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Investigating the Relationship between COMT Polymorphisms and Working Memory Performance among Childhood Brain Tumor Survivors

Robyn A. Howarth, PhD¹, Amanda M. Adamson, PhD², Jason M. Ashford, MS³, Thomas E. Merchant, DO, PhD⁴, Robert J. Ogg, PhD⁵, Stefan E. Schulenberg, PhD⁶, Susan Ogg, MSN⁷, Jiang Li, PhD⁸, Shengjie Wu, MS⁹, Xiaoping Xiong, PhD⁹, and Heather M. Conklin, PhD^{3,*}

¹Department of Neuropsychology, Children's Healthcare of Atlanta

²The Center for Pediatric Neuropsychology, Palm Beach Gardens, Florida

³Department of Psychology, St. Jude Children's Research Hospital

⁴Division of Radiation Oncology, St. Jude Children's Research Hospital

⁵Division of Translational Imaging Research, St. Jude Children's Research Hospital

⁶Department of Psychology, University of Mississippi

⁷Department of Epidemiology & Cancer Control, St. Jude Children's Research Hospital

⁸Department of Psychiatry & Behavioral Sciences, Northwestern University

⁹Department of Biostatistics, St. Jude Children's Research Hospital

Abstract

Background—Survivors of childhood brain tumors are at increased risk for neurocognitive impairments, including deficits in abilities supported by frontal brain regions. Catechol-O-methyltransferase (COMT) metabolizes dopamine in the prefrontal cortex, with the Met allele resulting in greater dopamine availability and better performance on frontally-mediated tasks compared to the Val allele. Given the importance of identifying resiliency factors against the emergence of cognitive late effects, the current study examined the relationship between COMT genotype and working memory performance among childhood brain tumor survivors.

Procedure—Children treated for a brain tumor with conformal radiation therapy (N=50; mean age at irradiation=7.41 ± 3.41; mean age at assessment=13.18 ± 2.88) were administered two computerized measures of working memory (self-ordered search verbal and object tasks). Buccal (cheek) swabs were used to provide tissue from which DNA was extracted.

*Corresponding Author: Heather M. Conklin, Department of Psychology, Mail Stop #740, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, Tennessee 38105. Telephone: 901-595-3585. Fax: 901-595-4701. heather.conklin@stjude.org.

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Results—Findings revealed an association between COMT genotype and performance on the self-ordered verbal ($p=0.03$) but not object task ($p=0.33$). Better performance was found for the Met/Val group compared to either Met/Met or Val/Val.

Conclusions—COMT may indicate a potential resiliency factor against neurocognitive effects of cancer and its treatment; however, there is a need for replication with larger samples of childhood brain tumor survivors.

Keywords

cancer; late effects; genetics; dopamine; prefrontal cortex; working memory

Introduction

Survivors of childhood brain tumors receiving therapies directed at the central nervous system (CNS) are at increased risk for cognitive impairments secondary to disease and treatment related factors, which subsequently impact quality of life [1]. Previous research has demonstrated global declines on measures of intellectual functioning [2–3] and, more recently, working memory has been identified as a core contributor to these changes [4]. Working memory is highly associated with IQ development in healthy children [5]. It represents a core cognitive function responsible for online storage and manipulation of information that is largely supported by frontal brain regions, including the prefrontal cortex [6–10]. Neurocognitive outcomes vary among childhood brain tumor survivors [11] and cognitive processes largely supported by the prefrontal cortex are particularly vulnerable [12]; hence, it is important to isolate those factors associated with resiliency against emergence of cognitive late effects.

Researchers have started examining the contribution of genetic variants to cognitive outcomes. For example, polymorphisms in the apolipoprotein E (APOE) gene (i.e., E4) have been shown to be associated with poorer outcome following acquired injury, including a small study of adult cancer survivors treated with chemotherapy [13]. Recent neuroimaging studies demonstrate increased activation in frontal brain regions among individuals treated with chemotherapy, suggesting the brain may compensate for treatment-related changes by recruiting additional brain regions to perform cognitive tasks [14–15]. Childhood brain tumor survivors are at risk for decreased efficiency in prefrontal cortex networks following radiation therapy secondary to treatment-related changes (e.g., disrupted myelination). Previous studies support this theory by demonstrating a reduction in white matter volumes [12], particularly in the frontal regions, and disrupted myelination processes on diffusion tensor imaging [16]. Emerging research in pediatric oncology has revealed associations between genotypes and cognitive outcomes in survivors of childhood leukemia, namely with regard to folate pathways and oxidative stress markers [17–19]; however, no prior studies have investigated genotypes related more generally to resiliency following acquired injury, including variations in dopamine availability, with a brain tumor population.

Dopamine is a neurotransmitter that is critically important for functions mediated by the prefrontal cortex. Working memory processes have been shown to be facilitated by a greater availability of dopamine in this brain region; relatedly, reduced availability has been

associated with performance deficits [20–21]. Catechol-O-methyltransferase (COMT) is an enzyme crucial for the metabolism of catecholamines, thus controlling levels of dopamine, namely in the prefrontal cortex [21–23]. The COMT gene contains two polymorphisms (Methionine [Met] and Valine [Val]), with the Met allele resulting in slower degradation and greater availability of dopamine. The frequency distribution of COMT alleles varies among ethnic groups, with individuals of European descent having nearly equal frequencies of the two alleles [24].

Previous studies have revealed a relationship between the COMT gene and specific prefrontal cortex processes, including working memory [25–27]. Specifically, research with healthy adults and schizophrenic patients found individuals who were homozygous for the Met polymorphism (Met/Met) performed significantly better than those with the Val allele (Met/Val, Val/Val) on frontally mediated tasks including the Wisconsin Card Sorting Test (WCST: [25–26]) and N-back test [27]. Another study with healthy adults showed a similar pattern of findings on the WCST and one of four working memory measures (Letter Number Sequencing), leading authors to conclude that genotype differences may be specifically related to the higher-order processing associated with these tasks [28].

In their study of typically developing children between the ages of 8 and 14 years, Diamond and colleagues [29] replicated adult findings by demonstrating an association between the Met/Met polymorphism and better performance on a working memory task dependent on the dorsolateral prefrontal cortex (Dots-Mixed Task). Of note, COMT genotype was not found to impact performance on measures dependent on other neural systems (e.g., recall memory and mental rotation), suggesting the role of COMT in modulating behaviors may be specific to the prefrontal cortex. Similarly, Wahlstrom and colleagues [30] demonstrated an association between COMT and performance on frontally-mediated tasks among a sample of children and adolescents 9 to 17 years of age; however, results revealed the Met/Val group performed better than the Met/Met group on measures of working memory and attention.

While some prior investigations have examined the relationship between COMT genotype and prefrontal processing in developmental samples, we are not aware of any prior studies including childhood brain tumor survivors. One recent study investigated this relationship among adult breast cancer survivors treated with radiotherapy and/or chemotherapy compared to healthy controls [31]. The authors were interested in determining the moderating role of COMT genotype on cognitive performance. Findings revealed an association between COMT and cognitive functioning characterized by worse performance for individuals with the Val allele (Val/Val; Met/Val) on measures of attention, verbal fluency, and motor speed relative to the Met/Met group. Poorer performance on tests of attention was further associated with chemotherapy treatment among individuals with the Val allele, suggesting those with the Val allele treated with chemotherapy may be more susceptible to cognitive effects. A significant interaction effect (group x COMT genotype) was also found for attention, indicating breast cancer survivors with the Val allele who were treated with chemotherapy performed worse on measures of attention than healthy controls.

Previous research suggests Met/Met individuals may perform better on frontally-mediated tasks than those with Met/Val or Val/Val genotypes secondary to greater dopamine

availability. Such a relationship may serve as a protective mechanism against late effects seen among childhood brain tumor survivors and has not previously been studied in this population. Based on prior research with normative groups, it seems reasonable to speculate that individuals with the less favorable genotype (e.g., Val/Val based on the healthy adult literature) would display less resiliency following CNS-directed therapy; these survivors would have less dopamine availability in the prefrontal cortex to draw upon to compensate for acquired brain changes.

The performance of brain tumor survivors on two experimental, computerized working memory tasks (Self-Ordered Search-Verbal [SOS-V] and Self-Ordered Search-Object [SOS-O]) was previously reported by Conklin and colleagues [28]. Briefly, brain tumor survivors displayed worsening performance on both the SOS-V and SOS-O tasks as array length increased, coinciding with greater working memory demands. Further, performance was significantly worse compared to healthy and cancer control groups, who did not differ from one another. The primary aim of the current study was to build upon these findings by examining the relationship between COMT genotype (Met/Met, Met/Val, Val/Val) and performance on working memory tasks among childhood brain tumor survivors. The present study applies a normative model to a sample with acquired brain injury to examine whether individuals with a particular genotype are more resilient to insult because of better ability to compensate after injury. Based on the existing literature, we hypothesized that Met/Met individuals would perform better on working memory tasks than Met/Val or Val/Val secondary to greater dopamine availability in frontal brain regions.

Methods

Participants

Participants included childhood brain tumor survivors treated homogeneously for a primary CNS tumor with conformal radiation therapy, per an institutional phase II trial. Diagnoses included ependymoma, low-grade glioma, and craniopharyngioma. Conformal radiation therapy was administered in daily fractions of 1.8 Gy to a target volume that included the tumor or tumor bed surrounding a clinical target margin of 1 cm. A geometric planning target volume was used that included an additional 0.3–0.5 cm margin to account for set-up uncertainty. Total radiation dose ranged from 54 to 59.4 Gy. Treatment was initiated at least two years prior to enrollment on this study without evidence of recurrent disease. Group enrollment was stratified by gender, age (8–12; 13–18), and tumor location (infratentorial; supratentorial).

Eligible participants were primary English speakers between the ages of 8 and 18 at the time of evaluation. Individuals with global intellectual impairment (IQ less than 70) were not considered for participation. Additional exclusion criteria included a history of CNS injury/disease or AD/HD prior to diagnosis, treatment with psychotropic or stimulant medication within two weeks of assessment, or a major sensory and/or motor impairment that would impact test validity.

Procedures

This study was approved by the Institutional Review Board and written informed consent was required prior to participation. Eligible participants were approached and enrolled in the order of visits for routine medical appointments. Following informed consent and assent procedures, participants completed cognitive measures and provided tissue samples through buccal (cheek) swabs.

Measures of Working Memory—Participants were administered two experimental, computerized tasks of working memory (Self-Ordered Search-Verbal [SOS-V] and Self-Ordered Search-Object [SOS-O]). These measures have been described elsewhere by our group [32]. In short, participants were seated in front of a computer screen for task completion. Stimuli were presented on the screen over the course of four trials in arrays of varying length for each successive trial. For the SOS-V, participants were shown four words on the first trial (2×2 array), six words on the second trial (3×2 array), nine words on the third trial (3×3 array), and twelve words on the fourth trial (4×3 array). The SOS-O task is parallel in format to the verbal task except geometric objects are presented instead of words and the most recently shown object location is covered with a black square. As such, array sizes for the SOS-O included three objects for the first trial (2×2 array), five objects for the second trial (3×2 array), eight objects for the third trial (3×3 array), and eleven objects for the fourth trial (4×3 array). For each individual trial, the goal was to select each of the target stimuli in as few responses as possible. The trial concluded when all stimuli were selected or after 3N responses (in which N is the number of stimuli in a given trial), whichever happened first. The error score (E) was the dependent variable of interest, which reflects the number of incorrect responses in the process of identifying the remaining stimuli.

Measure of General Cognitive Ability—To characterize the group at the time of assessment, an estimated level of general cognitive functioning was obtained with the two subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; [33]), which is highly correlated with the full scale (FSIQ) obtained from the Wechsler scales [5, 34].

DNA Extraction and Processing—Buccal swabs were used to provide tissue from which DNA was extracted. The procedure for COMT genotyping was adopted from a previous linkage study of COMT and AD/HD [35]. Primers for amplification were determined by PCR-RFLP (e.g., COMT-Forward, 5'-tcaccatcgagatcaacccc-3'; COMT-Reverse, 5'-gaacgtggtgtgaacacctg-3') and applied to samples. Amplification of the COMT polymorphism was completed in Invitrogen AccuPrime™ DNA Polymerase Kit (Cat. No: 12337). These primers amplify a fragment of 176 base pairs before restriction enzyme digestion. Digestion of this fragment with NlaIII (New England Biolabs, R0125S) results in bands of 82, 54 and 41 base pairs for the Val allele. Specifically, the 82 base pair fragment is cut into the 64 and 18 base pairs for the Met allele. These DNA fragments were identified following capillary electrophoresis by ABI3730 and data were analyzed by GeneMapper software (Applied Biosystems). The 82 and 64 base pairs were the primary bands of interest since a single 82 base pair band represents homozygous Val (Val/Val), a single 64 base pair band represents homozygous Met (Met/Met), and both existing bands represent

heterozygous Val/Met. COMT genotypes were confirmed by SNAPSHOT (Applied Biosystems, Cat. No: 4323155) using the same PCR primers (without labeling) and an extension oligo (CGGATGGTGGATTTCGCTGGC). GG, GA, and AA represent Val/Val, Val/Met, and Met/Met, respectively.

Demographic & Clinical Variables—Caregivers completed a structured questionnaire that included questions about family demographic characteristics to derive an index of socioeconomic status (SES). The Barratt Simplified Measure of Social Status was used [36], taking into account both parental education level and occupation. Based on the existing literature, clinical variables of interest were obtained from the patient medical records. Tumor location was categorized as infratentorial or supratentorial per initial neuroimaging scans and, when applicable, the extent of resection was categorized as biopsy, subtotal, near total, or gross total resection. In addition, treatment with chemotherapy, the presence of hydrocephalus, and placement of a ventriculo-peritoneal (VP) shunt were categorized as yes or no.

Data Analyses

Descriptive analyses of demographic and clinical variables were conducted to characterize the participant group. Linear mixed models were used to examine the relationship between COMT polymorphism and performance on working memory measures, accounting for age and array length. Appropriate post-hoc analyses were completed for statistically significant findings.

Results

Demographic and Clinical Characteristics

Demographic and clinical variables of interest are presented in Tables I and II by genotype. For the brain tumor group as a whole, descriptive analyses revealed survivors were 6.38 years of age (SD=3.43) at the time of diagnosis, 7.41 years of age (SD=3.41) at the time of conformal radiation therapy, and 6.80 years (SD=2.60) from diagnosis at the time of participation. The mean age of participants at the time of study enrollment was 13.18 years (SD=2.88). Results of an abbreviated measure of intellectual functioning revealed performance within the average range for age (mean=98.20; SD=13.91). Regarding clinical characteristics, the group was balanced with respect to diagnosis and tumor location. A minority of the brain tumor survivors (12%) received chemotherapy prior to radiation. Approximately 60% of the patients presented with hydrocephalus, most of whom required placement of a shunt. Half the group underwent an extensive surgical resection (i.e., near or gross total resection) of their tumor. Genetic analyses identified 11 participants with the Met/Met genotype (22%), 15 with the Met/Val genotype (30%), and 24 with the Val/Val genotype (48%). Examination of demographic and clinical variables by genotype revealed significant group differences for age at treatment, age at assessment, tumor diagnosis, tumor location, extent of surgical resection, and presence of hydrocephalus. It was previously demonstrated that these variables were not predictive of working memory performance in this sample [28].

COMT and Working Memory

To examine the relationship between COMT genotype and working memory performance (SOS-V, SOS-O) of brain tumor survivors, linear mixed models were used, accounting for age and array length. Performance means are presented in Figure 1 by genotype. For the SOS-V task, linear mixed models revealed a main effect for array size ($p<0.01$) and genotype ($p=0.03$). A significant interaction between genotype and array size was not found. Post-hoc comparisons revealed that those with the Met/Val genotype performed significantly better than those with the Met/Met genotype ($p<0.01$). No significant difference was found between individuals with Val/Val and Met/Val genotypes. For the SOS-O task, linear mixed models demonstrated a main effect for array size ($p<0.01$), but not genotype ($p=0.33$). As such, no post-hoc analyses were conducted.

Discussion

The current study sought to examine the relationship between COMT polymorphisms and working memory performance among childhood brain tumor survivors. Based on the limited amount of existing research with this population, it was important to apply a normative model to determine whether it was upheld within the context of acquired brain injury. Individuals with the less favorable genotype (e.g., Val/Val) were predicted to perform worse due to less resiliency given reduced prefrontal dopamine available to compensate for disease and treatment related brain changes. Contrary to *a priori* hypotheses and previous reports of better performance among adults [21, 25–27] as well as younger children [29] homozygous for the Met allele, results revealed better working memory performance for the Met/Val group. In addition, findings demonstrated COMT polymorphisms were differentially associated with performance on working memory tasks depending on the modality of stimuli, with greater association for verbal compared to object information.

Among brain tumor survivors, better working memory performance was associated with the Met/Val genotype. The presence of an inverted-U dose-response relationship between dopamine concentrations in the prefrontal cortex and cognitive performance has been well-established in the literature [21, 37], in which deficient or excessive levels of dopamine result in poorer performance [38–39]. As such, Met/Met individuals are thought to rest at the top of this response curve whereas Met/Val or Val/Val are at the lower end due to increased rates of dopamine metabolism. Met/Met adults have demonstrated improved efficiency on tasks mediated by the prefrontal cortex [21], which lends support to the notion that they rest near the peak of the inverted –U curve. One previous study found better performance for the Met/Val group among an adolescent sample, prompting authors to postulate that the Met/Met genotype may lead to excessive, or inefficient, levels of dopamine during this developmental stage [30]. However, a recent examination of a large cohort of healthy young adults did not find an association between COMT and working memory performance, even after controlling for multiple covariates [40].

Variations in performance among COMT genotypes may also depend on the differential demands of the working memory tasks. The dopamine system in the prefrontal cortex has higher baseline firing rate and decreased availability of dopamine transporter protein than other brain regions [41–42]. As a result, the prefrontal cortex relies more heavily on the

COMT gene to assist with the metabolism of released dopamine. Since COMT has been shown to impact dopamine levels in the prefrontal cortex, variations in this polymorphism may influence performance on cognitive tasks taxing both working memory and inhibition [25–26, 29], but not measures dependent on prefrontal processes without an inhibition component (e.g., recall memory or mental rotation [29]). Researchers have also revealed associations between COMT genotype and performance, specifically on tasks that require updating and temporal ordering of information [27] and the higher-order components of processing [28]. Hence, negative results in the current study could be explained by a lack of strong inhibition component among the self-ordered working memory tasks.

Differences found for SOS-V versus SOS-O tasks may be explained by the complex neural circuitry of working memory. In their review of neuroimaging studies, Wager and Smith [43] noted that working memory tasks involve the temporary storage of information, yet the specific frontal regions that become activated vary based on task demands and modality of information (e.g., verbal versus spatial versus object). Studies have consistently demonstrated that prefrontal contributions to working memory are multifaceted, rather than relying on a single cognitive process [7]. Given the different underlying neural circuitry of working memory depending on modality type, the significant association found between COMT and working memory for verbal but not object stimuli suggests performance may be differentially impacted by genetic polymorphisms.

Within the context of current findings, study limitations are acknowledged, which provide directions for future research. While comparable to most previous research [e.g., 26, 29–32], this study examined a small sample. Given the small sample size, current findings may have been driven by poor performance of the Met/Met group, which also has the smallest n, rather than significantly better Met/Val performance. Hence, there is a chance current results may be a spurious finding given a small sample size and/or reflective of atypical performance of a few individuals, particularly in light of the recent large cohort study showing no relationship between COMT and working memory performance in an adolescent sample [40]. While a novel and interesting finding, larger and better controlled studies with childhood brain tumor survivors are needed. Genotype subtypes within the current sample differed with regard to several demographic (e.g., age at treatment, age at assessment) and clinical variables (e.g., tumor diagnosis, tumor location, extent of resection, presence of hydrocephalus), which reiterates the importance of examining a larger sample and including more targeted behavioral assays to better understand the association between COMT and working memory within this population. Investigating a larger sample may also allow researchers to examine interaction effects, which could help to support the notion that a specific genotype increases risk for poorer cognitive outcome. Future studies should incorporate additional working memory tasks into the assessment battery, particularly measures varying in level of inhibitory control. Based on the complex neural circuitry of working memory, the inclusion of neuroimaging technology will be important. Specifically, incorporating neuroimaging findings may allow for the development of new methods to examine neurotransmitter and receptor levels as well as patterns of activation associated with different working memory tasks among childhood cancer survivors.

In conclusion, some evidence of an association between COMT and working memory performance among childhood brain tumor survivors was found. While current findings require confirmation, they may indicate a potential resiliency factor against the emergence of cognitive late effects. If replicated, genotyping childhood cancer survivors for the Met and Val alleles may help to inform upfront discussions regarding cognitive risk, guide treatment planning, and increase understanding of the trajectory of long-term cognitive outcomes. Further, conducting pharmacogenetic studies with childhood cancer survivors has the potential to more specifically identify targets for intervention (e.g., cognitive, pharmacologic) and inform the development of individualized treatment regimens; thus, improving long-term patient outcomes.

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Figure 1.

Self-Ordered Search (SOS) Tasks by Genotype. A. Error score means presented across the four trials of the SOS-Verbal task by genotype. Linear mixed models revealed main effects for array size and genotype, with post-hoc comparisons showing better performance among the Met/Val compared to the Met/Met group. B. Error score means presented across the four trials of the SOS-Object task by genotype. Linear mixed models revealed a main effect for array size but not genotype; hence, no post-hoc analyses were conducted.

Table I

Demographic Characteristics of Brain Tumor Survivors

	Met/Met n = 11 (22%)	Met/Val n = 15 (30%)	Val/Val n = 24 (48%)	p ^a
Gender (% male)	36.4	53.3	54.2	0.59
Race (% Caucasian)	100.0	93.3	87.5	0.80
SES ^{b,c}	34.82 ± 15.21	38.03 ± 10.59	38.63 ± 11.97	0.69
Age at assessment (years)	12.00 ± 3.00	12.15 ± 2.47	14.36 ± 2.69	0.02
Age at diagnosis (years)	4.93 ± 3.11	5.55 ± 3.44	7.56 ± 3.28	0.06
Age at treatment (years)	6.03 ± 2.99	5.96 ± 3.38	8.95 ± 3.05	<0.01
Time since diagnosis (years)	7.07 ± 3.02	6.60 ± 2.18	6.80 ± 2.74	0.91
WASI IQ (standard score) ^d	98.64 ± 15.72	96.13 ± 14.55	99.29 ± 13.10	0.79

^a P-value indicates whether group is equally distributed across sub-categories using One-Way ANOVA, Chi-square or Fisher's Exact test when necessary.

^b SES based on the Barratt Simplified Measure of Social Status. Scores range from 8 to 66 with higher scores indicative of higher SES.

^c All values are presented as mean ± standard deviation.

^d WASI=Wechsler Abbreviated Scale of Intelligence; standard scores have a mean of 100 and standard deviation of 15. (Note: significant p-values [<0.05] are bolded).

Table II

Clinical Characteristics of Brain Tumor Survivors

	Met/Met n = 11	Met/Val n = 15	Val/Val n = 24	p ^a
Tumor Diagnosis				
Ependymoma	7	10	5	0.02
Low Grade Glioma	2	1	9	
Craniopharyngioma	2	4	10	
Tumor Location				
Infratentorial	7	9	6	0.03
Supratentorial	4	6	18	
Pre-CRT Chemotherapy				
No	10	13	21	1.00
Yes	1	2	3	
Extent of Surgical Resection ^b				
Biopsy/STR	3	4	18	<0.01
NTR/GTR	8	11	6	
Hydrocephalus				
No	2	4	15	0.02
Yes	9	11	9	
CSF Shunting				
No	6	9	14	0.96
Yes	5	6	10	

^a P-value indicates whether group is equally distributed across sub-categories using Chi-square or Fisher's Exact test when necessary.

^b STR=subtotal resection, NTR=near total resection, GTR=gross total resection. (Note: significant p-values [<0.05] are bolded).