Acute Neurocognitive Response to Methylphenidate Among Survivors of Childhood Cancer: A Randomized, Double-Blind, Cross-Over Trial

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Objective To investigate the acute efficacy and adverse side effects of methylphenidate (MPH) among survivors of childhood cancer [acute lymphoblastic leukemia (ALL) or brain tumor (BT)] with learning impairments. **Methods** Participants ($N = 122$) completed a two-day, in-clinic, double-blind, cross-over trial during which they received MPH (0.60 mg/kg of body weight) and placebo that were randomized in administration order across participants. Performance was evaluated using measures of attention, memory, and academic achievement. **Results** A significant MPH versus placebo effect was revealed on a measure of attention, cognitive flexibility, and processing speed (Stroop Word-Color Association Test). Male gender, older age at treatment, and higher intelligence were predictive of better medication response. No significant differences were found for number or severity of adverse side effects as a function of active medication. **Conclusions** MPH shows some neurocognitive benefit and is well tolerated by the majority of children surviving ALL and BT.

Key words brain tumor; leukemia; methylphenidate; stimulant medication.

Children surviving acute lymphoblastic leukemia (ALL) and malignant brain tumors (BT) are at increased risk for cognitive impairments relative to their healthy peers (e.g., Moleski, 2000; Ris & Noll, 1994). While initial reports demonstrated declines on indices of global functioning, including intelligence and academic achievement, more recent studies suggest that attention and/or working memory difficulties may underlie these declines (Rogers, Horrocks, Gritton, & Kernahan, 1999; Schatz, Kramer, Ablin, & Matthay, 2000). Neuroimaging findings have revealed decreased cerebral white matter volumes following cancer treatment that, in part, may mediate these cognitive changes (Reddick et al., 2003). Consistent with this model, earlier age at treatment and increased levels of central nervous system (CNS)-directed treatment are predictive of greater impairments (Mulhern & Butler, 2004). Cognitive impairments in children surviving ALL and BT are of significant concern as they have been shown to be associated with academic difficulties, high unemployment rates, and a reduced quality of life (e.g., Haupt et al., 1994; Mostow, Byrne, Connelly, & Mulivhill, 1991). Yet, there have been very few systematic attempts to develop interventions for remediating cognitive impairments subsequent to treatment for childhood cancer.

The efficacy of stimulant medications is well established in improving sustained attention in otherwise healthy children diagnosed with attention deficit hyperactivity disorder (ADHD; American Psychiatric Association, 1994). Methylphenidate (MPH) is the most commonly prescribed medication for ADHD. It is a piperidine derivative that acts by releasing dopamine from presynaptic vesicles, reducing dopamine reuptake, and inhibiting

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monoamine oxidase (Nelson, 1995). The most consistent benefits of MPH have been demonstrated on measures of attention and concentration, as well as observable classroom and social behavior (Brown et al., 2005). Improvements also have been observed for reaction time, paired-associate learning, and perceptual efficiency (e.g., Reid & Borkowski, 1984; Stephens, Pelham, & Skinner, 1984).

While it may seem logical to treat attentional problems with stimulant medication in cancer survivors, there is reason to believe that response rates and adverse side effects may differ for individuals with compromised neurological status (Weber & Lutschg, 2002). Evidence for the efficacy of MPH for attentional problems presumably secondary to cancer treatment is mixed based on preliminary studies in the pediatric population. In one study, 12 children with BTs or ALL were treated with an ''adequate trial'' of MPH for 6 months to 6 years. Based on parent and teacher reports, as well as direct observations, response was described as ''good'' for eight children, ''fair'' for two children, and ''poor'' for two children (DeLong, Friedmian, Gustafson, & Oakes 1992). A second study included six children with a history of learning, attention, and memory difficulties secondary to treatment with whole-brain irradiation for BTs (Torres et al., 1996). No improvements on attention or memory measures were revealed following MPH administration (0.3 mg/kg twice daily). An open-label trial of MPH for adults treated for BTs found significant improvements in psychomotor speed, memory, and executive function, despite disease progression in many patients (Meyers, Weitzner, Valentine, & Levin, 1998). These studies were generally limited by small sample sizes, poor sample characterization, nonoptimal dosing, and lack of appropriate controls.

The first randomized, double-blind trial of MPH among childhood cancer survivors was conducted by Thompson and colleagues (2001). Children selected both for problems with attention and academic achievement ($n = 32$) were randomized to receive either MPH (0.6 mg/kg) or placebo. Significant improvement was demonstrated on a continuous performance measure of sustained attention but not for measures of verbal memory or visual–auditory association. It should be noted that this study employed a between-groups rather than a cross-over design that may have reduced sensitivity to detect MPH effects. The same group of investigators recently reported on 83 childhood cancer survivors who participated in a 3-week, placebo-controlled, double-blind, cross-over study comparing low (0.3 mg/kg) and moderate (0.6 mg/kg) dose MPH to placebo (Mulhern et al., 2004). Significant improvement on MPH relative to placebo was noted on parent and teacher ratings of attention and teacher ratings of social skills. No neurocognitive measures were administered to evaluate medication response as part of this investigation.

In the current study, we expand upon the existing literature by reporting on the results of a randomized, double-blind, placebo-controlled, cross-over study assessing the acute benefits of MPH on laboratory measures of attention, memory, and academic achievement. The primary goal of this investigation was to determine the acute efficacy of MPH among a large sample of childhood survivors of ALL and BT, all of whom were identified with learning impairments demonstrated during the late effects period. Secondary goals included assessing the heuristic value of brief, laboratory measures for detecting positive medication response and evaluating the tolerability of MPH based on potential adverse side effects. Due to the preponderance of literature demonstrating significant beneficial effects of MPH in children with ADHD on measures of attention and concentration (Brown & Daly, in press), we hypothesized that children would demonstrate an improvement on MPH relative to placebo, with greater improvement on measures specifically associated with attention and processing speed than on measures of memory encoding/retrieval and productivity. Finally, we predicted that childhood cancer survivors would demonstrate reduced MPH tolerance, as revealed by a high frequency of adverse side effects compared to children diagnosed with ADHD, given the extant literature to suggest greater adverse effects of stimulant medication for children with a positive neurologic history (for review see Weber & Lutschg, 2002).

Methods

Participants

Individuals eligible for study participation were treated for a malignant BT or ALL with chemotherapy and/or CNS directed radiation therapy. Children completed cancer treatment at least 12 months prior to study enrollment with no evidence of recurrent disease, were between 6 and 18 years of age, and were primary English speakers. Exclusionary criteria included a *premorbid* ADHD diagnosis (prior to cancer diagnosis) as solicited by caregiver interview, uncontrolled seizures, uncorrected hypothyroidism, severe sensory loss that precluded valid psychometric testing, patient or family history of Tourette's syndrome, glaucoma, substance abuse history, or current

use of psychotropic medication. The protocol was approved by the Institutional Review Boards of the participating sites [St Jude Children's Research Hospital (SJCRH), Duke University Medical Center (DUMC), and Medical University of South Carolina (MUSC)]. Written informed consent was required from a legal guardian prior to participation. Patient enrollment began in January of 2000.

Procedures—Study Screening Phase

Medical record review was used to establish initial study eligibility. The parents of identified patients were sent an introductory letter or approached during routine visits to the hospital. If interested in participation, the patient was scheduled for a clinic visit. A screening battery consisting of psychological tests was administered and parent/teacher report forms were obtained. This information was used to identify patients with a cognitive phenotype hypothesized to be responsive to MPH (Thompson et al., 2001), individuals with adequate global functioning, attention problems, and academic difficulties. Of the 428 patients screened, 188 met screening criteria. Nearly two-thirds of these qualifying participants ($N = 122$) agreed to participate in the MPH trial. Screening measures and inclusion criteria are described subsequently.

Wechsler Intelligence Scales

Intellectual functioning (IQ) was estimated based on the Information, Similarities, and Block Design subtests from the age-appropriate Wechsler scale [Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1991) and Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997)] using a formula provided in Sattler (Sattler, 1992). Age-based scaled scores, with a mean of 100 and SD of 15, were derived using each standardization sample. This method for estimating IQ has been demonstrated to correlate highly with IQs derived from full test administration ($r = .93$; Sattler, 1992). Participants were required to have an estimated IQ ≥ 50 to participate in this study.

Conners' Continuous Performance Test (CPT)

The CPT (Conners, 1995) is a computerized measure of selective and sustained attention. For this 14-min task, letters are presented one at a time on a computer screen for 250 ms each. Children are instructed to press the space bar as quickly and accurately as possible for any letter (targets) except the letter "X" (nontarget), which appears on 10% of the 360 trials. Interstimulus intervals vary by trial blocks with lengths of 1, 2, or 4 s. Test–retest reliability for the CPT, with a 3-month interval, ranges from .55 to .84 (Conners, 2000a). Construct validity is indicated by performance differences between children with and without ADHD diagnoses (Seidel & Joschko, 1990). The CPT is used regularly to monitor response to medication in children with ADHD and has negligible practice effects for repeat administration (Conners, 1995). The CPT program computes hit rates (correctly responding to a target), omission errors (failing to respond to a target, suggestive of inattention), commission errors (responding to the nontarget "X", suggestive of impulsivity), reaction time, sensitivity (d′), and response bias (β). For study inclusion, the participant was required to have omission errors $\geq$ 75th percentile for age and gender.

Conners' Rating Scales-Revised (CRS)

The Conners' Parent Rating Scale (CPRS) and Conners' Teacher Rating Scale (CTRS) are designed to assess symptoms and behaviors associated with ADHD (Conners, 2000b). The short form was used for screening purposes, which is comprised of 27 (parent) or 28 (teacher) items rated on a scale from 0 (not true at all) to 3 (very much true). From these items an ADHD Index and multiple behavior scales are derived. Internal consistency reliabilities for this measure range from .86 to .94 for the parent form and .88 to .95 for the teacher form. Evidence for criterion-oriented validity includes significant correlations with the Conners' CPT (e.g., CPT Overall Index correlates with Cognitive Problems/Inattention from the CRS .44 for the parent form and .53 for the teacher form). To be included in this study, participants were required to have a score $\geq$ 75th percentile on one or more of the following scales: ADHD Index, Hyperactivity, or Cognitive Problems/Inattention.

Wechsler Individual Achievement Test (WIAT)

The WIAT (Wechsler, 1992) is an individually administered test of academic achievement. For screening purposes, five subtests were administered: Basic Reading, Reading Comprehension, Spelling, Numerical Operations, and Mathematics Reasoning. The WIAT was standardized using the same sample as the WISC-III. Age-based standard scores, with a mean of 100 and SD of 15, were derived. Internal consistency reliabilities for the selected subtests range from .81 to .95. Criterion-oriented validity for these subtests, as derived from correlations with the Kaufman Test of Education Achievement, range from .73 to .87. For study inclusion, participants were required to have a standard score $\leq$25th percentile in at least one academic area.

Child Behavior Checklist (CBCL)

The CBCL is a parent rating measure of social competencies and behavior problems (Achenbach & Edelbrock, 1991). It is composed of 113 items rated on a scale from 0 (not true) to 2 (often true), from which standard scores are derived, each with a mean of 50 and *SD* of 10. Test–retest reliabilities for clinical scales range from .82 to .95. Criterion-oriented validity is indicated by correlations with the closest counterpart scales from the Conners' Parent Questionnaire ranging from .56 to .86.

The CBCL was used to screen for emotional problems that may impact MPH responsiveness (e.g., DuPaul, Barkley, & McMurray, 1994). A standard score $\geq$70 on the anxious/depressed scale prompted a diagnostic interview conducted by a psychologist to rule out mood disorders or anxiety-related disorders. Thirteen of the 188 patients meeting screening criteria exhibited this CBCL elevation; one was excluded from the study due to the presence of a mood disorder.

Procedures— Clinical Trial Phase

For those patients meeting the inclusion criteria outlined previously, arrangements were made for participation in the MPH clinical trial that took place in an out-patient clinic across two consecutive days. Participants were stratified on the basis of age at CNS treatment (<4 years and $\geq$4 years) and intensity of CNS therapies (mild— systemic and/or intrathecal chemotherapy only; moderate— $\leq$24 Gy CRT with or without systemic and/or intrathecal chemotherapy, and high— >24 Gy CRT with or without systemic and/or intrathecal chemotherapy) due to differential cognitive risk associated with these factors. Following stratification, participants were assigned to receive a single dose of MPH (0.60 mg/kg; maximum dose 20 mg) and placebo (consisting of an inert substance) in a randomized, double-blind, cross-over design. Randomization was conducted by the pharmacist at SJCRH and communicated to pharmacists at DUMC and MUSC. Other personnel were blind to the order of MPH and placebo administration. Approximately 90 min following MPH/placebo ingestion, testing was completed to investigate performance on and off active medication. The following measures were administered during both days of the cross-over trial.

Brief Continuous Performance Test (CPT)

The continuous performance test used during the cross-over MPH trial was developed in house using SuperLab Pro v2.0 (Cedrus Corp., Phoenix, AZ). The test was modeled after Conners' CPT, but was shortened for ease of administration and evaluation of short-form sensitivity. The test is one-sixth the length of the Conners' CPT, lasting 2.33 min with 54 total targets and six nontargets (10% of trials). Similar to the Conners' CPT, the interstimulus intervals also varied by trial blocks with lengths of 1, 2, or 4 s. CPT hits, omission errors, commission errors, reaction time, sensitivity (d′), and response bias (β) were derived. Correlations between this measure and the full length Conners' CPT for a subset of this sample ($n = 54$) are significant and of modest to moderate size for hits, omissions, commissions, reaction time, β, and d' ($p < .05$; $r = .30 - .63$), indicating criterion-oriented validity.

Stroop Word-Color Association Test (Stroop)

The Stroop is a timed measure of selective attention, impulsivity and cognitive flexibility (Golden, 1978). There are three conditions that require the examinee to: read the names of colors printed in black ink, name the ink color of printed ''X''s, and name the ink color in which an incongruent color name is printed (e.g., say ''blue'' for the word ''green'' written in blue ink). The core cognitive process is the ability to inhibit the prepotent response to read the word. The primary dependent variable is the age-standardized score representing the decrease in word reading speed for the incongruent ink-word condition. Standard scores for this measure have a mean of 50 and *SD* of 10. Test–retest reliabilities for each Stroop condition range from .73 to .89. Evidence for construct validity of the Stroop is provided by expected developmental improvements, lack of gender differences, and sensitivity to brain injury as documented in the test manual.

California Verbal Learning Test-Children's Version (CVLT-C)

The CVLT-C (Delis, Kramer, Kaplan, & Ober, 1994) is a verbal memory measure that requires the child to recall a list of 15 words (List A) after each of five exposure trials, after exposure to an interference list (List B), after short and long delays, and with semantic and recognition cues. The List A Total Recall score, representing the number of words recalled after five exposures, is converted to a standard score with a mean of 50 and *SD* of 10. In addition to this global score, variables from Donders' five-factor model (1999) were examined: words recalled following initial exposure to List A (Attention Span), words recalled following the fifth exposure to List A (Learning Efficiency), words freely recalled following a long delay (Free Delayed Recall), words recalled following a long delay with cueing (prompted to provide words from specific categories; Delayed Cued Recall), and false positives during the recognition trial (incorrectly answering ''yes'' to a word being from List A;

Inaccurate Recall Factor). These scores are converted to standard scores with a mean of 0 and *SD* of 1, provided in 0.5 increments. Internal consistency reliabilities for the CVLT-C range from.81 to.88. Support for CVLT-C construct validity comes from factor analytic findings revealing indices that cluster into theoretically meaningful factors that are consistent with experimental constructs and the adult version of the CVLT.

Visual-Auditory Learning Test (VAL)

The VAL subtest from the Woodcock Johnson Cognitive Battery (Woodcock & Johnson, 1989) requires the examinee to learn, store, and retrieve a series of visual–auditory associations. The child must learn to associate rebus figures (pictographic representations of words) with English words in order to read increasingly complex passages. A single age-corrected standard score, with a mean of 100 and *SD* of 15, is derived using the test's standardization sample, which represents the patient's rate of learning. The internal consistency reliability of this subtest ranges from .86 to .92. Construct validity for the VAL subtest is supported by a significant correlation of .65 with the long-term retrieval factor.

Wide Range Achievement Test (WRAT)

Math problems from alternate forms of the WRAT math subtest (Wilkinson, 1993) were administered in both medication conditions as a measure of productivity. The dependent variables of interest were the number of completed items and percentage of correct responses among completed items. The alternate forms of the WRAT math subtest have internal consistency reliabilities ranging from .78 to .89. Construct validity for the math subtest is provided by correlation with the California Test of Basic Skills, Fourth Edition ($r = .79$ with the total math score).

Barkley's Side Effects Rating Scales (SERS)

Participants were observed by the study team for 4–6 h (including the cognitive testing time) to monitor for side effects. At the end of this time period, the study nurse asked the child and parent questions to gain information about common side effects of stimulant medication prior to allowing them to leave the clinic. The family was also provided a list of common side effects (in the consent form), and was instructed to contact the study team if any symptoms developed after leaving the clinic. Any observed or reported symptoms were documented and discussed with the study physician and research team. The SERS was added to the study midway through participant accrual to supplement these subjective assessments of side effects. Parents ($n = 48$) completed the SERS (Barkley, 1981), which assesses 17 common side effects of stimulant medication rated on a severity scale from 0 (absent) to 9 (severe). Parents completed the SERS the morning after each of the two medication trial days in order to allow for a long enough evaluation period to rate symptoms such as sleep.

Statistical Considerations

As a consequence of using a cross-over design, performance on laboratory measures of cognition is not only affected by the treatment condition (MPH or placebo) but also potentially by carry-over effects from one period to the next (e.g., practice effects). The use of conventional repeated measures analysis of variance is precluded by significant carry-over effects, especially if they are asymmetric. Initial analyses of each of the cognitive outcome variables revealed significant ($p < .05$) carry-over effects for 8 out of 18 variables. Based on these findings, a model was developed that included factors for carry-over effects (Milliken, 1992) that was used to assess the effect of MPH relative to placebo on performance for each cognitive measure.[1] The SAS procedure for mixed models was used for analysis of this cross-over model

[1]The cross-over design is similar to pre-post tests in that different treatments are administered to the same participant in different periods rather than to different participants in one period. In a cross-over design, participant effects are canceled out such that sample sizes can be smaller for achieving the same power of statistical tests. These designs can only be used in studies in which the treatment effect tapers quickly after treatment stops. The cross-over design offers benefits over the pre-post design that include the ability to blind patients or investigators to treatment type and to estimate carry-over effects of treatments statistically in order to isolate true treatment effects.

For the current study, performance on laboratory measures are not only affected by treatment (placebo or MPH), but also potentially by the order of conditions (i.e., placebo preceding MPH or MPH preceding placebo) and carry-over effects (from previous period to the next period). Therefore, a model was developed including these factors: $Y_{ijkm} = \mu + D_j + P_k + C_{j(k-1)} + S_{im} + \varepsilon_{ijkm}$, where μ is the overall mean, D_j is the effect of the j-th treatment ($j = 1, 2$ for Placebo, MPH), P_k is the effect of the k-th period ($k = 1, 2$ for day one and day two), $C_{j(k-1)}$ is the carry-over effect of the dose in previous period [i.e., (k-1)-th period], S_{im} is a random effect of m-th patient (m-1, . . . ,) in the i-th permutation sequence ($i = 1, 2$), and ε_{ijkm} is a random error of response variable from the m-th patient taking the j-th dose at the k-th period of i-th sequence. There were not enough degrees of freedom for both period and carry-over effects due to confounding of the two factors. It is reasonable to assume that the effect of a period is completely specified by the combination of treatment effects and carry-over effects in that period such that inclusion of period effects in the model would be redundant and distorting to the treatment and carry-over effects. By imposing constraints of $P_k = 0$ for $k = 1, 2$, the model can be reduced to: $Y_{ijkm} = \mu + D_j + C_{j(k-1)} + S_{im} + \varepsilon_{ijkm}$ This second model was used for statistical analysis using the SAS procedure for mixed models.

(SAS Institute, Cary, NC). *P*-values $<.05$ were set as the threshold for statistical significance (two-tailed). To minimize the family-wise error rate, *p*-values were also adjusted using the Sidak method. These *p*-adjusted values were calculated by $\sim p_j = 1-(1-p_j)^k$, where p_j is the unadjusted *p*-value for the *j*-th test and *k* is the number of multiple tests.

To intuitively investigate MPH related changes in performance on cognitive measures, the percentage of participants showing a positive or negative change (for MPH relative to placebo) on each cognitive measure, taking into account mean carry-over effects, was compared using the binomial statistic. Logistic regression was used to estimate the effects of select clinical variables (ALL or BT diagnosis, age at treatment, time since treatment, gender, IQ and treatment intensity) on the cognitive score changes and odds ratios were computed as indicators of the magnitude of effect. MPH side effects, as rated by the primary caregiver on the SERS, were subjected to descriptive analyses. The percentage of reported symptoms both on placebo and MPH were compared statistically.

Results

Participant Characteristics

Of the 428 screened patients, 232 were ineligible based on neurocognitive performance: 5 for IQ < 50, 55 failed to demonstrate attention difficulties on the CPT and/or CRS, 59 failed to demonstrate achievement difficulties on the WIAT, and 113 failed to demonstrate achievement difficulties on the WIAT and attention difficulties on the CPT and/or CRS. Eight patients did not qualify based on other medical (e.g., progressive disease or contraindicated medications) or psychological (e.g., depression) reasons. For those children that qualified but whose parents refused study participation ($n = 66$), the most common reason cited was concern about placing their child on a stimulant medication. Other less frequently cited reasons included disinterest in having their child take any more medication, with no specific objection to stimulant medication, and disinterest in dedicating time for study participation.

Demographic and clinical characteristics of the sample included in the MPH trial are presented in Table I. The sample consisted of 122 participants (71 males, 51 females) between the ages of 6 and 18 years ($M = 11.76$; $SD = 2.30$) who were 1 to 14 years ($M = 4.71$; $SD = 2.90$) post-treatment initiation at the time of study participation. The sample was largely Caucasian (84%) and largely middle class based on parental education levels (~90% high school graduates, including ~20% college graduates). Half of the sample was diagnosed with a BT and half with ALL. Of the sample, 39% were treated with chemotherapy only (mild intensity), 14% with ≤24 Gy CRT with or without chemotherapy (moderate intensity), and 47% with >24 Gy CRT with or without chemotherapy (high intensity). The BT sample received more intense treatment with 8.2, 0, and 91.8% receiving mild, moderate, and high intensity treatment, respectively versus 70.5, 27.9, and 1.6% of the ALL sample receiving mild, moderate, and high intensity treatment, respectively.

Table I. Demographic and clinical characteristics of the childhood cancer survivor sample ($N = 122$)

	N	%
Gender		
Male	71	58.20
Female	51	41.80
Ethnicity		
Caucasian	103	84.43
African American	17	13.93
Other/Unknown	2	1.64
Father's level of education		
Did not complete high school	15	12.3
Completed high school	42	34.4
Some college/technical school	26	21.3
Bachelors degree	17	13.9
Graduate degree	13	10.7
Unknown	9	7.4
Mother's level of education		
Did not complete high school	12	9.8
Completed high school	44	36.1
Some college/technical school	37	30.3
Bachelors degree	20	16.4
Graduate degree	5	4.1
Unknown	4	3.3
Diagnosis		
Brain Tumor	61	50.00
ALL	61	50.00
Age at treatment		
<4 years old	44	36.1
≥4 years old	78	63.9
CNS treatment intensity		
Chemotherapy only	48	39.34
≤24 Gy CRT ± chemotherapy	17	13.93
>24 Gy CRT ± chemotherapy	57	46.72
	$M \pm SD$	Range
Age at cancer treatment (years)	5.29 ± 2.91	0.57–14.25
Age at study participation (years)	11.76 ± 2.30	6.64–18.26
Years after cancer treatment	4.71 ± 2.90	1.07–14.23
Estimated IQ at screening	87.15 ± 15.62	50.00–118.00

ALL, Acute Lymphoblastic Leukemia; CRT, Cranial Radiation Therapy.

Approximately one-third of the sample (36%) was treated at <4 years of age. Average estimated IQ at the time of screening was in the low average range ($M = 87$; $SD = 16$). Patients diagnosed with BT did not differ significantly from patients diagnosed with ALL on estimated IQ (BT $M = 86.46$; $SD = 2.10$ vs. ALL $M = 87.84$; $SD = 1.91$; $p = .63$).

Therapeutic Effects

The therapeutic effects of MPH were evaluated relative to placebo in terms of performance on laboratory measures of cognition, after correcting for carry-over effects. As shown in Table II, the only change to reach statistical significance using the mixed model is ink color naming time for the incongruent color name Stroop condition, with quicker times following MPH administration. Beta from the CPT reached the trend level of significance. For each cognitive measure, the percentage of participants showing a positive or negative change on MPH versus placebo, taking into account carry-over effects, was computed. Findings revealed a significantly greater positive than negative change on all Stroop indices and recognition false positives from the CVLT-C (binomial test; $p < .005$).

Logistical regression was used to estimate the effects of clinical variables on positive medication response. Diagnosis, treatment intensity, and time were not predictive of MPH response on any measure since treatment. Gender (better response for males) was predictive of Stroop ink color naming speed [$p < .05$, Odds Ratio (OR) = 2.71], age at treatment (better response for those > 4 years of age) was predictive of Stroop word naming and ink color naming speeds ($p < .05$, OR = 2.78; $p < .05$, OR = 2.72, respectively),

Table II. Mean values and group differences for placebo and methylphenidate (MPH)[a]

	Placebo value[b]		MPH change value[b]			
Variable	*M*	*SE*	*M*	*SE*	*p*	*p*-adjusted[c]
Continuous Performance Test						
Omission errors (#)	1.94	0.55	−0.50	0.77	.52	0.974
Commission errors (#)	3.67	0.25	−0.01	0.34	.97	1.000
Reaction time (ms)	344.23	10.15	4.83	14.35	.74	0.999
d' (raw)[d]	1.64	0.15	0.02	0.20	.92	1.000
β (raw)[d]	0.31	0.03	−0.09	0.06	.06[†]	0.262
California Verbal Learning Test						
Trials 1-5 (T-score)[e]	46.80	1.73	−1.17	2.43	.63	0.998
Trial 1 (Z-score)[f]	−0.24	0.20	0.17	0.28	.55	0.992
Trial 5 (Z-score)	−0.30	0.19	−0.24	0.27	.39	0.946
Long delay free recall (Z-score)	−0.21	0.15	−0.02	0.21	.92	1.000
Long delay cued recall (Z-score)	−0.27	0.15	−0.06	0.21	.76	1.000
Recognition false positives (Z-score)[g]	−0.32	0.22	0.35	0.30	.25	0.826
WJIII visual–auditory learning						
Total learning score (Standard score)[h]	96.07	2.50	−0.87	3.50	.80	0.800
Stroop Word–Color Association Test						
Word naming time (T-score)	37.69	1.08	1.52	1.51	.31	0.783
Color naming time (T-score)	39.64	1.07	1.40	1.50	.35	0.825
Ink color naming time (T-score)	41.38	1.09	3.88	1.53	.01*	0.047*
Interference score (T-score)	50.41	0.95	1.96	1.32	.14	0.449
Wide Range Achievement Test						
Number of problems completed[i]	4.38	0.14	−0.08	0.19	.69	0.961
Percent of problems correct[j]	1.00	0.03	−0.06	0.04	.20	0.360

[a]Group sample sizes vary slightly across measures due to missing data as follows: CPT ($N = 112$), STROOP ($N = 119$), CVLT-C ($N = 114$), WRAT ($N = 119$), VAL($N = 120$). [b]Scores are statistically corrected for carry-over effects. [c]To minimize the family-wise error rate, *p*-values were adjusted using the Sidak method. These *p*-adjusted values were calculated by $\sim p_j = 1 - (1 - p_j)^k$, where p_j is the unadjusted *p*-value for the *j*-th test and k is the number of multiple tests (e.g., k is 5 for the CPT). [d]Variables derived from signal detection theory. D′ is a measure of sensitivity of a person to the signal or target; a higher score is better. β is a measure of response tendency; higher scores indicate a more conservative response pattern. We used standard formulas for their calculation. D′ was calculated as z(hit) − z(commission). Z-scores were calculated using the NORMSINV function in Microsoft Excel. β was calculated using the formula = −d′*.5*(NORMSINV(hits)-NORMSINV(false alarms)). In the case where the false alarm rate = 0 or the hit rate = 1.0, we used the standard correction of 1/2*N* and 1- 1/2*N*, respectively. [e,f,h]T-scores have a normative mean score = 50 and an $SD = 10$; higher scores are better. *Z*-scores have a normative mean score = 0.0 and an $SD = 1.0$; higher scores are better. Standard scores have a normative mean score = 100 and an $SD = 15$; higher scores are better. [g]Recognition false positives are scored such that a higher score is worse. For consistency with other Z-scores reported here, they were reversed cued such that a higher score is better. [i]A square-root transformation was used to normalize the data. [j]An arcsine-root transformation was used to normalize the data. $*p < .05$. $^{\dagger}p < .10$.

and IQ (better response for IQ > 70) was predictive of Stroop ink color naming speed, and CVLT recognition false positive rate ($p < .05$, OR = 3.05; $p < .05$; OR = 0.21, respectively). Given the relatively low required IQ for study eligibility (i.e., estimated IQ ≥ 50) and the finding of IQ as a predictor of MPH response on certain cognitive measures, the analyses in Table II were repeated after excluding individuals with an IQ < 70. All the findings in Table II remain the same regarding statistical significance with two minor exceptions. Interestingly, the *p*-value for CPT β changes from a trend level, $p = .06$, to a significant value, $p = .01$, in the higher functioning IQ group. The *p*-value for Stroop ink color naming changes from a significant value, $p = .01$, to a trend level, $p = .06$, which likely results from the decreased power incurred with dropping one-fourth of the sample.

Group performance both following MPH and placebo was evaluated relative to normative samples for the cognitive measures by comparing the scores reported in Table II to normative sample means using one-sample *t*-tests (i.e., 50 ± 10 for T-scores, 0 ± 1 for Z-scores, and 100 ± 15 for standard scores). All variables of the Stroop were significantly below normative expectations (slower response rates) both on placebo and following MPH; performance was improved and less discrepant from norms following MPH. Select variables from the CVLT-C (Trial A Total Recall, List A Trial 5, and Long Delayed Cued Recall) also significantly differed from the normative sample. Performance was slightly lower than normative expectations following MPH but differences between MPH and placebo did not reach statistical significance.

Adverse Side Effects

Of the 122 patients participating in the MPH trial, 12 exhibited a serious reaction to MPH (equivalent to a SERS score ≥7) resulting in the research team discouraging future MPH use or recommending the use of a lower dose. Of these 12 patients, 6 had SERS ratings and 6 had ratings retrospectively determined based on earlier documentation of subjective assessments. Table III provides the percentage of participants exhibiting each SERS symptom for the 48 patients with parent ratings. At the symptom level, there was a significant difference for appetite loss and a trend level difference for tics/nervous movements, with more frequently reported

Table III. Parent report on Barkley's Side Effects Rating Scales (SERS; $N = 48$)[a]

	Placebo		Methylphenidate		
Side effect	Any[b]	Severe[c]	Any	Severe	*p* (*any*)
Trouble sleeping	7.50	0.00	20.90	0.00	.12
Prone to crying	12.50	0.00	23.30	2.33	.26
Irritable	25.00	0.00	30.20	2.33	.63
Anxious	17.50	0.00	30.20	0.00	.21
Sad/unhappy	12.50	0.00	23.30	2.33	.26
Decreased appetite	12.50	0.00	41.90	2.33	.00*
Drowsiness	15.00	0.00	18.60	2.33	.77
Stares a lot or daydreams	10.00	0.00	11.60	2.33	1.00
Talks less with others	10.00	0.00	11.60	2.33	1.00
Uninterested in others	5.00	0.00	9.30	2.33	.68
Bites fingernails	12.50	0.00	18.60	0.00	.55
Dizziness	7.50	0.00	18.60	2.33	.20
Euphoric/unusually happy	10.00	0.00	11.60	0.00	1.00
Headaches	7.50	0.00	20.90	2.33	.12
Nightmares	5.00	0.00	4.65	0.00	1.00
Stomachaches	10.00	2.50	20.90	0.00	.23
Tics or nervous movements	5.00	0.00	18.60	2.33	.09†
Summary statistics	*M* ± *SD*	*M* ± *SD*	*p*		
Number of symptoms endorsed[d]	3.52 ± 2.04	4.50 ± 2.79	.18		
Severity of symptoms rated	2.34 ± 1.72	2.68 ± 1.57	.46		
Maximum symptom severity	3.19 ± 1.99	3.69 ± 2.13	.40		

SERS assesses 17 common side effects of stimulant medication rated on a severity scale from 0 (absent) to 9 (severe).

[a]The SERS was added to the study mid-way through participant accrual to supplement subjective assessments of side effects. [b]Represents the percent of individuals rating the symptom >0. [c]Represents the percent of individuals rating the symptoms ≥7. [d]Numbers of symptoms endorsed is the total number of items with a severity rating >0.

*$p < .05$, in the reporting of any symptoms following placebo and MPH. †$p < .10$, in the reporting of any symptoms following placebo and MPH.

symptoms following MPH. SERS ratings did not reveal a significant difference between average number of symptoms endorsed or severity of ratings following MPH versus placebo.

Discussion

This investigation is unique as it is the first known study to employ a cross-over design to assess acute MPH response on laboratory measures of cognition among childhood cancer survivors. It is also the largest sample of cancer survivors in a report investigating the efficacy of MPH. Those domains most responsive to MPH in the current study were measures of processing speed and response tendency. Only a trend toward significance was revealed on the measure of sustained attention and concentration. Contrary to *a priori* hypotheses, measures of attention were not particularly sensitive to MPH effects, neither were most measures of memory encoding/retrieval or productivity. The current findings provide some evidence that male gender, older age at treatment, and higher intellectual functioning predict a better medication response.

Of particular interest is the significant MPH effect revealed on a measure of selective attention, impulsivity, and cognitive flexibility (Stroop Word-Color Association Test), while only a trend toward significance was revealed on the measure of sustained attention and concentration (Continuous Performance Task). The extant literature for children with ADHD has been fairly consistent in attesting to the efficacy of stimulant medication on tasks of sustained attention and concentration (for review, see Brown & Daly, in press). It is likely that our weak findings for the CPT reflect the use of a revised, shortened, CPT for this investigation that may have produced floor effects thereby mitigating the medication's potential efficacy on this particular measure. Emerging research findings indicate that children with ADHD also demonstrate an acute MPH response on the Stroop indicating that this measure is of heuristic value for monitoring clinical response (Bedard, Ickowicz & Tannock, 2002; Langleben, et al., 2006).

While the finding of selective impairment on the Stroop ink color naming condition was not predicted, there is evidence to support this finding in the literature. It has been argued that color naming requires greater attention than word reading, particularly for the incongruent condition (Stuss, Floden, Alexander, Levine, & Katz 2001). Consistent with this argument, Tannock, Martinussen, and Frijters (2000) found that children with ADHD, with or without a reading disorder, obtained longer response latencies on rapid naming of colors and objects, but not letters or numbers. Further, MPH selectively improved color-naming speed but had no effect on the speed of naming letters or digits. Tannock et al. concluded that effortful semantic processing (as required for color and object naming but not letter or number naming) was impaired in children with ADHD and that this can be improved but not normalized with stimulant medication. Stuss et al. (2001) demonstrated that performance on different Stroop conditions can be dissociated based on the location of brain lesions, with increased errors and slowness for the incongruent condition following bilateral, superior medial frontal damage. They posit that damage to the prefrontal lobes should disrupt performance most for the incongruent STROOP condition given their role in establishing response selection, maintaining constant activation of the intended goal, and inhibitory processes. Taken together, these findings suggest that childhood cancer survivors selected for attention difficulties may share a similar underlying functional deficit with children with ADHD, namely impairment in frontal lobe functioning, that is contributing selectively to color naming, and is improved by stimulant medication.

Our findings suggest that for childhood cancer survivors with learning impairments, stimulant medication exerts an influence on selective attention, impulsivity, and cognitive flexibility, impairments that are frequently observed among children with learning disabilities. These findings are of interest as they suggest that MPH exerts some response on learning impairments experienced by childhood cancer survivors. Unfortunately, in our investigation, no significant effects were revealed for a putative task of academic productivity or accuracy. Future research efforts will need to examine the effects of MPH on higher order academic skills to determine whether there is potential generalization from the positive effects of stimulant medication on selective attention and cognitive flexibility to specific academic skills (e.g., executive aspects of planning, organization, and monitoring). Further, it may be that a course of MPH, rather than a single dose, would result in academic improvement subsequent to improved on-task performance in the classroom. The latter question is currently under investigation.

Parent ratings of medication side effects were not greater in frequency or severity when compared to a large study of children treated with MPH for ADHD (Efron, Jarman, & Barker, 1997). However, there may be

a subset of childhood cancer survivors who are more sensitive to medication side effects as indicated by infrequent but extreme reactions in the current study. Consistent with this observation, prior work from our group has revealed severe reactions in a small group of brain tumor survivors on higher MPH doses (Mulhern et al., 2004). This finding suggests that children with neurological involvement may experience more adverse side effects to stimulant medications relative to their healthy peers. In considering treatment guidelines for childhood cancer survivors with attention problems, the practitioner must be judicious in prescribing stimulant medication and careful monitoring of side effects must be the standard of care.

When considered in the context of earlier research, the data are of particular interest. Thompson et al. (2001) employed the same patient selection criteria as used in the current study and investigated response to MPH in a randomized two group (versus cross-over) study design. Findings revealed a positive response on a continuous performance measure of attention but not on measures of verbal memory or visual-auditory learning. While largely consistent with the current findings, we did not obtain a significant medication response on the continuous performance measure. Future research must be conducted to shed light on this discrepancy. The most probable explanation is that the abbreviated continuous performance measure in the current study was not sufficiently sensitive to detect the effect of MPH. This is an important negative finding as it suggests that shortening the CPT for ease of administration is not an acceptable practice for assessing medication response.

Of the children in the current study, 83 went on to participate in a randomized, double-blind, placebo-controlled, home-crossover study (Mulhern et al., 2004). In that investigation, significant improvement on MPH relative to placebo was reported by both parents and teachers on standardized behavioral ratings of attention and by teachers on standardized behavioral ratings of social skills. Taken together, findings from these two studies suggest that parent and teacher ratings may be more sensitive to MPH response than laboratory, performance-based measures. These observations are, in part, consistent with the literature of children diagnosed with ADHD. A number of studies employing performance-based measures of attention, concentration, and executive functions have failed to detect differences between children with ADHD and their typically developing peers. Thus, one possibility for our failure to obtain significant differences in the current investigation is that the dependent measures chosen for this study may not have been sufficiently sensitive to identify medication effects. Our failure to obtain significant effects on measures of academic achievement and learning is consistent with the literature examining the effects of stimulant medication on academic achievement among children with ADHD. Findings from these studies have generally indicated that stimulant medications yield positive effects on direct observations of on-task behavior, including productivity, but have not revealed effects on standardized academic achievement tests (for review see Brown and Daly, in press).

The statistical model used in the current study is unique as it allows for careful analysis of carry-over effects from one period to the next. There were no significant carry-over effects for indices from the continuous performance measure of attention, in keeping with prior research, or the measure of academic achievement, in keeping with use of alternate forms. In contrast, both memory measures had significant carry-over effects. Thus, it is reasonable to suggest that many, if not all, of these carry-over effects relate to practice-effects, including prior exposure to memory stimuli. While the statistical model used in the current study provides sufficient power to detect differences after accounting for carry-over effects, the use of alternate forms, particularly for skill areas prone to practice effects, is recommended for future studies.

In the current study, the estimated mean IQ of individuals screened for participation and those participating in the clinical trial was within the average range. However, there was a group of participants ($n = 19$) with an IQ < 70 (mental retardation range), and they were found to have a less favorable medication response for specific cognitive domains. This finding suggests that those children most globally impaired following treatment for cancer may be least responsive to MPH. In fact, there is some indication in the literature that individuals diagnosed with mental retardation are less responsive to stimulant medication (e.g., Aman, 1982) and that poorer response to stimulant medication is associated with lower intellectual functioning (Handen, Janosky, McAuliffe, Breaus, & Feldman 1994). Given the increased rate of global cognitive difficulties in the childhood cancer population, this relationship is particularly important in determining the benefits of medication management of attention. Thus, the astute practitioner must be especially cautious in carefully monitoring not only safety but also efficacy in children with specific challenges including mental retardation.

The current findings should be interpreted in the context of study limitations. The use of an abbreviated continuous performance test likely limited sensitivity to detect MPH effects on attention and concentration. Careful replication of this finding with more sensitive measures in a cross-over design is warranted. The selection criteria in this study targeted those in greatest need of intervention; however, the comorbidity of both attentional and learning problems may not be truly representative of all pediatric late effects cancer samples. Future studies of children with attention problems without learning difficulties are warranted. The current study was not designed to investigate whether MPH benefits are maintained over time or observed in naturalistic settings. Greater research efforts are needed to evaluate behavior patterns across ecologically valid settings.

Despite these limitations, the current findings indicate that MPH provides improvement for some cognitive difficulties common to children surviving cancer with CNS directed therapy, problems for which competing interventions have been largely unsubstantiated (Butler & Mulhern, 2005). These findings highlight the importance of measure selection in assessing medication response and the benefits of including informant ratings of children's behavior in their naturalistic setting (e.g., at home or at school) by parents and teachers. Based on these findings, it is recommended that prescribing physicians work closely with psychologists in monitoring medication response for childhood cancer survivors in order to balance cognitive and behavioral benefits with potential adverse side effects.

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