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Influence of Methylphenidate on Long-Term Neuropsychological and Everyday Executive Functioning After Traumatic Brain Injury in Children with Secondary Attention Problems

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Abstract

Objective: To investigate the effects of methylphenidate on long-term executive and neuropsychological functioning in children with attention problems following TBI, as well as the relationship between methylphenidate associated changes in lab-based neuropsychological measures of attentional control, processing speed, and executive functioning and parent- or self-report measures of everyday executive functioning. **Method:** 26 children aged 6–17 years, who were hospitalized for moderate-to-severe blunt head trauma 6 or more months previously, were recruited from a large children's hospital medical center. Participants were randomized into a double-masked, placebo-controlled cross-over clinical trial. Participants completed a comprehensive neuropsychological battery and parent- and self-report ratings of everyday executive functioning at baseline, and at 4 weeks and 8 weeks following upward titration of medication to an optimal dose or while administered a placebo. **Results:** Methylphenidate was associated with significant improvements in processing speed, sustained attention, and both lab-based and everyday executive functioning. Significant treatment-by-period interactions were found on a task of sustained attention. Participants who were randomized to the methylphenidate condition for the first treatment period demonstrated random or erratic responding, with slower and more variable response times when given placebo during the second period. **Conclusion:** Results indicate that methylphenidate treatment is associated with positive outcomes in processing speed, sustained attention, and both lab-based and everyday measures of executive functioning compared to placebo group. Additionally, results suggest sustained attention worsens when discontinuing medication.

Keywords: Attentional control, processing speed, cross-over, reaction time, pediatric, ADHD

INTRODUCTION

Traumatic brain injury (TBI) is one of the most common causes of acquired morbidity and mortality in children (Taylor et al., 2017). Because these injuries occur at an early age, often before certain skills have emerged, they can result in residual deficits as the individual continues to develop (Anderson et al., 2009; Babikian et al., 2015), including psychiatric and neurobehavioral problems (Bryant et al., 2010; Dennis et al., 1995; Fenwick & Anderson, 1999; Massagli et al., 2004). Attention problems are prevalent following injury and can negatively impact school functioning, social relationships, emotional well-being, self-esteem, and quality of life (Anderson et al., 2009; Catroppa et al., 2007; Kaufmann et al., 1993). Many children with no premorbid diagnosis of ADHD meet diagnostic criteria for ADHD post-TBI. This condition, referred to as secondary ADHD (SADHD), is one of the most common secondary diagnoses in children after TBI (Bloom et al., 2001) with approximately

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16% of individuals meeting diagnostic criteria 6 months post-injury (Yeates et al., 2005), significantly higher than the estimated prevalence of primary ADHD in the United States of 7.8% (Bonfield, Lam, Lin, & Greene, 2013).

The use of stimulant medications in children with primary ADHD has been extensively studied, but there is a paucity of studies evaluating the use of stimulants in children with attention problems after brain injury (Pangilinan, Giacoletti-Argento, Shellhaas, Hurvitz, & Hornyak, 2010). Previous studies and clinical trials evaluating the use of stimulants for attention problems in children who sustained TBI have yielded inconsistent results regarding efficacy (Backeljauw & Kurowski, 2014; Dougall, Poole, & Agrawal, 2015; Warden et al., 2006). Research in a variety of neurological conditions (e.g., spina bifida, epilepsy, and among survivors of pediatric brain tumor) has revealed similar attention deficits, as well as mixed findings regarding efficacy of stimulant treatments (D'Agati, Cerminara, Casarelli, Pitzianti, & Curatolo, 2012; De la Torre, Martin, Cervantes, Guil, & Mestre, 2017; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Parisi, Moavero, Verrotti, & Curatolo, 2010; Wasserman, Stoner, Stern, & Holmbeck, 2016). Research investigating the use of stimulant medication in primary ADHD has found extensive evidence that long-term treatment with methylphenidate significantly improves attention-related behaviors (Abikoff et al., 2004) (Shaw et al., 2012). Side effects, including neurological (e.g., headache and dizziness), psychiatric (e.g., depressed or elevated mood), tic disorders, psychotic symptoms (e.g., hallucination), cardiovascular (e.g., blood pressure and pulse changes, racing heart), gastrointestinal (e.g., loss of appetite, weight loss during prolonged treatment), and dermatological (e.g., hives) events, are typically not disruptive to the child's overall functioning (Graham et al., 2011) and are potentially controlled by so-called "drug holidays" of interrupted use (Graham et al., 2011).

Executive dysfunction is one of the most common neurocognitive sequelae after pediatric TBI (Horton, Soper, & Reynolds, 2010). Executive function (EF) has been broadly defined as a superordinate, managerial capacity for directing more modular abilities (e.g., language, memory, psychomotor skills, and perception) with the objective of setting, managing, or attaining goals (Levin & Hanten, 2005). Deficits in EF differ between children who experience SADHD, those who have pre-injury ADHD, and those who sustain a TBI without SADHD. Particularly, children with SADHD demonstrate greater impairments in attention and working memory compared to those with pre-injury ADHD and TBI-only; these children also showed impaired psychomotor speed at both 6- and 12-month follow-ups, while attention deficits emerged at 12 months, suggesting that deficits in attention are not simply due to slowed cognition (Ornstein et al., 2014). SADHD is associated with slower response times and poorer planning abilities than those with primary ADHD. These findings indicate different underlying mechanisms between pre-injury ADHD and SADHD and suggest that different treatments may be necessary for SADHD (Ornstein et al., 2014). While it may be possible to differentiate between primary and secondary ADHD with neuropsychological testing, studies have found that children with both pre- and post-injury ADHD have increased difficulties with attention, EF (e.g., reaction time, response inhibition) and memory following TBI (De la Torre et al., 2017; Sinopoli & Dennis, 2012; Sinopoli, Schachar, & Dennis, 2011; Slomine et al., 2005). Executive dysfunction may persist up to 10 years post-injury (Muscara, Catroppa, & Anderson, 2008) and has been implicated as a factor in negative academic and social outcomes in children after TBI (Biederman et al., 2004; Yeates et al., 2004).

The primary goal of this study was to investigate the effects of methylphenidate on long-term executive and neuropsychological functioning in children with attention problems following TBI. Children with ADHD following TBI (either SADHD or primary ADHD plus TBI) have greater problems in these areas compared to those with primary ADHD alone or TBI without SADHD (Ornstein et al., 2014); therefore, it is critical to understand how treatment with stimulants influences EF, which has not previously been examined in this population. Additionally, we wanted to understand the relationship between methylphenidate associated changes in lab-based neuropsychological measures of attentional control, processing speed, and EF and parent- or self-report measures of everyday EF behaviors (i.e., in a real-world setting rather than laboratory-based measures obtained in a controlled environment) (Gioia, Isquith, Guy, & Kenworthy, 2000) in this population. We hypothesized that methylphenidate will improve everyday EF and that improvements on these dimensions will be associated with lab-based measures of attentional control, processing speed, and EF. Specifically, we hypothesized that improvements in these measures will mediate improvements in everyday EF behaviors.

METHOD

Design

The design was a randomized, double-masked, placebo-controlled cross-over clinical trial. An in-depth description of the intervention and efficacy of methylphenidate for the management of attention problems, based upon parent- and self-report of attention rating scales, after pediatric TBI is reported in a separate paper (Kurowski et al., 2018). Following a screening interview and completion of informed consent and assent, participants completed a baseline visit and were randomized to the experimental (methylphenidate) or the control (placebo) condition for 4 weeks (period 1). At the end of 4 weeks, participants immediately crossed over to the other condition for another 4 weeks (period 2). Participants were assessed at baseline and weeks 4 and 8 to examine differences in outcomes between the medication and placebo conditions. The total duration of the trial originally planned for 8 weeks, but took up to 12 weeks for some participants due to scheduling issues, with a total of three full assessment visits (i.e., baseline and optimal visits) and six titration visits (Kurowski et al., 2018). Participants weighing

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less than 25 kg received 18 mg (low), 27 mg (medium), and 36 mg (high) dosages; participants weighing above 25 kg received 18 mg (low), 36 mg (medium), and 54 mg (high) dosages during the trial. During the placebo condition, participants underwent the same procedures as during the medication condition due to the masked nature of the study. The mean optimal dose of methylphenidate was 40.5 mg (1.00 mg/kg/day) (Kurowski et al., 2018). Testers were masked to the medication status of the child. Participants were instructed to take their medication at a consistent time in the morning; average time of medication administration was 8:22 a.m. Study visits typically occurred in afternoons and evenings; however, there may have been variation depending on the schedules of participants and their families. Further details of the trial procedures and design can be found in a previously published paper (Kurowski et al., 2018).

Participants and Recruitment

Children aged 6–17 years, who were hospitalized for a moderate-to-severe blunt head trauma 6 or more months previously, were recruited from a large children's hospital medical center. Six years of age was chosen as the lower age limit based on clinical practice guidelines, which recommend the use of stimulants as first-line treatment for ADHD at 6 years and older (Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, 2011). To study the efficacy of methylphenidate following pediatric TBI specifically, the upper age range of 17 years was chosen. Consistent with previous investigations, TBI severity was categorized by the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) score and neuroimaging (Kurowski et al., 2018). The Vanderbilt ADHD parent rating scales (Wolraich, Feurer, Hannah, & Baumgaertel, 2003) were used to determine eligibility based on a parent report of at least six current symptoms on the inattentive and/or hyperactive subscales. Participants actively receiving medications for attention problems and or other attention related treatments (e.g., attention training) were eligible if treatments were discontinued prior to study enrollment (Kurowski et al., 2018).

Three hundred and twenty-one participants were assessed for the basic criteria of age, diagnoses of a TBI, and time since injury. Of these, 118 declined to participate. Twenty did not want to start or change medications, 26 were not having attention difficulties per their parent and were not screened, 3 did not want to burden their child, 19 declined due to the time commitment, 7 declined due to the distance to the hospital, 4 were not interested in this study, 23 declined all research, and 16 did not give a reason for refusal. One hundred and sixty-three potential participants were excluded from the study. Eighty-eight of these turned 18 prior to contact, 6 turned 18 after initial contact was made, 54 were ineligible due to Vanderbilt scores, 3 were ineligible due to neurological impairments, 2 were excluded due to pre-injury intellectual disability, and two were excluded due not meeting injury severity criteria.

Demographics and baseline assessments

Twenty-six individuals completed baseline assessments and were randomized. Of those randomized, the mean age at injury and baseline visit were 6.3 (*SD*: 4.1) and 11.5 (*SD*: 2.8) years, respectively. Mean GCS was 11.9 (*SD*: 4.2), and 25 (92.6%) of participants had evidence positive neuroimaging findings consistent with brain trauma. Six participants were female and 19 were white. See Table 1 for additional demographics. A consort flow diagram is provided in more detail elsewhere (Kurowski et al., 2018). Mechanisms of injury for the 20 participants who completed the study were falls ($n = 6$), bicycle accidents ($n = 3$), motor vehicle accidents ($n = 3$), sledding accidents ($n = 3$), other accidents (e.g., assault, running into another child, accidental hit by a baseball bat, $n = 3$), and being struck by a car ($n = 2$). Mechanisms of injury for the six participants who did not complete the study were falls ($n = 2$), motor vehicle accidents ($n = 2$), being struck by a car ($n = 1$), and abusive head trauma ($n = 1$).

To determine ADHD diagnostic status at the time of enrollment, the ADHD portion of the K-SADS-P/L (Kaufman et al., 1997) was administered at baseline. At the time of enrollment, 6 participants had combined presentation ADHD, 18 had predominantly inattentive, and 2 had predominantly hyperactive-type ADHD; ADHD subtype did not differ between those with primary *versus* secondary ADHD. There were no demographic or baseline assessment differences between groups that received medication *versus* placebo first.

Measures

The executive and neuropsychological outcomes were obtained at baseline and at each optimal dose visit (week 4 and week 8) for a total of three assessments (Kurowski et al., 2018).

The Behavior Rating Interview of Executive Function (BRIEF) is standardized and validated for use in children ages 5–18 years, including those with pediatric TBI (Gioia & Isquith, 2004; Gioia et al., 2000). Both parent- and self-report (age 11 and older) were used to obtain ratings of everyday EF behaviors. The global executive composite (GEC), behavior regulatory index (BRI), and metacognitive index (MI) *T*-scores were used in the analyses, with higher scores reflecting poorer EF.

The Continuous Performance Test II (CPT II) was used to assess various aspects of attentional control, including sustained and selective attention/response accuracy, processing speed, reaction time, and inhibitory control (Conners, 2004; Conners, 1995, 2000). The CPT II is recommended as a supplemental pediatric TBI Common Data Elements outcome measure (McCauley et al., 2012) has been used previously to assess attentional control after severe TBI in children age 6–18 years (Galbiati et al., 2009) and is relatively unaffected by practice effects (Conners, 2004; Conners, 1995, 2000). The following scores were included in the current

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Table 1. Demographics

	Intent to treat				Completers		
	Randomized ($n = 26$)	Non-completer ($n = 6$)	Completer ($n = 20$)	*p*-value	Medication first ($n = 10$)	Placebo first ($n = 10$)	*p*-value
Demographics							
Female, *n* (%)	6 (23.1)	1 (16.7)	5 (25.0)	1.0	1 (10.0)	4 (0.0)	.30
Caucasian, *n* (%)	19 (73.1)	3 (50.0)	16 (80.0)	.29	8 (80.0)	8 (80.0)	1.0
Household income ≥$70,000, *n* (%)	9 (34.6)	2 (33.3)	7 (35.0)	1.0	4 (40.0)	3 (30.0)	1.0
Mother graduate college, *n* (%)	8 (30.8)	2 (33.3)	6 (30.0)	1.0	4 (40.0)	2 (20.0)	.63
Abnormal CT, *n* (%)	25 (96.2)	6 (100)	19 (95.0)	1.0	9 (90.0)	10 (100)	1.0
Severe TBI, *n* (%)	8 (30.8)	2 (33.3)	6 (30.0)	1.0	4 (40.0)	2 (20.0)	.63
GCS, *M* (*SD*)	11.9 (4.2)	10.7 (4.6)	12.4 (4.1)	.45	11.6 (4.1)	13.2 (4.2)	.42
Age at injury, *M* (*SD*)	6.3 (4.1)	6.9 (3.8)	6.1 (4.3)	.68	5.7 (5.2)	6.5 (3.5)	.70
Time since injury, *M* (*SD*)	5.2 (3.8)	5.2 (4.2)	5.2 (3.8)	1.0	5.2 (4.2)	5.3 (3.7)	.97
Age at baseline, *M* (*SD*)	11.5 (2.8)	12.1 (2.7)	11.3 (2.8)	.57	10.9 (2.9)	11.7 (2.7)	.52

analyses: accuracy, coefficient of variation, mean response time, and standard deviation (SD) of response time. Higher accuracy scores reflect better performance; whereas higher scores on the other three measures reflect slower and more variable responses, suggesting difficulties in attention regulation.

The D-KEFS Verbal Fluency (D-KEFS VF) (Delis, Kaplan, & Kaplan, 2001) measures both lexical ability (e.g., letter fluency, category fluency) and executive functioning (e.g., category switching accuracy and total number if correct switching). The D-KEFS is sensitive to TBI severity (Strong, Tiesma, & Donders, 2011) and focal left frontal lesions (Levin, Song, Ewing-Cobbs, Chapman, & Mendelsohn, 2001). Participants were asked to verbalize words beginning with a designated letter according to specific rules (letter fluency), verbalize exemplars of specific categories (category fluency), and verbalize exemplars of semantic category switches (category switching accuracy and total correct), thus increasing the demand on EF. The D-KEFS Trail Making subtest assesses the ability to shift sets, specifically the Number–Letter Sequencing subtest assesses how quickly individuals switch between connecting numbers and letters (number–letter sequencing). Higher scores on the D-KEFS subtests reflect better function.

The Wechsler Intelligence Scale for Children, 4th Edition Processing Speed Index (WISC-IV-PSI) has been designed for children 6–16:11 years of age and provides a measure of processing speed and sustained attention (Wechsler, 2003). It is comprised of two subtests: Coding and Symbol Search. The information processing indexes are highly sensitive to TBI and its severity (Allen, Thaler, Donohue, & Mayfield, 2010; Donders & Janke, 2008; McCauley et al., 2012), with higher scores reflecting better processing speed. One child who was 17 was administered the Wechsler Adult Intelligence Scale, 4th Edition Processing Speed Index (WAIS-IV- PSI; (Wechsler, Coalson, & Raiford, 2008). Because both measures yield highly correlated standard scores (Wechsler, 2003), their score was included with the others in a combined WISC/WAIS processing speed variable.

Analysis

Descriptive statistics were used to characterize the sample. Comparisons between groups were assessed with *t* tests and Fisher's Exact tests when appropriate. Repeated measures linear mixed models (Cnaan, Laird, & Slasor, 1997) were used to determine the association of methylphenidate with dependent variables. The dependent variables included the BRIEF (MI, BRI, and GEC), WISC/WAIS PSI (Coding and Symbol Search subtests), the CPT (accuracy, coefficient of variation, mean response time, and SD of response time), and the DKEFS (Trail Making Number–Letter Switching subtest and Verbal Fluency subtests). Other independent variables were the period of the evaluation (week 4 or week 8) and the interaction between period and treatment (this interaction term captures the potential carry over effect). Separate univariate regression analyses were performed to assess potential covariates, including age, sex, time since injury, injury severity (GCS score), race, and socioeconomic status (as measured by maternal education, college graduate or not). Injury factors and socioeconomic status were also considered as covariates because they predict the development of SADHD within the first 24 months after pediatric TBI (Max et al., 2004; Max et al., 2005; Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, 2011) prior to constructing multivariate models, each potential covariate was examined individually with treatment group and period, as well as the baseline value of the measure of interest in order to determine its relationship with the dependent variable (in the presence of group and period effects). Covariates that had a *p*-value below .05 in this

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Table 2. Neuropsychological outcomes

	Placebo, *M* (SE)	Methylphenidate, *M* (SE)	*t* (df)	*d*
WAIS PSI				
PSI overall (standard score)	91.25 (2.24)	96.05 (2.24)	−2.55 (18.0)*	−0.60
Coding overall (scaled)	7.55 (0.48)	8.60 (0.48)	−2.47 (18.0)*	−0.58
Symbol search overall (scaled)	9.30 (0.56)	9.95 (0.56)	−1.49 (18)	−0.35
CPT II				
Coefficient of variation – overall	42.21 (3.18)	32.76 (3.07)	2.29 (13.8)*	0.62
Coefficient of variation – period 1	34.28 (4.20)	35.00 (4.20)	−0.12 (30.7)	−0.02
Coefficient of variation – period 2	50.15 (4.78)	30.53 (4.46)	3.00 (31.4)*	0.53
Mean RT – overall	480.15 (14.16)	430.54 (13.72)	2.51 (32.0)*	0.44
Mean RT – period 1	463.08 (19.15)	424.31 (19.36)	1.40 (32.0)	0.25
Mean RT – period 2	497.22 (21.15)	436.78 (20.06)	2.06 (32.0)*	0.36
SD RT – overall	216.61 (20.92)	145.90 (20.25)	2.42 (32.0)*	0.43
SD RT – period 1	167.30 (27.84)	155.01 (28.03)	0.31 (32.0)	0.05
SD RT – period 2	265.93 (31.14)	136.79 (29.32)	3.02 (32.0)**	0.53
D–KEFS VF (scaled score)				
Switch accuracy – overall	7.87 (0.48)	8.24 (0.48)	−0.56 (17.0)	−0.14
Switch accuracy – period 1	8.30 (0.66)	6.78 (0.70)	1.58 (32.7)	0.28
Switch accuracy – period 2	7.44 (0.70)	9.70 (0.66)	−2.35 (17.0)	−0.41
Correct switches – overall	8.00 (0.61)	8.82 (0.61)	−1.25 (17.0)	−0.30
Correct switches – period 1	8.96 (0.84)	7.38 (0.89)	1.28 (27.1)	0.25
Correct switches – period 2	7.04 (0.89)	10.26 (0.84)	−2.61 (27.1)	−0.50

*$p < .05$, **$p < .01$, ***$p < .0001$, CPT II = Continuous Performance Test II, RT = Reaction Time, STD RT = Standard Deviation of Reaction Time, DKEFS-VF = D-KEFS Verbal Fluency, PSI = Processing Speed Index, and WAIS = Wechsler Adult Intelligence Scale.
Note: "period 1" refers to the first 4 weeks of the study, and "period 2" refers to the final 4 weeks after cross-over.

analysis were to be included in the final model; however, no potential covariates significantly contributed to the models. Given the potential profile differences in children with primary *versus* secondary ADHD (Slomine et al., 2005), diagnosis type was also explored as a covariate in the models, but it was not found to have a significant effect. Therefore, we did not differentiate between diagnosis type in the current analyses. All analyses were based on intention to treat principles (Gupta, 2011). Effect sizes were derived based on least squares (adjusted) mean differences divided by an adjusted estimate of the SD: the standard error of the difference multiplied by the square root of the adjusted degrees of freedom (Lakens, 2013). The mediation effects of processing speed (WISC/WAIS PSI measures) were examined by fitting a regression model (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Mackinnon, Warsi, & Dwyer, 1995) of processing speed and treatment effect on responsiveness of parent-reported everyday EF behaviors. The coefficients of the treatment effect in the model were compared and we estimated the effect and the related standard error of the mediation effect. The direct and indirect effects were derived using software that was written specifically for two-treatment two-period crossover designs, as we have in this study (MEMORE for SAS version 1.1, Copyright 2016, AK Montoya and AF Hayes). All analyses were conducted using the SAS ® statistical software package version 9.3 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a *p*-value of .05. Magnitude of effect sizes are reported to assist with interpretation. Due to the exploratory nature of this medication trial, we did not apply multiple testing corrections.

RESULTS

Neuropsychological Outcomes

Methylphenidate was associated with significant improvements in processing speed, sustained attention, and EF. WISC/WAIS PSI scores during the optimal dose week of the medication condition were lower than during the optimal dose week of the placebo condition ($p = .02$, effect size = −0.60; Table 2), driven by the Coding subtest ($p = .02$, effect size = −0.58; Table 2). No significant differences were found on the Symbol Search subtest ($p = .15$; Table 2), suggesting that the overall effect was due to improved psychomotor speed rather than visual scanning ability. Similar results were seen on the CPT. The medication condition showed less response variability (Coefficient of Variation; $p = .04$, effect size = 0.62; Table 2), faster reaction times ($p = .02$, effect size = 0.44; Table 2), and a lower SD in reaction time ($p = .02$, effect size 0.43; Table 2).

Three significant treatment-by-period interactions were found on the CPT. When the methylphenidate condition was first, the placebo condition in the second period was associated with higher response variability (coefficient of variation; $p = .01$, effect size = 0.53; Table 2), slower response times ($p = .05$, effect size = 0.36; Table 2), and

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Table 3. BRIEF outcomes

	Placebo, *M* (SE)	Methylphenidate, *M* (SE)	*t* (df)	*d*
BRIEF parent report (T score)				
	65.20 (1.30)	60.05 (1.30)	4.10 (18)***	0.97
1	64.49 (1.84)	61.61 (1.84)	1.10 (26.5)	0.21
2	65.91 (1.84)	58.49 (1.84)	2.85 (26.5)**	0.55
BRI – overall	58.00 (1.33)	54.30 (1.33)	2.44 (18)*	0.57
	57.29 (1.88)	55.51 (1.88)	0.67 (30.6)	0.12
	58.71 (1.88)	53.9 (1.88)	2.11 (30.6)*	0.38
	67.75 (1.52)	62.40 (1.52)	3.79 (18)**	0.89
	67.18 (2.15)	63.82 (2.15)	1.11 (25.8)	0.22
	68.32 (2.15)	60.98 (2.15)	2.42 (25.8)*	0.48
BRIEF self report (T score)				
GEC – overall	46.03 (3.53)	41.10 (3.53)	2.71 (7.0)*	1.02
BRI – overall	44.85 (3.31)	41.33 (3.31)	2.10 (7.0)	0.79
MI – overall	47.46 (3.52)	41.81 (3.52)	3.09 (7.0)*	1.17

*p< .05, **p< .01, ***p< .0001, BRI = Behavioral regulation index, GEC = Global executive composite, and MI = Metacognitive index. Individual period results are not given for the self report measures because the treatment-by-period interaction terms were not statistically significant.
Note: "period 1" refers to the first 4 weeks of the study, and "period 2" refers to the final 4 weeks after cross-over.

higher SD of response time ($p = .005$; effect size = 0.53; Table 2). These findings suggest that, after switching from methylphenidate to placebo, participants were slower to respond with more variation in response times, and responded randomly or erratically compared to those treated first by placebo.

While no overall differences were found on the DKEFS measures, there were two significant treatment-by-period interactions. Compared to placebo, the methylphenidate condition in the second period was associated with higher scores on category switch accuracy ($p = .03$, effect size = −0.30; Table 2) and category switch total correct ($p = .01$, effect size = −0.50; Table 2) indicating better ability to switch between sets.

Everyday EF Behavior Outcomes

There were overall differences in mean scores between placebo and medication groups at optimal dose visits for the parent-BRIEF GEC ($p = .001$, effect size = 0.97), MI ($p = .03$, effect size = 0.57), and BRI scores ($p = .001$, effect size = 0.89). Three significant treatment-by-period interactions were found on the parent-BRIEF. When the methylphenidate condition was first, the placebo condition in the second period was associated with higher scores on the GEC ($p = .01$, effect size = 0.55), the MI ($p = .04$, effect size = 0.38), and the BRI ($p = .02$, effect size = 0.48), indicating poorer everyday EF behaviors. Overall differences were found on the self-BRIEF GEC and MI scores after controlling for baseline scores, period (i.e., first or second 4 weeks), and interaction term of treatment by period (which was not statistically significant in these cases) (Table 3), with the methylphenidate condition associated with improved EF.

Mediation outcomes

No significant mediation effects were found in the models exploring processing speed as a mediator of the treatment response of parent- or self-report ratings of everyday EF behaviors to methylphenidate (all $p > .05$).

DISCUSSION

This study provides a further understanding of the potential influence of methylphenidate on EF and neuropsychological outcomes in children with attention problems after TBI. The results suggest that methylphenidate treatment is beneficial for processing speed, sustained attention, lab-based measures of EF, and everyday EF behaviors. These results also suggest that when switching off methylphenidate, performance on sustained attention tasks may worsen, leading to slower reactions, more variable reaction times, and more random and erratic responses.

Previous studies of methylphenidate treatment for attentional impairments following TBI have revealed similar results. Many studies have found that methylphenidate treatment enhances processing speed in both adult and pediatric TBI populations (Willmott & Ponsford, 2009). Similar results have been found on measures of attention in both adult and pediatric TBI populations (Kim et al., 2012; Konrad, Günther, Hanisch, & Herpertz-Dahlmann, 2004; Mahalick et al., 1998). The results of the current study add to the literature by demonstrating the efficacy of using dose titration to determine an optimal dose. Previous studies have utilized only one (Kim et al., 2012; Mahalick et al., 1998; Willmott & Ponsford, 2009) or two (Konrad et al., 2004) weight-dependent doses of methylphenidate. As assessments were administered while participants were taking their optimal dose, these results may be more representative of the

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performance of individuals being treated with methylphenidate in the long term.

A unique finding from this study is that it suggests there may be a negative cognitive "rebound effect" following discontinuation of or a "drug holiday" from methylphenidate. An international literature review revealed that drug holidays were a common practice with 25%–70% of families partaking in one (Ibrahim & Donyai, 2015). These holidays were more likely to coincide during weekends or school holidays and were thought to help alleviate or mitigate common negative side effects of methylphenidate, such as those affecting growth, sleep, and appetite; however, their effectiveness remains poorly understood (Graham et al., 2011). This decline in performance suggests that the estimated 40% of children who do not take medications when they are not in school (Charach & Gajaria, 2008) may be at risk for increased impaired attention until treatment is resumed. Furthermore, this study suggests there may be negative cognitive effects that should be considered when families and doctors decide to discontinue medication or take a drug holiday.

In addition, because mediation models were not significant, this suggests that improvements in processing speed performance are not the driving force in reported improvements in everyday EF behaviors. This finding is consistent with other literature in the ADHD population, which suggests performance-based measures account for little unique variance in predicting ADHD status and demonstrates little overlap with behavioral ratings (Toplak, Bucciarelli, Jain, & Tannock, 2008). A better understanding of neural mechanisms of recovery and treatment is needed to better understand improvements following medication trials. Future research should consider including neuroimaging and other biological markers as part of an assessment for treatment outcomes (Berridge et al., 2006; Hart et al., 2013; Solanto, 1998; Swanson, Baler, & Volkow, 2011; Volkow, Fowler, Wang, Ding, & Gatley, 2002).

Another promising direction for future research is combining medication and behavioral treatments for children following a TBI. Several studies have demonstrated that interventions targeting parenting skills, family distress, and problem-solving abilities post-injury can improve cognitive and behavioral outcomes for children and families after TBI (Antonini et al., 2014; Wade, Kurowski, et al., 2015; Wade, Taylor, et al., 2015). Research from the ADHD population suggests that best practice for treating symptoms of ADHD incorporates both medical and behavioral interventions subcommittee (Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, 2011). Future studies should explore whether a similar approach for children with TBI and SADHD would be beneficial.

Limitations

This study adds to the prior literature on TBI treatment of EF and attentional issues with methylphenidate, but has several limitations to consider when interpreting the findings. Due to the cross-over design of the study, children were given the same neuropsychological measures three times within an 8- to 12-week period. However, the pattern of performance in the current study did not suggest that improvements in scores were due to practice or learning effects because improvement across time, regardless of group, was absent. In addition, the finding that performance on assessments worsened after switching from methylphenidate to placebo would be unexpected if significant practice/learning effects were present. The study does not account for teacher reports of behavior, which may differ from parent report (Lavigne, Dulcan, LeBailly, & Binns, 2012). Study participants included children with attention problems after injury; however, these were a mix of children with and without primary ADHD. Prior research suggests that there may be different profiles for each group; however, when pre-injury ADHD status was included as a covariate in the models, we did not find a significant influence on findings. Larger sample sizes are likely needed to explore profile differences between primary and secondary ADHD and between differing subtypes of ADHD. The study demographics should also be considered in interpreting the results as the population consisted of approximately 75% males, 75% whites, and primarily moderate injuries with a mean age of injury of approximately 6 years and time since injury at enrollment of approximately 5 years. Finally, further research is needed to understand how individual (e.g., genetics) and environmental factors (e.g., home environment, parenting) interrelate to influence treatment response and determine who is most likely to benefit from medication *versus* other treatments.

CONCLUSION

Findings from this double-masked, placebo controlled, upward titration, cross-over clinical trial support the use of long-acting methylphenidate for management of neuropsychological and everyday EF behavior problems long-term after pediatric brain injury. There is currently a lack of evidence-based trials for management of the sequelae of pediatric brain injury, as well as possible interventions to help improve common EF deficits following injury. Due to the high incidence of brain injury in children and the significant impact of executive problems, especially in children with SADHD, on functioning, larger trials of stimulant medications are warranted. Further research is also needed to explore "cognitive rebound effects" and how these may impact doctors' and families' decisions around taking medication holidays. The relationship between improvements of neuropsychological and everyday EF behavior assessments following medication treatment is currently poorly understood and further research is warranted to understand the relationship. Furthermore, the neural physiology of EF problems and neural mechanisms of treatments need to be better characterized in childhood brain injury populations.

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