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Executive Impairment Determines ADHD Medication Response: Implications for Academic Achievement

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Abstract

Methylphenidate (MPH) often ameliorates attention-deficit/hyperactivity disorder (ADHD) behavioral dysfunction according to *indirect* informant reports and rating scales. The standard of care behavioral MPH titration approach seldom includes *direct* neuropsychological or academic assessment data to determine treatment efficacy. Documenting “cool” executive-working memory (EWM) and “hot” self-regulation (SR) neuropsychological impairments could aid in differential diagnosis of ADHD subtypes and determining cognitive and academic MPH response. In this study, children aged 6 to 16 with ADHD inattentive type (IT; $n = 19$) and combined type ($n = 33$)/hyperactive-impulsive type ($n = 4$) (CT) participated in double-blind placebo-controlled MPH trials with baseline and randomized placebo, low MPH dose, and high MPH dose conditions. EWM/SR measures and behavior ratings/classroom observations were rank ordered separately across conditions, with nonparametric randomization tests conducted to determine individual MPH response. Participants were subsequently grouped according to their level of cool EWM and hot SR circuit dysfunction. Robust cognitive and behavioral MPH response was achieved for children with significant baseline EWM/SR impairment, yet response was poor for those with adequate EWM/SR baseline performance. Even for strong MPH responders, the best dose for neuropsychological functioning was typically lower than the best dose for behavior. Findings offer one possible explanation for why long-term academic MPH treatment gains in ADHD have not been realized. Implications for academic achievement and medication titration practices for children with behaviorally diagnosed ADHD will be discussed.

Keywords

ADHD, executive function, methylphenidate, medication response

Children with attention-deficit/hyperactivity disorder (ADHD) exhibit complex and severe neuropsychological and cognitive deficits that profoundly impact behavioral, social, and academic functioning both at home and in school (DuPaul & Stoner, 2004; Reddy & De Thomas, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). In addition to telltale signs of developmentally inappropriate inattention, impulsivity, and hyperactivity, these children experience poor planning, organization, self-monitoring, problem-solving, and social skills (Hale, Reddy, Wilcox, et al., 2009). Prevalence rates are fairly consistent across class, culture, and race (Barkley, 2006), with approximately 5% of children affected with ADHD worldwide (Polanczyk & Rohde, 2007), making it one of the most common neuropsychiatric childhood disorders (Konrad, Gunther, Hanisch, & Herpertz-Dahlmann, 2004).

Considered by many to be a disruptive behavior disorder (American Psychiatric Association, 2000), ADHD frequently

co-occurs with other psychiatric disorders (Spencer, 2006) and is often accompanied by poor academic achievement when executive function deficits are present (Biederman et al., 2004). Many children with ADHD are also diagnosed with specific learning disabilities (SLD) in reading, writing, and/or mathematics (e.g., Capano, Minden, Chen, Schachar, & Ickowicz,

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2008; Mayes & Calhoun, 2006; Semrud-Clikeman, 2005). It remains unclear whether these learning problems are due to behavioral interference with learning, such as on-task behavior (DuPaul & Stoner, 2004), comorbidities separate and distinct from the ADHD (Isles & Humby, 2006), and/or core ADHD neuropsychological deficits (e.g., sustained attention, planning, working memory) that may lead to inadequate academic achievement (Goldstein & Naglieri, 2008; Hale, Reddy, Wilcox, et al., 2009).

Methylphenidate Treatment in ADHD

With the ADHD diagnostic focus on informant reports of overt behavior problems, it is not surprising that educators and clinicians frequently use child and parent behavior training for affected children (e.g., Fabiano et al., 2009) and behavioral strategies that improve academic performance (e.g., DuPaul & Stoner, 2004). However, the most common and efficacious form of ADHD treatment remains psychotropic medication, with methylphenidate (MPH) being the most researched and prescribed (Barkley, 2006). MPH is a dopamine agonist that can impact levels of dopamine and a related neurotransmitter norepinephrine availability in the prefrontal cortex (Berridge et al., 2006). By blocking the dopamine transporter, MPH inhibits dopamine reuptake into the presynaptic membrane and thus increases overall dopamine concentrations in the prefrontal and associated subcortical structures (Julien, 2005).

Dopamine is a critical neurotransmitter for prefrontal-subcortical circuit control of attention and executive function (Lichter & Cummings, 2001) circuits that meta-analyses suggest are hypoactive in ADHD (Dickstein, Bannon, Castellanos, & Milham, 2006). These frontal-subcortical circuits are highly interrelated and may be impacted by different medications that target cortical (e.g., prefrontal) or subcortical (e.g., striatum) structures. MPH appears to influence dopamine and norepinephrine availability in both regions, leading to cognitive (e.g., attention, response inhibition) and behavioral (e.g., on-task behavior) improvement as a result (Engert & Pruessner, 2008). Positive effects on hippocampal functioning have been reported also, which could account for improved learning and memory in children with ADHD treated with MPH (Dommett, Henderson, Westwell, & Greenfield, 2008).

Animal research suggests that the prefrontal cortex and associated circuits are highly sensitive to changes in catecholamine modulation, with variations affecting executive control of behavior (Arnsten & Li, 2005). Although MPH clearly enhances executive modulation of cognition and behavior, evidence is emerging that differences among dopamine receptors (Floresco & Magyar, 2006) could lead to differential MPH effects, with low doses improving attention control and working memory and higher doses impairing these functions (Arnsten, 2006b; Berridge et al., 2006). These findings are consistent with results that suggest higher MPH doses may be necessary to reduce behavioral intensity and disruption in

children and adolescents, while lower doses may be best for improving executive control of attention (e.g., Konrad et al., 2004).

MPH Effects on Cognitive and Neuropsychological Functioning

The extant treatment literature suggests that MPH is highly effective in reducing noncompliant and disruptive behaviors in children with ADHD (e.g., Abikoff et al., 2004; Pearson et al., 2003; Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008; Waxmonsky et al., 2008), yet comparatively few investigations have examined the MPH effects on cognition and/or academic functioning. While some propose MPH improves neuropsychological functioning in children with ADHD (e.g., Bedard, Martinussen, Ickowicz, & Tannock, 2004; Hood, Baird, Rankin, & Isaacs, 2005; Langleben et al., 2006; Wilson, Cox, Merkel, Moore, & Coghill, 2006), others assert that MPH does not show beneficial cognitive effects (e.g., Kemner et al., 2004; Kobel et al., 2008; Lufi, Parish-Plass, & Gai, 1997). Inconsistent findings may be in part due to differential MPH dose-response effects on cognitive and behavioral functioning, even within the same child (e.g., Hale, Fiorello, & Brown, 2005; Konrad et al., 2004; Pearson et al., 2004), with some arguing MPH dosages above optimal levels may exacerbate cognitive dysfunction in children with ADHD (e.g., Kuhle et al., 2007).

One of the earliest MPH studies found positive drug effects on cognition and behavior but noted deterioration of cognitive functioning at higher doses (Sprague & Sleator, 1976). High doses of MPH have been shown to produce "zombie effects" in which children can become quiet, unresponsive, hypoactive, and hyperfocused, with poorer cognitive performance as a result (Swanson, Cantwell, Lerner, McBurnett, & Hanna, 1991; Tannock, Shachar, & Logan, 1995). With response curves inconsistent across variables and children diagnosed with ADHD, Hoepfner and colleagues (1997) argued for careful examination of cognitive and behavior MPH dose-response relationships, particularly for children with ADHD-inattentive type or those with comorbid internalizing disorders, who have been found to be poor responders to stimulant treatment (e.g., Barkley, DuPaul, & McMurray, 1991; Tannock, Ickowicz, & Schachar, 1995).

Despite early findings supporting evaluation of cognitive/neuropsychological and behavioral MPH response in ADHD, it continues to be a behaviorally diagnosed disorder (McKenzie & Wurr, 2004), with little attention given to the potential MPH effects on cognition. In the 1990s, the movement away from examining cognitive/neuropsychological MPH effects was spurred, in part, by contradictory early evidence that suggested no untoward cognitive effects with increasing MPH dosage (Berman, Douglas, & Barr, 1999; Douglas, Barr, Desilets, & Sherman, 1995; Solanto & Wender, 1989), the absence of cognitive MPH effects in the presence of robust behavioral MPH response (Lufi et al., 1997), and the limited utility of

neuropsychological tests of executive functioning in ADHD diagnosis (Brown & LaRosa, 2002). Similar executive deficits are found among other neuropsychiatric disorders (Sergeant, Geurts, & Oosterlaan, 2002), leading to what many have called the “discriminant validity problem” in using executive function measures for ADHD differential diagnosis (Ozonoff & Jensen, 1999).

Renewed Interest in Assessing Neuropsychological Response to MPH

Given recent meta-analytic evidence confirming frontal-subcortical hypoactivity using MRI/fMRI (Dickstein et al., 2006) and response inhibition-executive impairments (Willcutt et al., 2005) in ADHD, there has been renewed interest in direct assessment of neuropsychological medication response. Considering neuropsychological MPH response may be especially important given behavioral titration methods alone do not appear to lead to long-term treatment gains (e.g., Jensen et al., 2007). A recent review found approximately 66% of studies showed positive cognitive-MPH effects, with improvement in attention, visual tracking, planning, cognitive flexibility, vigilance, inhibition, and memory/working memory noted (Pietrzak, Mollica, Maruff, & Snyder, 2006). Positive MPH effects on sustained attention, visual-spatial working memory, interference control, and response inhibition have also been reported (e.g., Bedard et al., 2004; Hood et al., 2005; Langleben et al., 2006; McClines, Bedard, Hogg-Johnson, & Tannock, 2007; Tamm & Carlson, 2007; Wilson et al., 2006), with reductions in impulsivity cited as the possible source of positive MPH treatment effects (e.g., Huang, Chao, Wu, Chen, & Chen, 2007). Such a finding would be consistent with Barkley’s (1997) ADHD theory, which argues that response inhibition is a core deficit in ADHD. Although MPH-cognitive effects are often positive in children with ADHD, such children may show slower processing speed as a result, a finding often termed the “speed-accuracy trade-off” (Lajoie et al., 2005).

The long-term use of MPH on cognitive functioning has also been studied. Sustained use of MPH has been found to improve global IQ (Gimpel et al., 2005), executive functioning (Vance, Maruff, & Barnett, 2003), and motor timing deficits, but apparently not time perception (Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003), among ADHD children. A recent study comparing medicated and nonmedicated children with ADHD found potential benefits in extended MPH treatment over time, with normalized or improved attention, working memory, interference control, and academic performance in those treated relative to treatment naïve and control children (Semrud-Clikeman, Pliszka, & Liotti, 2008).

MPH Dose-Response Effects on Academic Functioning

MPH may improve academic performance in children with ADHD (e.g., Balthazor, Wagner & Pelham, 1991; Chacko

et al., 2005), but findings have not been consistent (e.g., Tucha & Lange, 2005; Van der Oord et al., 2008). Volkow, Fowler, Wang, and Swanson (2004) argued that MPH appears to increase reward-related DA availability in the striatum and associated structures (e.g., nucleus accumbens), thereby increasing motivation for academic tasks, suggesting MPH may make classroom reinforcers more salient (Northrup, Fusilier, Swanson, Roane, & Borrero, 1997). This increased availability for learning likely leads to long-term positive MPH-achievement outcomes as measured by both standardized tests and grades (Powers, Marks, Miller, Newcorn, & Halperin, 2008). Direct positive MPH effects have been reported for writing legibility (Tucha & Lange, 2001), math computation (Gorman, Klorman, Thatcher, & Borgstedt, 2006), reading performance (Keulers et al., 2006), and listening comprehension (McInnes et al., 2007), with recent longitudinal evidence suggesting both math and reading improvement with MPH treatment (Scheffler et al., 2009).

Several MPH outcome studies on academic functioning have also reported that medication produced no effect on math computation accuracy and completion (Benedetto-Nash & Tannock, 1999) and led to poorer handwriting fluency (Tucha & Lange, 2005). Frankenberger and Cannon (1999) reported no change in achievement scores for MPH-treated children with ADHD followed longitudinally. Although behavioral gains are common, meta-analyses suggest that both MPH and psychosocial treatments, even when combined, do not lead to better academic achievement in children with ADHD (Van der Oord et al., 2008). The nonspecific MPH effects found in many studies led some early researchers to conclude that only academic task-related behavior improved on medication (Balthazor et al., 1991).

Inconsistent MPH-achievement findings may be in part due to differences in cognitive and behavioral dose-response relationships. When differential MPH dose-response relationships have been reported, lower doses typically improve academic behavior, with little or no additional benefit found for higher doses. For instance, Chacko et al. (2005) found positive MPH effects on academic and social behavior, but few children showed significant academic improvement with increased dosage. Similarly, Evans et al. (2001) found improved academic performance (e.g., note-taking, quiz performance, written language, on-task behavior, and homework completion) for low MPH dosing, with high doses improving performance for very few children and deterioration noted for others. This pattern replicates earlier studies that showed academic gains were associated with low MPH doses, and increasing dosage beyond low to moderate levels produced little additional academic benefit (e.g., Greenhill et al., 2001; Pelham & Gnagy, 1999; Smith, Taylor, Brammer, Toone, & Rubia, 1998; Swanson et al., 1995).

Purpose of Current Study

The present investigation builds upon previous research documenting cognitive and behavioral MPH effects at the single

subject (Hale et al., 1998; Reddy & Hale, 2007) and group (Hale, Blaine-Halperin, & Beakley, 2007; Hale et al., 2005; Hale, Mulligan, & Simmerman, 2006; Hoepfner et al., 1997) levels of analyses. In this investigation, a double-blind placebo controlled study of MPH response in children with ADHD was conducted to examine whether executive-working memory (EWM) and self-regulation (SR) neuropsychological impairments affected cognitive and behavioral MPH response. There were two predictions. First, it was predicted that level and pattern of baseline data obtained from EWM/SR neuropsychological measures would differentiate MPH responders from nonresponders. Second, it was predicted that the best MPH dose for improving EWM/SR neuropsychological functioning would be lower than the best MPH dose for home/classroom behavioral functioning.

Method

Participants

The study sample was drawn from a group of 65 elementary and high school children diagnosed with ADHD and referred by physicians in the northeastern United States for double-blind placebo controlled MPH trials. The participants had to meet several inclusion and exclusion criteria. First, physicians determined if children met diagnostic criteria for ADHD-inattentive type (IT), ADHD-hyperactive-impulsive type (HIT), or ADHD-combined type (CT) based on semi-structured diagnostic interview, *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition—Text Revision (DSM-IV-TR*; American Psychiatric Association, 2000) criteria, and behavior rating scales. Second, *DSM-IV-TR* diagnosis was confirmed independently by a licensed or certified psychologist using a semi-structured interview of parent, child, and/or teacher, including medical, developmental, social, and academic histories; *DSM-IV-TR*; and objective behavior rating scales. Comorbid diagnoses were also obtained by licensed and/or certified psychologists in the schools or clinic following comprehensive evaluation of cognitive, academic, and behavior functioning. Third, participants demonstrated significant attention, hyperactivity, and/or impulse control problems that interfered with a major life function in both home and school settings. Fourth, participants were rated at least 1.5 *SDs* above the mean ($M = 50$, $SD = 10$; higher scores more problematic) on at least one of the following rating subscales: *Attention Problems* of the Achenbach (1991) *Child Behavior Checklist (CBCL)* or *Teacher Report Form (TRF)*, or the *DSM-IV-TR Inattention* and/or *Hyperactive-Impulsive* subscales of the *Conners' Parent Rating Scales—Revised: Long Form (CPRS-R:L)* or *Conners' Teacher Rating Scales—Revised: Long Form (CTRS-R:L)* (Conners, 1997). Participants from this sample were excluded if they had more than one comorbid secondary diagnosis; had a history of mental retardation, seizure disorder, brain injury, or other medical condition

affecting cognitive or neuropsychological performance; or had missing or different instruments for measuring MPH response (i.e., missing data).

The final sample consisted of 39 males and 17 females ranging in age from 74 to 200 months ($M = 120.84$ months, $SD = 30.85$). Most participants were in the first through fifth grades ($n = 43$; 77%) and were European American ($n = 46$; 82%), with the remainder African American. A majority were from middle ($n = 44$) or lower ($n = 12$) socioeconomic backgrounds living in urban ($n = 36$), suburban ($n = 13$), or rural ($n = 7$) communities. Consistent with epidemiological studies (Barkley, 2006), most children were diagnosed with ADHD-CT ($n = 33$), with fewer diagnosed with IT ($n = 19$) and HIT ($n = 4$). Comorbid diagnoses included specific learning disability ($n = 13$), oppositional defiant disorder/conduct disorder (ODD/CD; $n = 11$), and anxiety/depression (A/D; $n = 6$). Fairly equal numbers of children in the ADHD-IT ($n = 6$) and ADHD-CT ($n = 7$) groups were diagnosed with comorbid LD. Most of the children diagnosed with ODD/CD were in the CT group ($n = 9$). Consistent with the ADHD and internalizing disorders literature (e.g., Biederman, Faraone, & Lapey, 1992), all children diagnosed with A/D were in the IT group ($n = 6$). Most participants were receiving regular education or inclusion classroom instruction ($n = 44$; 79%), with the remainder receiving resource or self-contained special education services. Available intelligence test data suggested the group to be relatively high functioning compared to most children with ADHD (see Barkley, 2006), with global IQ scores in the average range ($M = 99.56$, $SD = 6.84$; $n = 41$). All participants were either medication naïve or received an appropriate wash-out period of 2 days before the medication trial began.

Procedure

After physician evaluation and referral to the principle investigator for an MPH medication trial, parents were sent an information packet addressing the medication, potential side effects, and medication trial protocol. Those interested were evaluated by a licensed psychologist who conducted a semi-structured interview, determined *DSM-IV-TR* and parent behavior rating scale inclusion criteria, and obtained informed consent. A teacher meeting was then held where the treatment protocol and classroom observation schedule were discussed. The TRF (Achenbach, 1991) was used for the classroom behavior baseline assessment only. Four other forms were used for classroom behavior assessment at baseline and treatment follow-up: the *CTRS-R:L*, *School Situations Questionnaire-Revised (SSQ-R)*; DuPaul & Barkley, 1992), *Academic Performance Rating Scale (APRS)*; DuPaul, Rapport, & Perriello, 1991), and the *Side Effects Rating Scale (SERS)*; Barkley, 1990).

After the initial parent and teacher meetings were completed, each 4-week trial (baseline, placebo, low MPH dose, high MPH dose) began with a 45-minute classroom

observation and a 1-hour baseline assessment. The participants were not medicated during baseline (B) assessment. All medications and placebos were prepared by the study pharmacist who randomly assigned children to one of six trial orders of the placebo (P), low dose (L), and high dose (H) conditions (P-L-H, P-H-L, L-P-H, L-H-P, H-L-P, H-P-L). For the active drug phase, the doses were calculated at 0.15 mg/kg/dose for the low dose and 0.30 mg/kg/dose for the high dose and rounded to the nearest 2.5 mg (range 2.5 mg to 30 mg per dose). The ground MPH tablet was placed in lactose-filled opaque capsules for the active drug conditions, with lactose only for the placebo condition, and was administered twice per day. The research assistants, teacher, parents, and participants were blind as to the order of conditions. To ensure quality control and patient safety, the physician, pharmacist, and principal investigator (PI) were not blind, but they were not involved in direct data collection.

Several neuropsychological instruments were used to assess attention, working memory, executive function, inhibition, and self-regulation through auditory, visual, verbal, and motor domains. The tests were administered in the same order on the last day of each condition by graduate students trained and supervised by the first author. The instruments that were administered in the following order include: the *Hale-Denckla Cancellation Task* (HDCT; Hale, Reddy, Decker, et al., 2009), alternate forms of the *Wisconsin Selective Reminding Test* (WSRT; Newby, 1999), an audiotaped version of the *Go-No Go Test* (Go-No Go; Trommer, Hoepfner, & Zecker, 1991), the *Conners Continuous Performance Test-II* (CPT-II; Conners & MHS Staff, 2000), *Stroop Color Word Test* (Stroop; Golden, 1978), alternate forms of the *Trail Making Test-Part B* (TMT-B; Reitan & Wolfson, 1985), constructed by Hale (1997), and *Test of Memory and Learning Digits Backward* subtest (DB; Reynolds & Bigler, 1994). Baseline assessment also included the *Wisconsin Card Sorting Test* (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993) and *Controlled Oral Word Association Test* (COWAT; Spreen & Benton, 1977). The utility of these reliable and valid instruments when diagnosing ADHD and determining treatments effects is well documented in the literature (Hale & Fiorello, 2004; Pennington & Ozonoff, 1996; Sergeant et al., 2002; Willcutt et al., 2005), and previous studies have shown no significant practice effects during medication trials (Hale et al., 2005, 2006; Hoepfner et al., 1997).

The assessments took place approximately 1 to 2 hours after medication was administered. Classroom observations took place on the same day as neuropsychological testing, approximately 1 to 2 hours after the administration of the other daily dose of medication. An adaptation of the *Restricted Academic Task* (RAT; Barkley, 1990) was used to determine off-task, fidgeting, vocalizing, playing with objects, and out of seat behaviors. The observational procedure included a 20-second momentary time sampling technique during classroom instructional activities. Prior to data collection, the first author used videotaped classroom recordings to measure

interrater reliability of the observational methods. All graduate students met .90 or higher interrater reliability after receiving training in the observational procedures.

Following protocol completion, each dependent variable was rank ordered from 1 to 4 across conditions, with a lower rank representing better performance or behavior (i.e., ratings of 1 indicating good performance/behavior and ratings of 4 indicating poor performance/behavior). As has been argued in Hale et al. (1998, 2005, 2006) and Hoepfner et al. (1997), the instruments utilized have different numbers of items (i.e., sample space) and this procedure ensures that each instrument weighs equally when determining outcome. This assessment approach has been found to accurately determine neuropsychological and behavioral medication response (Hale et al., 1998, 2005, 2006; Hoepfner et al., 1997). For each participant, mean rank scores were computed separately for the cognitive and behavior ranks and displayed graphically to help evaluate individual medication response. Following rank-ordering procedures, the ordinal data was subjected to a non-parametric randomization test for ranks (NPStat; May, Masson, Hunter, & Wells, 1990), which approximates repeated measures multivariate analysis of variance (MANOVA) in the absence of normal data, to determine individual MPH dose-response patterns. After the results were analyzed, the order of conditions was revealed.

Analyses

In a previous study (Hale et al., 2005), structural equation modeling (SEM) was used to develop a model of the Executive/Working Memory and Self-Regulation factors, hypothesized to reflect dorsolateral-dorsal cingulate and orbital-ventral cingulate frontal-subcortical circuits based on baseline, non-medicated, neuropsychological test performance of children with ADHD. The nonsignificant χ^2 , Bentler-Bonett Non-normed Fit Index, LISREL Goodness of Fit Index, and root mean square residual values indicated the model adequately represented the obtained data (see Figure 1; Hale et al., 2005).

Hale et al. (2005) hypothesized that the EWM factor would be correlated with *DSM-IV-TR* inattentive symptoms and the SR factor would correlate with *DSM-IV-TR* hyperactive/impulsive symptoms, but this was not the case. Instead, both the EWM ($r = .502, p = .001$) and SR ($r = .327, p = .034$) factors correlated only with hyperactive/impulsive symptoms across subtypes, consistent with the notion that response inhibition is the primary deficit associated with ADHD executive impairments (Barkley, 1997). As a result, regression-based saved factor scores derived from baseline performance were added to produce a combined EWM/SR impairment score, with resultant z scores used to calculate no apparent (N/A; +1.01 or higher), low (0.01 to +1.00), moderate (0.00 to -1.00), and significant impairment (-1.01 or lower) executive impairment groups.

The medication trial data were subjected to a MANOVA to determine treatment effects, with cognitive ranks and

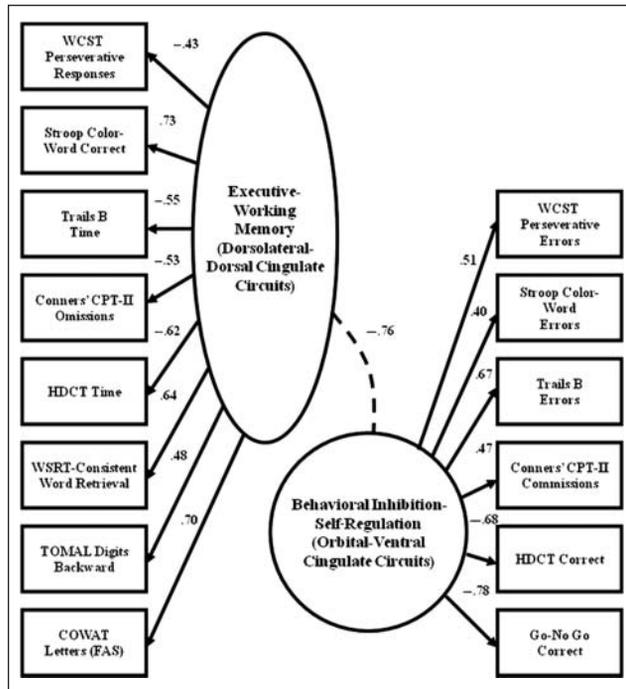


Figure 1. Frontal-subcortical circuit Confirmatory Factor Analysis (CFA).

Source: Adopted from Hale, Fiorello, and Brown (2005).

Note: WCST = Wisconsin Card Sorting Test; CPT-II = Conners Continuous Performance Test-II; HDCT = Hale-Denkla Cancellation Task; WSRT = Wisconsin Selective Reminding Test; TOMAL = Test of Memory and Learning; COWAT = Controlled Oral Word Association Test.

behavior ranks serving as dependent variables in two separate equations and impairment group as the independent variables. As a result, there were effects calculated for the one within-subject variable for drug conditions (B, P, L, H) and one for the between-subject variable for impairment group and the interaction of the two. The homogeneity of variance assumption was tested using Box's M test for the equality of homogeneity of the covariance matrices, and Mauchly Sphericity tests were used to examine the null hypothesis that the error covariance matrices of the orthonormalized transformed variables met sphericity assumptions. Levine's test was used to assess for equality of error variances. Planned contrasts were used to determine treatment effects, and orthogonal polynomial contrasts were used to examine linear, quadratic, or cubic trends as previous research has suggested that there is sample heterogeneity in medication response with neuropsychological response patterns related to treatment efficacy (Hale et al., 1998, 2005; Hoepfner et al., 1997).

Results

A cross-tabulation of impairment group by diagnosis revealed that seven of nine children with N/A executive impairment were diagnosed ADHD-IT, and comorbid diagnoses included SLD ($n = 2$) and anxious/depressed ($n = 2$). There was one

ADHD-HIT child diagnosed with comorbid ODD/CD in this group. Most of these children were boys ($n = 8$) and tended to be older than other groups ($M = 151.11$ months, $SD = 39.93$), with six of nine children in Grades 7 through 11. An examination of the *DSM-IV-TR* inattentive ($M = 6.60$, $SD = 1.94$) and hyperactive-impulsive ($M = 3.20$, $SD = 2.58$) symptoms collected during the psychological evaluation revealed this group to have few endorsed ADHD symptoms. Their mean EWM/SR executive impairment determined by saved factor z scores was $+2.33$ ($SD = .45$).

For the low impairment group, the 8 females and 13 males were fairly equally represented in the ADHD-CT ($n = 10$) and ADHD-IT ($n = 9$) diagnostic groups, but both children with ADHD-HIT were males. More than half of these children had comorbid diagnoses, including SLD ($n = 4$), ODD/CD ($n = 5$), and anxious/depressed ($n = 3$). Unlike the N/A group, these children tended to be in Grades 1 through 6 ($n = 19$), with a mean age of 123.19 months ($SD = 24.47$). The *DSM-IV-TR* inattentive ($M = 7.22$, $SD = 1.69$) and hyperactive-impulsive ($M = 5.38$, $SD = 2.56$) symptoms were more consistent, but many in this group failed to meet criteria for CT. EWM/SR executive impairment was $+0.84$ ($SD = .57$).

For the moderate impairment group, 14 of the 16 children were classified with ADHD-CT with one ADHD-IT and one ADHD-HIT, and most were males ($n = 12$). Comorbid diagnoses included SLD ($n = 5$) and ODD/CD ($n = 3$), but none of the children were diagnosed with anxiety/depression. All children were in Grades 1 through 5, with a mean age of 110.63 months ($SD = 16.40$). The *DSM-IV-TR* inattentive ($M = 7.28$, $SD = 1.48$) rather than hyperactive-impulsive ($M = 7.50$, $SD = 1.69$) symptoms were comparable for this group. All 16 children were again in Grades 1 through 5, with a mean age of 110.63 months ($SD = 16.40$). The EWM/SR executive impairment factor z score was $-.80$, with an associated SD of $.55$.

For the significant impairment group ($n = 10$), eight of the six males and four females were classified as having ADHD-CT, with the rest ADHD-IT. Two children in this group had comorbid SLD, two had comorbid ODD/CD, and surprisingly one had anxious/depressed comorbidity. In Grades 1 through 4, these children were the youngest of the four impairment groups ($M = 95.50$, $SD = 16.63$). The high executive impairment group had high levels of inattentive ($M = 7.75$, $SD = 1.38$) symptoms, but fewer hyperactive-impulsive symptoms ($M = 6.87$, $SD = 1.46$). Their EWM/SR executive impairment, determined by saved EWM-SR factor z scores, was -2.79 ($SD = .72$).

Cognitive and Behavioral MPH Response for Impairment Groups

A repeated measures MANOVA was computed with drug condition (B, P, L, H) as the within-subjects factor and impairment (N/A, low, moderate, high) serving as the between-subjects

Table 1. MPH Dose-Response Relationships for EWM/SR Impairment Groups

Impairment	Baseline		Placebo		Low Dose		High Dose		F	p
	M	SD	M	SD	M	SD	M	SD		
Cognitive ranks										
N/A	2.69	.28	2.69	.35	2.35	.47	2.28	.35	1.82	.260
Low	2.83	.38	2.69	.32	2.40	.37 ^a	2.09	.43 ^{a,b}	7.55	.002
Moderate	3.03	.39	2.80	.25	1.99	.39 ^{a,b}	2.19	.44 ^{a,b}	16.70	<.001
High	3.16	.47	2.98	.26	1.89	.29 ^{a,b}	1.98	.27 ^{a,b}	48.01	<.001
Behavioral ranks										
N/A	3.39	.46	2.31	.29 ^a	2.18	.66 ^a	2.13	.61 ^a	8.32	.022
Low	3.23	.43	2.54	.53 ^a	2.28	.60 ^a	1.96	.39 ^{a,b}	19.34	<.001
Moderate	3.43	.36	2.70	.49 ^a	1.97	.57 ^{a,b}	1.91	.55 ^{a,b}	33.52	<.001
High	3.34	.33	3.05	.38	1.94	.45 ^{a,b}	1.67	.36 ^{a,b}	62.85	<.001

Note: Lower ranks indicates better performance and behavior; MPH = methylphenidate; EWM/SR = executive-working memory/self-regulation; N/A = no apparent EWM/SR executive impairment.

^aLess than baseline with Bonferroni correction.

^bLess than placebo with Bonferroni correction.

factor for the cognitive ranks. Although the Mauchly's test of sphericity assumption for drug was met, $\chi^2(5) = 7.52, p = .18$, as was Levene's test for the equality of error variances (p range .296 to .884), a multivariate approach to the data could not be completed due to violation of the equality of covariance matrices as determined by Box's M test, $F(30, 2,905.05) = 2.36, p < .001$. Huynh-Feldt univariate tests of within-subjects effects showed a highly significant effect for drug, $F(3, 147) = 44.83, p < .001, \eta^2 = .47$, power = 1.00. The interaction of drug and impairment was also significant, $F(9, 147) = 3.11, p = .002, \eta^2 = .16$, power = .97. Tests of within-subjects contrasts demonstrated a linear, $F(1, 49) = 94.30, p < .001, \eta^2 = .65$, and a cubic effect, $F(1, 49) = 16.09, p < .001, \eta^2 = .24$, for drug condition, suggesting response curves were not uniform. The drug by impairment interaction also demonstrated linear, $F(3, 49) = 3.67, p = .01, \eta^2 = .18$, and cubic, $F(3, 49) = 3.14, p = .03, \eta^2 = .16$, effects, indicating different response curves for different levels of impairment. However, there was no main effect for impairment group, $F(3, 49) = .41, p = .74, \eta^2 = .025$, suggesting no defining overall drug trial performance pattern between groups across conditions.

To determine if this finding was also relevant for behavioral MPH response, a repeated measures MANOVA was computed with drug condition (B, P, L, H) as the within-subjects factor and impairment (N/A, low, moderate, high) serving as the between-subjects factor for the behavioral rank data. There were no violations of MANOVA assumptions, with Box's M test, $F(30, 2,905.05) = .794, p = .779$, Mauchly's test of sphericity, $\chi^2(5) = 8.94, p = .112$, and Levene's test for the equality of error variances (p range .122 to .594) all nonsignificant. Using the multivariate approach, Hotelling's trace was highly significant for drug, $F(3, 47) = 75.64, p < .001$, partial $\eta^2 = .82$, power = 1.00, across the levels of impairment. The drug by impairment interaction was also significant, $F(9, 137) = 1.96,$

$p = .04$, with partial $\eta^2 = .11$, and fairly adequate power = .82. Tests of within-subjects contrasts demonstrated a linear effect for drug, $F(1, 49) = 212.00, p < .001, \eta^2 = .81$, and a quadratic effect as well, $F(1, 49) = 13.16, p < .001, \eta^2 = .21$. Tests of between-subjects effects for impairment group was not significant, with an associated $F(3, 49)$ of 2.38 ($p = .08$), suggesting no uniform level of behavior impairment regardless of MPH conditions.

MPH Dose Response Differences for Impairment Groups

With MANOVA results suggesting that cognitive and behavioral dose-response curves were different based on level of EWM/SR impairment, repeated measures MANOVAs were then computed for each of the four impairment groups, with planned Bonferroni contrasts of drug conditions for cognitive and behavioral ranks reported in Table 1 and graphically displayed in Figure 2 to facilitate interpretation. Mauchly's test for sphericity was nonsignificant for all analyses, so a multivariate approach to the data was utilized.

For the N/A group cognitive ranks, the repeated measures MANOVA was nonsignificant for drug, $F(3, 5) = 1.82, p = .26$. Power was low (.24) and partial η^2 was .51. Orthogonal polynomial tests of within-subjects contrasts revealed a linear effect for drug, $F(1, 7) = 7.30, p = .03, \eta^2 = .51$. For behavioral ranks, the MANOVA was significant for drug, $F(3, 5) = 8.32, p = .02, \eta^2 = .83$, power = .80. Orthogonal polynomial within-subjects contrasts revealed a linear effect for drug, $F(1, 7) = 17.06, p = .004, \eta^2 = .70$, with quadratic effects approaching significance, $F(1, 7) = 5.45, p = .05$. However, Bonferroni adjusted pairwise comparisons revealed that while all blind conditions were lower than baseline behavior (indicating better behavior), none of the blind conditions (including placebo) were different

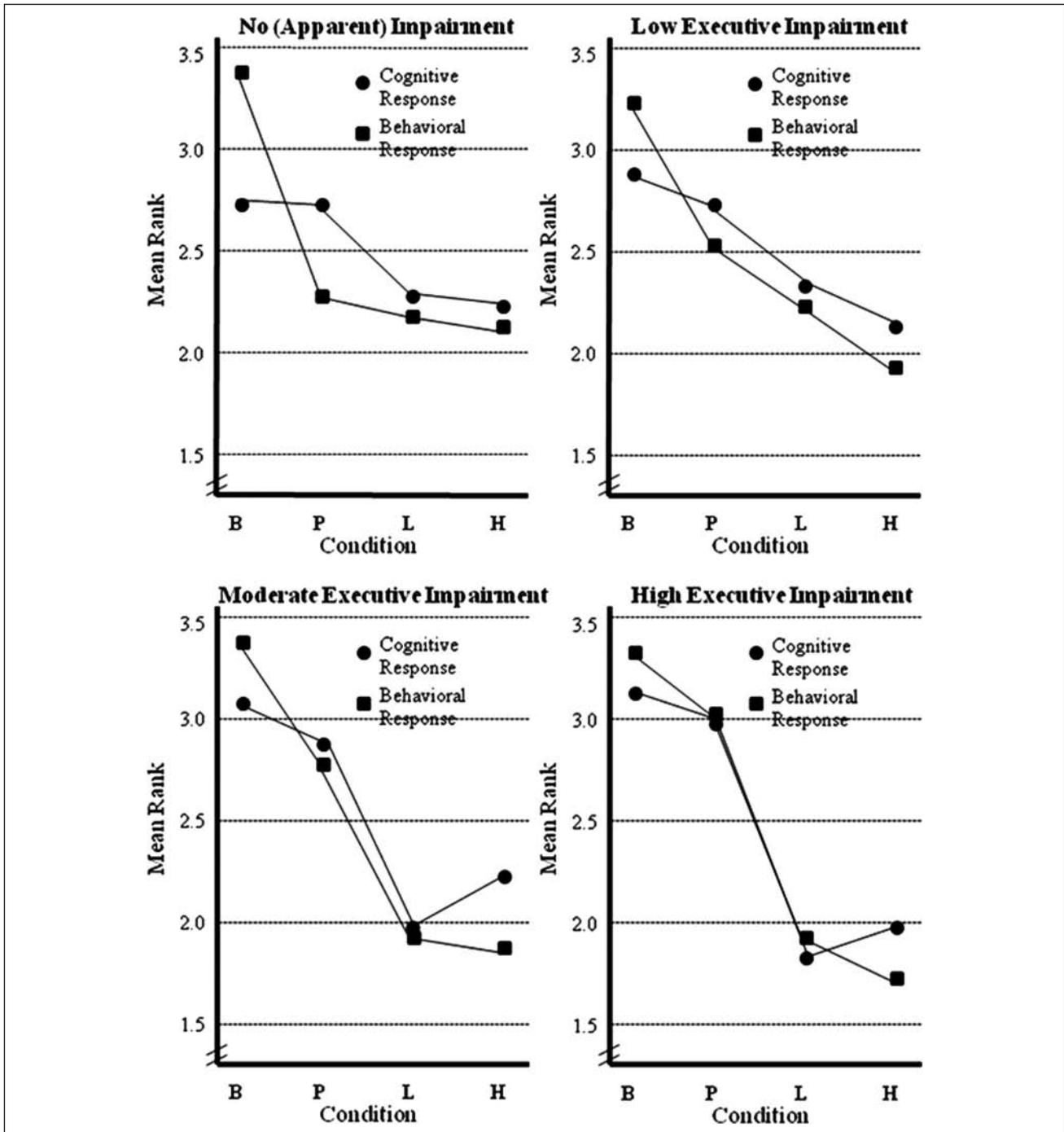


Figure 2. Medication response based on level of frontal-subcortical circuit dysfunction

Note: Lower ranks = better performance and behavior. B = baseline; P = placebo; L = low dose methylphenidate; H = high dose methylphenidate.

from each other. This suggests a placebo effect for behavior ranks, but no significant MPH treatment effect. As a group, these physician and psychologist behaviorally diagnosed children with ADHD did not show EWM/SR impairment and did not appear to benefit from MPH treatment as a result.

For the low impairment group cognitive ranks, the repeated measures MANOVA was significant for drug, $F(3, 17) = 7.55$, $p = .002$, $\eta^2 = .57$, power = .95, indicating a difference among cognitive/neuropsychological functioning across drug conditions. Orthogonal polynomial tests of within-subjects contrasts

revealed a linear effect for drug, $F(1, 19) = 24.02, p < .001, \eta^2 = .55$. Bonferroni contrasts revealed cognitive ranks were lower (i.e., better performance) during the active drug conditions as compared to baseline, but the high dose condition was also better than the placebo condition, indicating those with low impairment did respond to the higher MPH dose. For behavioral ranks, the MANOVA was significant for drug, $F(3, 17) = 19.34, p < .001, \eta^2 = .77$, power = 1.00. Orthogonal polynomial contrasts revealed a linear effect for drug, $F(1, 19) = 55.04, p < .001, \eta^2 = .74$, with quadratic effects approaching significance, $F(1, 19) = 3.95, p = .06$. Bonferroni comparisons revealed that all blinded conditions were lower (better behavior) than baseline, and the high dose condition was lower than the placebo condition, suggesting that for this group, MPH improved cognition and behavior at the high dose only. However, placebo effects were also noted for this group.

For the moderate impairment group cognitive ranks, the repeated measures MANOVA was again significant for drug, $F(3, 12) = 16.70, p < .001, \eta^2 = .807$, power = 1.00, indicating a difference among cognitive/neuropsychological functioning across drug conditions. Orthogonal polynomial contrasts revealed linear, $F(1, 14) = 33.67, p < .001, \eta^2 = .70$, quadratic, $F(1, 14) = 4.72, p = .048, \eta^2 = .25$, and cubic, $F(1, 14) = 11.57, p = .004, \eta^2 = .45$, effects for drug. This finding suggests cognitive response was not uniform across participants within this group. Unlike the other impairment groups, Bonferroni comparisons revealed both active drug conditions to be different from both baseline and placebo, but they were not different from one another. Similarly, there was no difference between baseline and placebo conditions. For the behavior rank repeated measures MANOVA, there was again a significant within-subjects effect, $F(3, 12) = 33.52, p < .001, \eta^2 = .89$, power = 1.00, with linear, $F(1, 14) = 78.79, p < .001, \eta^2 = .84$, and quadratic, $F(1, 14) = 6.61, p = .022, \eta^2 = .32$, effects found for dosage. This time Bonferroni comparisons revealed all blind conditions to be lower than baseline, and the high dose to be lower than placebo, but the low dose only approached significance with placebo.

For the significant impairment group, those with significant baseline EWM/SR deficits, the effect for drug on cognitive ranks was highly significant, $F(3, 7) = 48.01, p < .001, \eta^2 = .954$, power = 1.00, even with the small sample size. An examination of orthogonal polynomials revealed linear, $F(1, 9) = 57.69, p < .001, \eta^2 = .86$, and cubic, $F(1, 9) = 19.45, p = .002, \eta^2 = .68$, effects, indicating nonuniform response patterns. Bonferroni contrasts revealed that the baseline and placebo conditions were different from the active drug conditions, but these were not different from each other. However, it is interesting to note that the cognitive rank was qualitatively lower for the low dose than the high dose, where cognition appeared to deteriorate. For the behavior rank repeated measures MANOVA, there was again a significant drug effect, $F(3, 7) = 62.85, p < .001, \eta^2 = .964$, power = 1.00, with strong linear, $F(1, 9) = 226.66,$

$p < .001, \eta^2 = .96$, effects found for dosage, and cubic, $F(1, 9) = 5.99, p = .03, \eta^2 = .40$, effects found as well. As was the case with cognitive response, Bonferroni contrasts revealed that the baseline and placebo conditions were different from the active drug conditions, but these were not different from each other.

Analysis of Single Subject MPH Dose-Response Relationships

With findings demonstrating differential treatment effects based on level of EWM/SR impairment, an examination of individual case dose-response relationships based on NPStat nonparametric randomization test results was undertaken. These single subject results were provided to parents and referring physicians in each child's medication trial report. Although NPStat statistical response does not necessarily reflect clinical response, which was determined by referring physicians, results suggest that most of those with N/A or low executive impairment tended to be in the ADHD-IT group, and often did not show a significant MPH response. However, those with moderate or significant impairment tended to fall into the ADHD-CT group. These individuals were more likely to show a significant cognitive and behavioral medication response, with no nonresponders found in these impairment groups, regardless of behavioral ADHD diagnosis.

Discussion

In this study, children with behaviorally diagnosed ADHD underwent double-blind placebo controlled MPH trials with baseline cognitive/neuropsychological direct assessments of the child, indirect behavior ratings obtained from parents and teachers, and classroom observations used to calculate cognitive and behavioral ranks. These data were subsequently submitted to NPStat nonparametric randomization tests to determine statistical response. Results revealed highly significant MPH treatment effects, but response differences emerged for children based on the SEM-determined level of EWM/SR executive impairment. For those with N/A baseline EWM/SR executive impairment, MPH response was poor. For those with significant impairment, every single child showed a significant MPH response. In addition, differential cognitive and behavioral patterns of MPH response emerged for those with moderate and significant EWM/SR impairment, with the best dose for cognition lower than the best dose for behavior.

MPH Effects on "Hot" Versus "Cool" Frontal-Subcortical Circuits

Although the exact neurophysiological explanation for these MPH findings is beyond the scope of this article, some speculation appears to be warranted given similar findings reported

elsewhere (e.g., Arnsten, 2006a; Berridge et al., 2006; Konrad et al., 2004). Solanto et al. (2001) suggest that the tasks evaluating response inhibition or reward or punishment may reflect different types of executive functioning, which explains the differential findings for EF tasks on and off of medication found here. Zelazo and Muller (2002) suggest that cognitive aspects of EF may be associated with the dorsolateral prefrontal cortex and are characterized as “cool” EF. In contrast, EF tasks that pull for affect (reward/punishment) are referred to as “hot” EF and may be associated with the orbital and medial prefrontal cortices. Castellanos, Sonuga-Barke, Milham, and Tannock (2006) suggest that cool EF is associated with more cognitively loaded types of tasks such as IQ, response inhibition, and working memory while hot EF is associated more with risk-taking and externalizing behaviors, but not inattention. Conceptualizing EF as having both cognitive and affective aspects may help explain the differing findings in children with ADHD, particularly in regard to stimulant medication and, as we have demonstrated, with level of MPH. The phylogenetically older hot ventral circuits are important for behavioral self-regulation or affective decision making, while the younger cool dorsal circuits are involved in deliberative executive processing and attention control (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Figner, Maklinlay, Wilkening, & Weber, 2009; Roiser et al., 2009; Steinberg, 2008).

A differential effect by MPH on the hot (e.g., SR; orbital-medial-ventral cingulate) and cool (e.g., EWM; dorsolateral-dorsal cingulate) frontal-striatal-thalamic circuits (Castellanos et al., 2006; Kelly, Sonuga-Barke, Scheres, & Castellanos, 2007) may explain the difference in improvement in behavior versus cognition. MPH has been demonstrated to increase activation in the areas associated with behavioral and risk-taking behaviors compared to those involved with higher level executive functioning (Zametkin et al., 1990). Support for this conclusion comes from an fMRI study that showed less activation in the dorsolateral region in children with ADHD, particularly those with no history of medication treatment (Pliszka et al., 2006). Moreover, a comparison of event-related potentials in children with a history of MPH or no history of MPH on a task requiring inhibition found less activation to “failed” trials than to “successful” trials (Liotti, Pliszka, Perez, Glahn, & Semrud-Clikeman, 2008). In these cases children with a history of MPH treatment showed improvement in the areas involved in inhibitory skills (behavior) compared to those without such a history. Thus, children with a history of MPH at generally accepted levels were found to show improvement in the hot circuit even when *off* medication. Perhaps MPH is more likely to have a strongly linear effect on the hot circuit, but a curvilinear one for the cool circuit, where balance of catecholamines becomes more important.

ADHD Subtypes: Are They Distinct Disorders?

This MPH response pattern in this investigation is not surprising given the preponderance of evidence that response inhibition is the primary deficit in ADHD (Houghton et al., 1999; Willcutt et al., 2005; Wodka et al., 2007), which secondarily affects attention and other more traditional executive functions (e.g., Barkley, 1997). This assumption is partially supported by findings in this investigation, where both the EWM and SR factors reported in Hale et al. (2005) were found to be related to *DSM-IV-TR* hyperactive-impulsive symptoms, but not inattentive ones, suggesting that ADHD-IT and ADHD-CT may be distinct disorders (Milich, Balentine, & Lynam, 2001). Certainly, inattention, or at least intention control (Denckla, 1996; Hale, Reddy, Decker, et al., 2009), is another primary deficit in ADHD. Several studies have suggested that there are few differences among ADHD subtypes (e.g., Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2005; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002), with inattentive symptoms associated with executive dysfunction, not hyperactive impulsive ones (Chhabildas, Pennington, & Willcutt, 2001), and results vary based on the study design and methodology. Perhaps inconsistent findings might be in part due the behavioral definition of the ADHD populations used in these studies, where some children have “primary” ADHD-IT, while others have secondary or “pseudo” ADHD due to other psychiatric and/or learning problems (Hale, Reddy, Wilcox, et al., 2009).

Results from this study suggest that there are multiple causes of inattention symptoms in children behaviorally diagnosed as ADHD, suggesting informant reports and behavioral rating scales are insufficient for differential diagnosis. Although behavior rating scales are important sources of information in a multimethod, multisource evaluation, they remain summative behavioral judgments of children, effectively intertwining subjective source opinion with objective facts about the child (Demaray, Elting, & Schaefer, 2003; DuPaul, 2006). When multiple causes of attention problems are subsumed under a heterogeneous ADHD behavioral umbrella, the diagnostic sensitivity and specificity of our tools is reduced, and treatment efficacy is likely attenuated (Hale, Reddy, Decker, et al., 2009).

Evidence for this assertion can be seen in the lower correlation between EWM and SR factors and *DSM-IV-TR* inattention symptoms in this study. Also, the four EWM/SR executive impairment groups differed on *DSM-IV-TR* hyperactive-impulsive symptoms but did not differ on *DSM-IV-TR* inattention ones, suggesting that only those with “true” ADHD and hot circuit involvement are more likely to respond to MPH. The cool dorsolateral and dorsal anterior cingulate circuits also cause attention deficits in other disorders, such as depression (Liotti & Mayberg, 2001), so perhaps the MPH nonresponder ADHD-IT children in this study have this type

of impairment or another form of “pseudo” ADHD such as parietal lobe dysfunction (Hale, Reddy, Wilcox, et al., 2009).

These arguments are consistent with findings that the ADHD-IT is likely to be a heterogeneous disorder (e.g., Hale, Reddy, Decker, et al., 2009; Johansen, Aase, Meyer, & Sagvolden, 2002) in that only some of these children display subthreshold behavioral/self-regulation/response inhibition problems that are characteristic of children with ADHD-CT (Weiss, Worling, & Wasdell, 2003). A subsequent chart review of the ADHD-IT group in this study supported this conclusion, with children with ADHD-IT and comorbid anxiety/depression often showing low executive impairment and no MPH response, and those with higher impairment had subthreshold reported hyperactive-impulsive symptoms and showed good MPH response. It is clear that multiple data sources, including informant reports, neuropsychological assessment of executive functions, and careful clinical evaluation of child and family histories, is essential practice for determining the various causes of attention problems (Hale, Reddy, Wilcox, et al., 2009; Reddy & Hale, 2007).

Implications for Academic Achievement in ADHD

When medication is considered for a child with ADHD, some teachers may be most immediately concerned about MPH effects on improving overt behavior problems. However, the results presented here and reported in the literature (e.g., Chacko et al., 2005; Evans et al., 2001; Horrigan & Barnhill, 2000; Pliszka, Liotti, Bailey, Perez, Glahn, & Semrud-Clikeman, 2006; Teicher, Polcari, & McGreenery, 2008) suggest the best MPH dose for cognition may be lower than the best MPH dose for behavior. These differential dose-response relationships for children with ADHD could explain why long-term treatment MPH efficacy remains limited (e.g., Jensen et al., 2007) and that MPH has equivocal effects on academic achievement (Balthazor et al., 1991; Frankenberger & Cannon, 1999; Van der Oord et al., 2008) because clinical attention has been focused on MPH behavior control, not maximizing cognitive functioning. If the optimal dose for behavior is chosen, children will likely struggle with learning, memory, and achievement because the higher dosage limits executive attention control/working memory functions (e.g., Berridge et al., 2006).

The cool dorsolateral-dorsal cingulate executive functions such as sustained attention, executive planning, flexible problem solving, fluid reasoning, processing speed, and working memory are important predictors of academic domains such as math calculation and reasoning, reading comprehension, written expression, higher level implicit language, and reading, math, and writing fluency (e.g., Biederman et al., 2004; Bryan & Hale, 2001; Decker, Hill, & Dean, 2007; Denckla, 1996; Goldstein & Naglieri, 2008; Hale & Fiorello, 2004).

If MPH titration was based on maximizing cognitive functioning and adjunct behavior therapy was used to help reduce problematic behaviors not adequately addressed by the lower MPH dose, perhaps then we would see long-term academic and behavior improvement in children with ADHD.

The results presented here suggest that practitioners need to reconsider use of standard *indirect* behavioral approaches to ADHD diagnosis and determining MPH treatment efficacy. Instead, it may be useful to incorporate *direct* measurement of cognitive, neuropsychological, academic, and behavioral functioning when conducting comprehensive evaluations to ensure children referred for attention problems do indeed have “true” ADHD (Hale, Reddy, Decker, et al., 2009). Even for those with “true” ADHD, many have comorbid behavioral and academic concerns, and differential cognitive, academic, and behavioral MPH dose-response relationships appear to be common, so it may be useful to compare short- and long-term MPH treatment effects on *all* of these critical functions. Multimethod, multisource evaluations using both neuropsychological and behavioral assessment methods minimize the individual limitations of both approaches, and in combination can construct a better diagnostic picture for clinicians, thereby leading to targeted interventions tailored to individual needs and better treatment efficacy as a result.

Limitations and Future Directions

Several study limitations are worth noting. First, the sample included children aged 6 to 16, with a majority of the children in Grades K through 5. Developmental differences in ADHD neuropsychological and behavioral functioning are well known (Barkley, 1997), so future research should examine if these MPH findings are consistent across age ranges. Second, the neuropsychological tests used here were not counterbalanced and analyzed for order effects; however, they were specifically chosen because order effects have not been found in previous studies (e.g., Hale et al., 2005; Hoepfner et al., 1997). Third, research assistants who conducted classroom observations were proficient at collecting reliable observational data before medication trials, but future research could also examine interrater reliability during MPH trials. Fourth, all participants were thought to have average intellectual functioning by report, but only some of the children had been administered a standardized intelligence test prior to the medication trial. Although the baseline and placebo conditions in part guard against intelligence differences, future research should at least include a cognitive screening of all children. Finally, it will be important to consider teacher, instructional, or classroom management practices in future research to determine if these variables influence or moderate MPH treatment response.

Future research could examine children with MPH titration based on direct neuropsychological baseline function compared to those who receive standard indirect behavioral titration

approaches to determine if cognitive, academic, and behavioral outcomes are differentially affected. In addition, further research examining MPH response in relation to, and in combination with, other interventions is needed. While this study provides additional evidence supporting evaluation of both cognitive and academic MPH response, the exact neurophysiological nature of differential MPH response curves was not directly evaluated. These response curves could also differ for alternative ADHD medications (e.g., Adderall, Strattera) or MPH dosing regimens (e.g., Concerta, Metadate). Additional research is needed to explore MPH response for the different hot orbital-ventral cingulate and cool dorsolateral-dorsal cingulate circuits, how this impacts SR and EWM. This empirical work could help determine whether MPH dose-response curves differ for the circuits and ultimately lead to better titration practices that foster academic achievement and psychosocial functioning for children with ADHD.

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