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EVIDENCE OF A PHARMACOLOGICAL DISSOCIATION BETWEEN THE ROBUST EFFECTS OF METHYLPHENIDATE ON ADHD SYMPTOMS AND WEAKER EFFECTS ON WORKING MEMORY

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ABSTRACT

Working memory (WM) deficits often co-occur with, but do not define, attention deficit hyperactivity disorder (ADHD). Preclinical and neuroimaging studies show that ADHD and WM deficits are dissociated at the level of individual dopamine receptor function. We hypothesized that there would also be a pharmacological dissociation of the effects of stimulants on ADHD and WM. ADHD subjects were derived from three prospective clinical trials involving treatment with OROS methylphenidate for at least 6 weeks. Subjects were adolescents and adults with DSM-IV ADHD with systematic assessments of WM and ADHD symptoms. Cohen's d was used to evaluate effect size between baseline and week 6 for all assessments, and Pearson correlations were used to evaluate the relationship between assessments at baseline and between change scores for assessments from baseline to week 6. Cohen's d estimates for the Cambridge Neuropsychological Test Automated Battery spatial working memory measures differed significantly by 1.8 standard deviations ($t = -10.8$, $df = 70$, $p < 0.001$) and 1.9 standard deviations ($t = -11.1$, $df = 70$, $p < 0.001$) for the strategy and total between errors subcategories respectively. Confidence intervals did not overlap with those of the Adult ADHD Investigator Symptom Rating Scale (AISRS). A similar effect was observed for changes in AISRS and the Behavior Rating Inventory of Executive Function working memory scale where the Cohen's d estimates differed significantly by 1.1 standard deviations ($t = -2.5$, $df = 137$, $p =$

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0.015) and confidence intervals did not overlap. These findings provide further evidence for the dissociation between ADHD and WM deficits.

Keywords: ADHD, Working memory, Dissociation, Pharmacology, Methylphenidate.

Contribution/ Originality

This study documents that responses to methylphenidate in ADHD symptoms and working are dissociated, indicating that a sizeable number of ADHD subjects may continue to struggle with residual working memory impairments despite good clinical response to methylphenidate.

1. INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent, persistent, and morbid neurobiological disorder estimated to affect up to 11% of children [1] and 5% of adults worldwide [2]. While a wide range of neurobiological differences in ADHD relative to controls have often been reported [3-6], a unifying model of the neurobiology of ADHD has remained elusive. One of the prevailing neuropsychological models of ADHD suggests that ADHD arises from deficits in executive functions (EFs). These high order cognitive functions are well documented to be a source of morbidity and disability in individuals with ADHD [7-10]. Among these EF deficits, working memory (WM) is a prominent component [11]. Over half of individuals diagnosed with ADHD do not have deficits in EFs or WM, suggesting that although these deficits frequently co-occur with ADHD they are not synonymous with the disorder [8, 12]. Supporting this notion, preclinical studies showed that hyperactivity and WM deficits were dissociable at the level of individual dopamine receptor function in a prenatal nicotine exposure (PNE) mouse model of ADHD [13, 14]. Further evidence of a dissociation between ADHD and WM was recently documented in a resting state functional magnetic imaging study where well-characterized, longitudinally followed participants with persistent and remitted ADHD in adult years and controls were scanned while they performed a standard working memory experiment. The dissociation between WM and ADHD was apparent in the relation between adult ADHD diagnostic status and WM ability. Spared or compromised working memory ability occurred regardless of persistent ADHD diagnostic status, with deficits appearing equally often in persistent or remitted ADHD groups. Both the controls and the ADHD participants with unimpaired spatial working memory exhibited significant linearly increasing activation as a function of working-memory load in the dorsolateral prefrontal cortex, intraparietal sulcus, and cerebellum, and these activations did not differ significantly between these groups, whereas ADHD participants with impaired spatial working memory exhibited significant hypoactivation in the same regions of the left hemisphere (Mattfeld, submitted). These findings provide further neurobiological evidence for the dissociation between ADHD and WM deficits that often accompany but do not define ADHD. While stimulants remain the mainstay of treatment for ADHD due to their large effect size [15-19], their effects on EF deficits (EFDs) in general and WM in particular are more equivocal [20]. Considering the well-documented morbidity associated with EFDs in individuals with ADHD of all ages [7-10], further knowledge of the

effects of stimulants on EFDs is an area of high clinical and scientific importance. Such knowledge will help clinicians and patients have more realistic expectations regarding whether the scope of benefits expected from stimulants includes EFDs.

The main aim of the present study was to test the hypothesis that there would be a pharmacological dissociation of the effects of stimulants on ADHD symptoms and WM. To this end, we analyzed data from previously reported prospective clinical trials of adolescents and adults with DSM-IV diagnosed ADHD involving treatment with extended release methylphenidate (OROS MPH) for at least 6 weeks. Subjects underwent systematic assessments of psychometrically (Cambridge Neuropsychological Test Automated Battery [CANTAB]) [21] and behaviorally (Behavior Rating Inventory of Executive Function [BRIEF] or BRIEF – Adult Version [BRIEF-A]) [22, 23] defined measures of WM as well as assessments of ADHD symptoms.

2. MATERIALS AND METHODS

2.1. Subjects

ADHD subjects were derived from three prospective clinical studies (Studies A, B, and C) involving OROS MPH. All three studies included subjects that satisfied full diagnostic criteria for DSM-IV ADHD [24] on the basis of clinical assessment by an expert clinician and received treatment with OROS MPH for at least 6 weeks. Study A Biederman [25] was a double-blind, randomized, 6-week, placebo-controlled trial of OROS MPH in outpatient adults with ADHD aged 19-60 years. Study B Hammerness [26] was a prospective open label clinical study of OROS MPH in adolescents with ADHD. Study C Biederman [27] was a double blind, placebo-controlled, randomized clinical trial to compare the efficacy and tolerability of memantine for EFDs in ADHD as a supplement to open-label treatment with OROS MPH. Detailed methodologies for these studies have been previously reported [25-27]. In all three studies, OROS MPH was started at 36 mg and increased at weekly intervals by 18-36 mg based on response and adverse effects. All studies were approved by the MGH Institutional Review Board, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects signed a written consent form. In the adolescent study, parents signed consent and adolescent subjects also signed a written assent form.

2.2. Assessment

As previously detailed, subjects in all studies underwent a clinical assessment by an expert clinician to establish a DSM-IV diagnosis of ADHD and evaluate inclusion and exclusion criteria.

2.3. Assessment of ADHD Symptoms

The Adult ADHD Investigator Symptom Report Scale (AISRS) [28], shown to be sensitive to drug effects in pediatric and adult populations, assesses each of the 18 individual criteria symptoms of ADHD in DSM-IV on a severity grid (0 = not present; 3 = severe; overall minimum score = 0; maximum score = 54).

2.4. Working Memory Measures

The CANTAB [29-31] is a computerized neuropsychological battery. The CANTAB includes complex cognitive tests of sustained attention, planning, shifting, and working memory. To assess working memory, we used two subcategories of the CANTAB spatial working memory subtest: strategy and total between errors. Both subcategories were evaluated as z-scores standardized by age. The strategy subcategory of the spatial working memory task records the number of distinct boxes used by the subject to begin a new search for a token, within the same problem. The total between errors subcategory of the spatial working memory task counts the times the subject revisits a box in which a token has previously been found. The BRIEF [23] and BRIEF-A [22] are standardized measures of behavioral manifestations of EFDs. The BRIEF/BRIEF-A working memory scale assesses an individual's ability to hold information in mind while completing a task. Items include: "I have trouble with jobs or tasks that have more than one step" and "I forget instructions easily." We evaluated this scale as a t-score standardized by age. In the adult studies, the BRIEF-A was completed directly by the subject, and in the adolescent study, the BRIEF was completed indirectly by a parent of the subject. Sixty-three adults completed the BRIEF-A, and 75 BRIEFs were completed for adolescents.

2.5. Statistical Analysis

Pearson correlations were used to evaluate the relationship between assessments at baseline and between change scores for assessments from baseline to week 6. Cohen's d was used to evaluate effect size between baseline and week 6 for all assessments, and a paired t-test was used to evaluate whether there was a significant change from baseline to week 6. To compare the baseline to endpoint changes in AISRS scores with the baseline to endpoint changes in working memory scores, we computed confidence intervals for the Cohen's d standardized effect size and paired t-tests to compare the standardized change scores. For the paired t-test of change scores we first normalized each change score by dividing by its standard deviation. We also completed these analyses separately for the adolescent (Study B) and adult (Studies A and C) groups to examine age effects. All tests were two-tailed and statistical significance was defined at the 5% level.

3. RESULTS

3.1. Sociodemographic Characteristics

Table 1 shows the demographic information for all three studies and the combined information for all the studies together. The weight corrected dose of OROS-MPH in Study C was somewhat lower than those used in the other two studies.

3.2. Correlations between ADHD Symptom and Working Memory Measures

The AISRS total score and BRIEF/BRIEF-A working memory scale were significantly correlated at baseline ($r = 0.25$; $p = 0.004$) and week 6 ($r = 0.49$, $p < 0.001$). The two CANTAB spatial working memory subcategories of strategy and total between errors were also highly

correlated with each other at baseline (r = 0.77, p < 0.001) and week 6 (r = 0.58, p < 0.001), but with neither the AISRS nor the BRIEF/BRIEF-A working memory scale at either point in time (AISRS & strategy: baseline r = 0.14, p = 0.2; week 6 r = 0.04, p = 0.7; AISRS & between: baseline r = 0.14 p = 0.2, week 6 r = 0.09 p = 0.4, BRIEF/BRIEF-A & strategy: baseline r = 0.07, p = 0.5; week 6 r = -0.05, p = 0.7; BRIEF/BRIEF-A & between: baseline r = 0.04, p = 0.7; week 6 r = -0.08 p = 0.5).

Table-1. Sociodemographic Characteristics of Sample.

	Study A	Study B	Study C	Overall
N	86	135	13	234
Female	36 (42%)	33 (24%)	7 (54%)	76 (32%)
Mean Age ± SD	34.6 ± 9.1	14.3 ± 1.8	37.8 ± 10	23.1 ± 12
Min Age	20	11	25	11
Max Age	54	20	57	57
Mean Dosage ± SD (mg/kg/day)	1.04 ± 0.3	1.02 ± 0.36	0.76 ± 0.29	1.01 ± 0.34

Study A was a double blind adult study of OROS-MPH, Study B was a open label adolescent study of OROS-MPH, Study C was a double blind adult study of memantine with OROS-MPH as the placebo.

3.3. Change from Baseline to Week 6

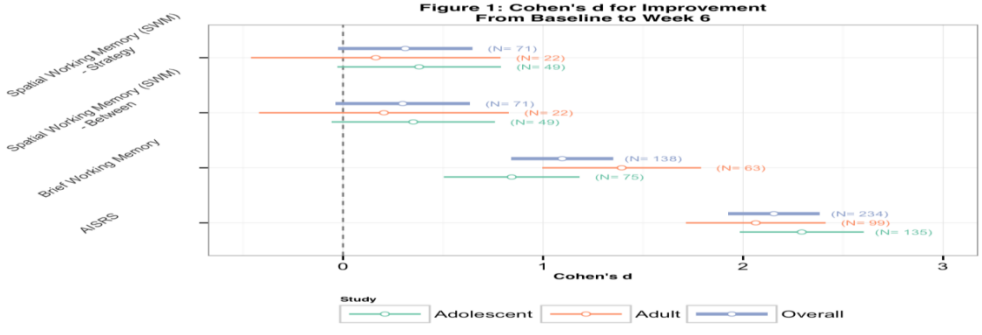

Figure-1. shows the comparisons of Cohen's d standardized effect sizes for each assessment. The center points show the means and the lines show the 95% confidence intervals.

As shown in Figure 1, comparing the Cohen's d for changes in AISRS and the Cohen's ds for CANTAB spatial working memory measures, the effect size estimates differ significantly by 1.8 standard deviations (t= -10.8, df= 70, p < 0.001) and 1.9 standard deviations (t= -11.1, df= 70, p < 0.001) for the strategy and total between errors subcategories respectively. These confidence intervals did not overlap with the AISRS confidence intervals. This same effect was observed when we separated out adults (strategy: t= -4.4, df= 21, p < 0.001; between: t= -5.9, df= 21, p < 0.001) and adolescents (strategy: t= -10.6, df= 48, p < 0.001 and between: t= -9.6, df= 48, p < 0.001). Comparing the Cohen's d for changes in AISRS and the Cohen's d for the BRIEF/BRIEF-A working memory scale, we see that the estimates differ significantly by 1.1 standard deviations (t= -2.5, df= 137, p = 0.015) and the confidence intervals do not overlap. However, when we split into adolescent and adult groups this effect remains significant in the adolescents (t= -2.6, df= 74,

p = 0.01), but in the adult group the Cohen's ds differ non-significantly by 0.7 standard deviations (t= -0.5, df= 62, p = 0.7) and the confidence intervals slightly overlap.

4. DISCUSSION

The main aim of the present study was to compare the effects of robust daily doses of OROS-MPH administered prospectively in the context of a clinical trial on ADHD symptoms and WM. Results show that treatment with OROS MPH is associated with robust effects on ADHD symptoms, more modest effects on WM assessed behaviorally (BRIEF/BRIEF-A) and small, non-significant effects of WM assessed psychometrically (CANTAB). These findings are consistent with the study hypothesis of a pharmacological dissociation between the effects of OROS-MPH on symptoms of ADHD and those on WM. These results are consistent with those of a recent open label study of lisdexamphetamine that showed that 40% of adults with ADHD were considered to have unresolved and clinically significant impairments in self-reported EFDs despite improvements in ADHD symptoms [32]. Similarly, a large randomized placebo-controlled clinical trial of OROS-MPH in adults with ADHD found that ADHD participants continued to have a large burden of impairing self-reported EFDs, despite robust improvements in ADHD symptoms [33]. Our group also used data from a longitudinal naturalistic study of ADHD children treated in their communities with stimulants and reported that stimulants had limited effect on self-reported measures EFDs [34]. Finally, the limited effects of OROS-MPH on WM are consistent with clinical observations of continued problems with academic and work performance in individuals with ADHD despite well-controlled ADHD symptoms. A recent review by Swanson, et al. [35] that observed that stimulants appear to have differential effects on cognition depending on type of task conducted. Stimulant related improvements in ADHD children were more prominent on simpler cognitive tasks (e.g., spatial recognition memory reaction time, and delayed matching-to-sample) as compared to more complex tasks tapping executive function (e.g., working memory, planning, and set-shifting) [35]. Pre-clinical studies have raised concern about neurotoxicity to dopaminergic neurons with high stimulant dosing [36]. An inverted U-shaped relationship between catecholamine (i.e., dopamine) release and cognitive performance was suggested, in which cognition is enhanced only in the context of a yet to be determined optimal stimulant exposure [35, 37]. The limited effects of OROS-MPH on WM are further demonstrated in preclinical findings that have shown hyperactivity and working memory to be dissociated at the dopamine receptor level (D1-hyperactivity and D4-working memory) in the PNE mouse model, suggesting that these symptoms can be treated by rectifying the specific underlying impairments that sub serve them.

Whereas increases in extracellular dopamine levels via blockade of dopamine reuptake may be needed to mitigate ADHD symptoms, a more direct effect on dopamine receptor D4 (DRD4) may be necessary for improvements in WM. Consistent with this hypothesis, administration of a selective DRD4 agonist improved WM deficits in the PNE animal model of ADHD, but did not have significant effects on hyperactivity. Similar results reported by Browman [38] showed significant dose-dependent cognitive enhancing properties of specific DRD4 agonists in

comparison with two less selective DRD4 agonists in rat models of ADHD. These findings further emphasize the intriguing implication that specific dopamine receptor subtypes may be associated with specific ADHD symptoms or remedies. However, the highly heterogeneous distribution of the dopamine receptor subtypes in different brain regions (e.g. basal forebrain *versus* frontal cortex) and the global increases in dopamine produced by the stimulants that result in therapeutic benefits render it virtually impossible to assign a specific dopamine receptor to a specific ADHD symptom. However, now we offer the very first insight into a potential association between a specific cognitive function namely, WM/EFD and specific dopamine receptor namely, DRD4.

Considering the critical importance of WM for adequate cognitive functions and its ubiquity in subjects with ADHD [39], the limited effects of OROS MPH on WM are noteworthy. Etchepareborda and Abad-Mas [40] found that impaired working memory negatively influences academic learning processes such as focusing attention, inhibition of irrelevant stimuli, recognition of priority patterns, ability to recognize hierarchies and the meaning of stimuli (analysis and synthesis), establishing an intention, and recognizing and selecting the goals that are best suited to solving a problem. Since these cognitive processes are critical for learning, their impairment can lead to educational dysfunction, low educational status, and can have a serious impact on educational success and employment opportunities. Working memory tasks are also considered to be robust probes of prefrontal function (as described by Cohen [41]), and abnormalities in frontal-striatal regions are hypothesized to contribute to ADHD symptomatology. Taken together, these findings support the search for safe and effective treatments to help address WM deficits in individuals with and without ADHD. The absence of associations between CANTAB and BRIEF/BRIEF-A based definitions of WM are consistent with previous reports documenting similar absence of associations between psychometrically and behaviorally defined assessments of executive function deficits [42]. Taken together, these findings indicate that CANTAB and BRIEF/BRIEF-A definitions of WM are independent of each other. Strengths of this study include the reliance on findings ascertained in the context of prospective clinical trials, the common assessment battery, the use of standardized measures of WM and ADHD symptomatology, and the robust doses of stimulants deployed for several weeks. In contrast, a fundamental limitation to the literature is that the majority of studies to date that have examined cognitive outcomes were conducted in the context of limited stimulant exposure, used low doses of stimulants and had a brief treatment duration. In Pietrzak [20] review of the cognitive effects of MPH, all 40 studies involved immediate release MPH formulations, with dosing limited to 5-20 mg. With few exceptions, "high dose" was typically no more than 20 mg or 0.6 mg/kg. In addition, study designs were primarily single, fixed dose, crossover trials, with "chronic" exposure considered to be only 4 weeks [20]. Another important strength of the present study is the use of the CANTAB [29-31], a computerized technology for cognitive assessments that provides an important source of objective, reproducible methodology to assess the impact of stimulants upon cognitive function in subjects with ADHD [43]. However, our findings should be considered in light of some methodological limitations. The CANTAB

represents one of many batteries used in the assessment of neuropsychological functioning. Likewise, the BRIEF/BRIEF-A represents one of many methods to assess behavioral manifestations of EFDs. We aggregated data from three similarly designed prospective clinical trials. The effect sizes were calculated from contrasting baseline and post treatment findings, which probably yielded larger effect sizes than would have been seen in drug vs. placebo comparisons. Finally, because the majority of our subjects were Caucasian, our results may not generalize to other ethnic groups. Despite these limitations, our results show that the responses to methylphenidate in ADHD symptoms and WM are dissociated, indicating that a sizeable number of ADHD subjects may continue to struggle with residual WM impairments despite good clinical response to OROS-MPH. More work is needed to help identify safe and effective treatments for WM deficits within and outside of the context of ADHD.

5. ACKNOWLEDGMENTS

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5.1. Conflicts of Interest

Dr. Joseph Biederman is currently receiving research support from the following sources: The Department of Defense, AACAP, Alcobra, Forest Research Institute, Ironshore, Lundbeck, Magceutics Inc., Merck, PamLab, Pfizer, Shire Pharmaceuticals Inc., SPRITES, Sunovion, Vaya Pharma/Enzymotec, and NIH. In 2014, Dr. Joseph Biederman received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses. He has a US Patent Application pending (Provisional Number #61/233,686) through MGH corporate licensing, on a method to prevent stimulant abuse. Dr. Biederman received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Ingenix, Prophase, Shire, Bracket Global, Sunovion, and Theravance; these royalties were paid to the Department of Psychiatry at MGH. In 2013, Dr. Joseph Biederman received an honorarium from the MGH Psychiatry Academy for a tuition-funded CME course. He received research support from APSARD, ElMindA, McNeil, and Shire. Dr. Biederman received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Shire and Sunovion; these royalties were paid to the Department of Psychiatry at MGH. In 2012, Dr. Joseph Biederman received an honorarium from the MGH Psychiatry Academy and The Children's Hospital of Southwest Florida/Lee Memorial Health System for tuition-funded CME courses. Dr. Thomas Spencer has received research support from, has been a speaker for or on a speaker bureau or has been an Advisor of on an Advisory Board of the following sources: Alcobra, Cephalon, Eli Lilly & Company, Glaxo-Smith Kline, Heptares, Impax, Ironshore, Janssen Pharmaceutical, Lundbeck, McNeil Pharmaceutical, Novartis Pharmaceuticals, Pfizer, Shire Laboratories, Inc, Sunovion, VayaPharma, the National Institute of Mental Health and the Department of Defense. Dr. Spencer receives research support form Royalties and Licensing fees on copyrighted ADHD scales through MGH Corporate Sponsored Research and Licensing. Dr. Spencer has a US Patent Application pending (Provisional Number 61/233,686), through MGH corporate licensing, on a method to prevent stimulant abuse. Dr. Pradeep Bhide is

President and Chief Scientific Officer of Avekshan, LLC a pharmaceutical company engaged in the business of developing pharmaceuticals for the treatment of ADHD and related disorders. He is a member of the board of managers, and the managing member of Avekshan LLC. In the past year, Dr. Faraone received income, travel expenses and/or research support from and/or has been on an Advisory Board for Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, Neurovance, Impax, NeuroLifeSciences and research support from the National Institutes of Health (NIH). His institution is seeking a patent for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by: Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health and Oxford University Press: Schizophrenia: The Facts.

For the remaining authors, no conflicts were declared.

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