudinal changes in the scores). The TOH ratio score was reverse coded to be commensurate with all other cognitive tasks (i.e., higher score = better performance). The means and standard deviations for all measures are listed in Table 2. Two statistical analyses were performed. First, confirmatory factor analyses were run with the LISREL 8.52 program (Jöreskog & Sörbom, 2000) to test the underlying structure of three indicators of executive functions at Waves 1 and 2, separately. Second, repeated-measures ANOVA were run to examine associations between COMT, age, and cognitive functioning (i.e., executive functioning and visuospatial ability), over a 5-year period. For all the analyses reported, alpha levels of $p = .05$ were specified to indicate statistical significance.

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