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Methylphenidate and *Memory and Attention Adaptation Training* for persistent cognitive symptoms after traumatic brain injury: a randomized, placebo-controlled trial

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Methylphenidate and Memory and Attention Adaptation Training for Persistent Cognitive Symptoms after Traumatic Brain Injury: A Randomized, Placebo-Controlled Trial

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Methylphenidate and *Memory and Attention Adaptation Training* for persistent cognitive symptoms after traumatic brain injury: a randomized, placebo-controlled trial

Running title: Methylphenidate and cognitive rehabilitation after TBI

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Abstract

The purpose of this multicenter, prospective, randomized, placebo-controlled study was to evaluate and compare the efficacy of two cognitive rehabilitation interventions (Memory and Attention Adaptation Training (MAAT) and Attention Builders Training (ABT)), with and without pharmacologic enhancement (i.e., with methylphenidate (MPH) or placebo), for treating persistent cognitive problems after traumatic brain injury (TBI). Adults with a history of TBI at least four months prior to study enrollment with either objective cognitive deficits or subjective cognitive complaints were randomized to receive MPH or placebo *and* MAAT or ABT, yielding four treatment combinations: MAAT/MPH (N=17), ABT/MPH (N=19), MAAT/placebo (N=17), and ABT/placebo (N=18). Assessments were conducted pre-treatment (baseline) and after six weeks of treatment (post-treatment). Outcome measures included scores on neuropsychological measures and subjective rating scales. Statistical analyses used linear regression models to predict post-treatment scores for each outcome variable by treatment type, adjusting for relevant covariates. Statistically significant ($p < 0.05$) treatment-related improvements in cognitive functioning were found for word list learning (MAAT/placebo > ABT/placebo), nonverbal learning (MAAT/MPH > MAAT/placebo and MAAT/MPH > ABT/MPH), and auditory working memory and divided attention (MAAT/MPH > ABT/MPH). These results suggest that combined treatment with metacognitive rehabilitation (MAAT) and pharmacotherapy (MPH) can improve aspects of attention, episodic and working memory, and executive functioning after TBI.

Introduction

Functionally important cognitive impairments are common in the late period following traumatic brain injury (TBI). Working and episodic memory, attention, speed of information processing, and aspects of executive functioning are among the most common post-traumatic cognitive impairments, and are typical targets of rehabilitative efforts (Cappa *et al*, 2005; Cicerone *et al*, 2011). Treatment of cognitive complaints and deficits in individuals with TBI has taken the form of either cognitive rehabilitation or pharmacologic augmentation.

The two principal approaches to cognitive rehabilitation after TBI include remediation and compensatory training. Remediation (“cognitive retraining”) approaches are based on the theory that cognitive abilities can be improved by activating particular aspects of the cognitive process through graded mental exercise (Sohlberg *et al*, 2003; Tate, 1997). The techniques employed in a remediation approach often focus on repetitive practice regimens within a specific cognitive domain. Work using the Attention Process Training (APT) intervention has shown significant improvements on measures of objective and subjective attentional and executive functioning after TBI (Palmese and Raskin, 2000; Sohlberg *et al*, 2000). Similarly, treatments targeting “working attention” have been shown to improve performance on objective measures of attention as well as reduce self-reported attentional difficulties in daily functioning (Cicerone, 2002).

Compensatory training approaches focus on adapting to and compensating for cognitive impairment by capitalizing on remaining cognitive strengths and functional abilities. Many such approaches incorporate “metacognitive training” using cognitive domain-specific compensatory

techniques and evidence-based remediation techniques (where available) in order to develop strategies to improve performance and generalization of skills to daily tasks. Such metacognitive approaches can include training in cognitive strategy use, self-monitoring, self-regulation, and therapist feedback (Cicerone *et al*, 2011). Systematic reviews and meta-analyses have suggested that the evidence for the efficacy of such interventions is sufficiently strong to rise to the level of a practice guideline for treatment of cognitive deficits after TBI, and that inclusion of metacognitive training strategies is likely to be more effective than direct attention training alone (Cicerone *et al*, 2011).

Pharmacotherapy of cognitive complaints and deficits generally targets major neurotransmitter systems modulating the function of brain regions underlying the relevant cognitive process (e.g., attention, working or episodic memory). Both human and animal studies suggest that the neural circuitry and neurochemistry of different components of memory and attention overlap significantly, and involve broad networks of brain regions including bilateral prefrontal and parietal cortices, cingulate gyrus, basal ganglia, hippocampus and related mesial temporal structures, and regions of the brain stem and midbrain forming the reticular activating system (Arciniegas *et al*, 2013). Cerebral catecholamines, as well as catecholaminergic-acetylcholinergic interactions, modulate the function of several of these large-scale distributed networks, which subservise attention, episodic and working memory, and executive control of these cognitive functions, and in which the dorsolateral and inferolateral prefrontal cortices are critical nodes (Arciniegas, 2013).

Methylphenidate (MPH) augments cerebral dopaminergic and adrenergic systems. Evidence suggests that MPH improves performance on measures of attention, memory, verbal fluency, processing speed, motor performance, and arousal, and is also associated with improvements in subjective (self or informant) assessment of cognitive functioning (Gualtieri and Evans, 1988; Johansson *et al*, 2015; Kaelin *et al*, 1996; McAllister *et al*, 2015; Plenger *et al*, 1996; Whyte *et al*, 1997; Whyte *et al*, 2004; Whyte *et al*, 2002; Willmott and Ponsford, 2009). Indeed, the Defense and Veterans Brain Injury Center's Neurobehavioral Guidelines Working Group evidence-based review of pharmacotherapies for post-traumatic cognitive impairments recommended MPH at the Guideline level for attention and processing speed impairments, and at the Option level for general cognitive deficits and memory impairments (Warden *et al*, 2006). More recent meta-analyses also concluded that the evidence supports MPH as a treatment for attention impairments, including working memory impairments, after TBI (Huang *et al*, 2016; Wheaton *et al*, 2011). MPH therefore appears to be a promising agent for remediation of persistent cognitive deficits after TBI.

The available literature suggests that domain-specific evidence-based cognitive rehabilitation and symptom-targeted pharmacotherapy can improve cognitive problems after TBI. Preliminary reports suggest that pharmacologic facilitation of brain injury rehabilitation may improve cognitive outcomes (Berthier *et al*, 2009; Bragoni *et al*, 2000); however, few studies examine the efficacy of pharmacologically facilitated cognitive rehabilitation, and none have focused specifically on this approach to the treatment of cognitive impairments in the late period following TBI. This study implemented a double-blind, placebo-controlled trial of the effectiveness of two forms of cognitive rehabilitation (remediation and compensatory training)

and MPH, alone and in combination, to treat cognitive symptoms after TBI. We hypothesized a synergistic effect, such that participants receiving MPH and a compensatory training intervention would show greater improvement than those receiving other treatment combinations. Based on the available literature, we focused on outcome measures testing attention-related functions, including working memory and processing speed. As downstream effects of improved attention can also result in better performance in other cognitive domains, we also examined episodic memory and executive function.

Patients and Methods

Design and Participants

Overview: This double-blind, placebo-controlled, 2x2 factorial design tested the efficacy of pharmacotherapy, cognitive rehabilitation, and combination therapies for persistent cognitive symptoms and/or deficits after TBI in a six-week trial (ClinicalTrials.gov Identifier NCT00453921). Participants gave written informed consent approved by the Institutional Review Boards of Dartmouth-Hitchcock Medical Center, Indiana University School of Medicine, and University of Colorado School of Medicine.

Inclusion criteria: (1) age 18-65 at study entry (2) TBI of at least mild severity (Kay *et al*, 1993) at least 4 months prior to study entry; and (3) self-report of cognitive deficits as a result of the injury of sufficient severity to interfere with social and/or occupational functioning as measured by a score at least one standard deviation above the normative mean on the Multiple Abilities Self-Report Questionnaire (MASQ) (Ahles *et al*, 2008; Seidenberg *et al*, 1994), and/or objective evidence of cognitive deficits represented by either (a) score two or more standard deviations below age-adjusted normative data or estimates of premorbid function (Barona *et al*, 1984) on one or more tests of attention and/or memory, or (b) score one or more standard deviations below either age-adjusted normative data or estimates of premorbid function on two or more tests of attention and/or memory administered as part of the screening cognitive battery.

Exclusion criteria: (1) history of other neurologic or systemic medical disorder that was unstable, likely to need repeated medication adjustments, or likely to affect cognitive function or be a contraindication to use of MPH; (2) current DSM-IV (APA, 2000) Axis I diagnosis of psychiatric illness, other than mild-moderate depression or anxiety, screened for using the Mini-International Neuropsychiatric Interview (M.I.N.I. English Version 6.0.0, modified based on the version for ADHD studies) (Sheehan *et al*, 1998), Beck Depression Inventory-II (Beck *et al*, 1996), State-Trait Anxiety Inventory (Spielberger, 1983), and PTSD Checklist-Stressor Specific (PCL-S) (Weathers *et al*, 1993); (3) currently pregnant or lactating; (4) pre-injury diagnosis of learning disability or attention-deficit/hyperactivity disorder (ADHD); (5) lack of English fluency sufficient to complete study measures; or (6) standard score below 70 on the Wide Range Achievement Test-4 Word Reading subtest (Wilkinson and Robertson, 2006), to ensure reading ability sufficient to participate in cognitive rehabilitation.

Study Protocol: Eligible participants underwent a pre-treatment baseline assessment, then were randomized to receive MPH or placebo and one of two cognitive rehabilitation interventions, a metacognitive intervention, *Memory and Attention Adaptation Training* (MAAT, designed by R.J.F.), or *Attention Builders Training* (ABT), a manualized repetitive practice intervention with no active cognitive-behavioral component. This resulted in four treatment combinations: MAAT/MPH, ABT/MPH, MAAT/placebo, and ABT/placebo. Phone contacts (weeks 1, 3, and 5) assessed for side effects and monitored compliance. At in-person study visits (weeks 2 and 4) participants also engaged in their assigned therapy (MAAT or ABT). After six weeks of treatment, participants completed post-treatment outcome measures (see **Supplemental Figure 1** for study flow).

Cognitive Assessment: The test battery emphasized cognitive domains most commonly reported as impaired after TBI, including memory, attention-related and executive functions, and processing speed, and included measures of general cognitive ability for sample characterization. Cognitive eligibility screening included the California Verbal Learning Test-II (Delis *et al*, 2000), Delis-Kaplan Executive Function System (Delis *et al*, 2001) Trail Making, Verbal Fluency, and Color-Word Interference subtests, Paced Auditory Serial Addition Test (Gronwall, 1977), Wechsler Adult Intelligence Scale-III (The Psychological Corporation, 1997) Letter Number-Sequencing Test, and Gordon Diagnostic System Continuous Performance Test (Gordon *et al*, 1996). Assessments at the pre-treatment visit included the Vocabulary and Block Design subtests of the Wechsler Abbreviated Scale of Intelligence (The Psychological Corporation, 1999), Wechsler Adult Intelligence Scale-III Digit Symbol-Coding and Digit Span subtests, Delis-Kaplan Executive Function System Sorting Test, Craft Story Memory Test (Craft *et al*, 1996), Brown Location Test (Brown *et al*, 2007), Grooved Pegboard Test (Lafayette Instrument, 1989), Finger Tapping Test (Reitan and Wolfson, 1993), and Thumb-Finger Sequencing Test (Saykin *et al*, 1995). The complete neuropsychological battery and the MASQ were repeated at post-treatment, with alternate test forms used where possible.

Interventions

Memory and Attention Adaptation Training (MAAT): MAAT is a brief cognitive-behavioral therapy aimed at enhancing skills for self-managing and coping with cognitive failures in daily life. Initially developed for use in patients experiencing postconcussive symptoms (Ferguson and

Mittenberg, 1996), MAAT was later adapted for treatment of cognitive symptoms after breast cancer chemotherapy, where preliminary data showed good feasibility and acceptability and beneficial treatment outcomes (Ferguson *et al*, 2007; Ferguson *et al*, 2012). The version of MAAT used in this study consisted of four biweekly 50-minute individual office visits focused on cognitive-behavioral strategy use. Briefer telephone contacts between visits were intended to reinforce use of new behaviors or modify the strategy to enhance effectiveness.

MAAT includes four cognitive-behavioral components: (1) Education regarding “normal” cognitive failures, as well as potential effects of TBI on cognitive function; (2) self-awareness training to identify “at-risk” situations where cognitive failures are likely to occur; (3) self-regulation training emphasizing applied relaxation techniques and stress management; and (4) cognitive compensatory strategy training. Each participant received a MAAT workbook with detailed descriptions of compensatory strategies, educational material, and guides on how to apply compensatory strategies. Clinicians followed a detailed manual to enhance treatment fidelity. R.J.F. trained and supervised therapists in conducting the MAAT treatment protocol, reviewed recordings of treatment visits, and provided corrective feedback as necessary.

Attention Builders Training (ABT): ABT was modeled after Berg, Koning-Haanstra, and Deelman (Berg *et al*, 1991). Participants were provided information about cognitive remediation techniques related to the use of repetitive cognitive tasks to build skills through “mental exercise” (Tate, 1997), akin to the direct attention training approaches discussed above. Visit timing and duration were identical for ABT and MAAT. ABT also included an educational component discussing common cognitive symptoms after TBI, but did not emphasize behavioral

compensatory and functional reorganization strategies, nor was instruction provided on how to implement the exercises in daily living situations.

At the initial therapy visit, participants were given an ABT manual and a packet consisting of a variety of tasks, which were carefully explained and practiced to ensure understanding. A repetitive practice regimen was assigned. Tasks were not tailored to the participant's cognitive complaints/deficits, there was no "coaching" on the tasks, and no compensatory strategy training was provided. On subsequent visits the home-practice regimen was reviewed, refresher drills and practice sessions were performed, and new assignments were given. Phone contacts entailed evaluation of the home practice regimen by the therapist and empathetic listening without any instructions.

Methylphenidate: Participants weighing <100 kg received MPH 0.1 mg/kg of body weight twice daily (BID) for 2-4 days, then 0.2 mg/kg BID for 2-4 days (default choice for both intervals was two days; study physicians could extend the titration interval to four days at their discretion), then 0.3 mg/kg BID for the remainder of the study. Doses were rounded to the nearest 2.5 mg increment. Those weighing \geq 100 kg received doses of 10 mg BID, then 15 mg BID, then 30 mg BID for the same intervals. Therefore, dosing did not exceed 60 mg/day total. For an average 70 kg adult, this translates into about 20 mg BID. This target dose was based on studies demonstrating efficacy in improving cognitive function in TBI populations (Plenger *et al*, 1996; Whyte *et al*, 1997; Whyte *et al*, 2002). Participants with modest side effects who wished to continue in the protocol were allowed dose reduction at physician discretion, but needed to be able to tolerate a dose of at least 10mg/day to remain in the study.

Placebo: Placebo was provided in capsules indistinguishable from the MPH capsules in taste and appearance, with BID dosing and similar titration increases (i.e., an increase in number of capsules of placebo).

Randomization and Masking: Group assignment occurred through block randomization. Group allocation was concealed. Therapists were blind to outcome data, and staff conducting outcome assessments were blind to participant randomization. Medications were prepared and distributed by site-specific pharmacies which maintained the allocation code and ensured blinding of study medications.

Adverse events and treatment compliance were monitored via phone contacts and at in-person visits, and by inventorying study capsules at in-person visits.

Statistical Analysis: Demographic and clinical covariates were assessed for group differences using ANOVA or chi-square tests as appropriate. Primary outcome variables included measures of episodic memory (California Verbal Learning Test-II initial encoding over trials 1-5 number correct: *CVLT*), attention (Continuous Performance Test Distractibility trial reaction time: *CPT_RT*), divided attention and working memory (Paced Auditory Serial Addition Test Trial 3 (1.6" pacing) number correct: *PASAT*), processing speed (Wechsler Adult Intelligence Scale-III Digit Symbol-Coding number correct: *DSC*; Delis-Kaplan Executive Function System Trail Making Test, trial 2 completion time: *DTR2*), and self-reported cognitive function (MASQ total score: *MASQ*). Secondary outcome measures included additional measures of episodic memory

(Craft Stories immediate recall total score: *CRAFT*; Brown Location Test initial encoding over trials 1-5 number correct: *BLT*), and executive function (D-KEFS Sorting Test free sorting description total score: *SORT*).

All analyses were conducted using the R statistical software package (v3.1.2), as follows. Main effects of MAAT, MPH, and their interaction were examined via nonparametric Kruskal-Wallis test for changes between baseline and post-treatment measurements. Linear regression models were fit for post-treatment scores for each outcome variable for the primary factors of interest, cognitive rehabilitation (MAAT vs. ABT) and pharmacotherapy (MPH vs. placebo), together with their interaction, adjusting for baseline performance, study site, days since injury (log transformed), and treatment adherence (percent of prescribed doses taken). Post-treatment scores adjusted for covariates are referred to as “predicted” scores. For each treatment combination the estimated means were obtained at the average value of the adjustment variables. It was hypothesized that the MAAT/MPH group would show greater cognitive improvement than the other groups. A p-value <0.05 was considered to indicate statistical significance. Standardized (adjusted) coefficients and effect sizes (unadjusted) are reported. Standardized coefficients are estimated from the regression model used to predict post-treatment scores. To create comparable adjusted coefficients among outcome variables, both outcome and adjustment variables are standardized to have the mean equal to zero and standard deviation equal to one. Effect sizes (Cohen’s d) are estimated by the ratio of the difference between the post-treatment and baseline scores for each treatment combination and the pooled standard error estimate of the differences.

Results

101 individuals consented to participate and were screened for eligibility; 76 were randomized to the four treatment arms (see CONSORT flow diagram (**Figure 1**)). One participant who completed the study was subsequently diagnosed with a confounding medical condition, and so was excluded from all analyses. Demographics and injury severity by treatment group are shown in **Table 1**. Time since injury for the 75 participants included ranged from five months to 35 years. Forty-nine participants (65%) were eligible for the study based on both subjective and objective symptom entry criteria. Thirteen participants (17%) were eligible based on objective cognitive deficits, but did not have subjective cognitive complaints based on the MASQ threshold, and 13 participants (17%) were eligible based on MASQ score, but did not have objective cognitive deficits per the entry thresholds. Entry eligibility criteria met did not significantly differ by treatment group ($p=0.44$).

Treatment groups did not significantly differ for age, education, race, ethnicity, handedness, sex, time since injury, or injury severity (all $p>0.05$). Four participants (one from each study arm) enrolled in the study and began treatment but chose not complete the trial, and so were not included in outcome analyses. This resulted in a final sample of 71 participants for analysis: MAAT/MPH (N=17), ABT/MPH (N=19), MAAT/placebo (N=17), and ABT/placebo (N=18). Medication adherence and pre-treatment cognitive performance data are presented in **Supplemental Table 1**. Subjective and objective cognitive performance showed no significant differences between groups pre-treatment (all $p>0.05$), though the ABT/MPH group showed somewhat lower PASAT performance than the other groups ($p=0.09$).

Medication adherence and mean total daily dose of study medication did not differ significantly between treatment groups (both $p>0.05$). Vital signs, including blood pressure and heart rate, were checked at in-person visits and compared to pre-treatment measurements, and no clinically meaningful changes were noted. The two most common side effects, reported in $>25\%$ of the overall sample, were headache (47.1%) and insomnia (27.9%); frequency did not differ between patients receiving placebo and MPH (both $p>0.05$). Four symptoms were significantly more common in patients receiving MPH: nervousness, appetite loss, palpitations (all $p<0.05$), and abdominal discomfort ($p<0.01$). Side effects led to dose reduction for nine participants (including one who received placebo); dose reduction was significantly more common in patients receiving MPH ($p<0.05$). No participant withdrew from the study due to adverse events, and no serious adverse events were reported.

As described under Statistical Analysis above, outcome variables were examined post-treatment for each treatment condition relative to the other three conditions, adjusting for pre-treatment performance, study site, time since injury, and treatment adherence. Predicted scores for all outcome variables are shown in **Table 2**, and between-group treatment-related comparison data are presented in **Table 3**. Raw scores for post-treatment cognitive performance can be found in **Supplemental Table 2**. For the primary outcome variables, at post-treatment the MAAT/Placebo group showed significantly higher CVLT performance relative to the ABT/Placebo group ($p=0.040$, **Figure 2a**). For PASAT, the MAAT/MPH group showed significantly higher performance than the ABT/MPH group ($p=0.021$, **Figure 2b**). For the secondary outcome variables, the MAAT/MPH group showed significantly higher BLT performance (**Figure 2c**) than both the MAAT/placebo ($p=0.021$) and ABT/MPH ($p=0.030$)

groups. No significant differences were seen for CRAFT, CPT_RT, DSC, DTR2, MASQ, or SORT.

In addition to these significant results, moderate to large effect sizes (**Table 3**) were noted for some primary and secondary outcome variables where statistical tests demonstrated p values which did not rise to the a priori threshold of $p < 0.05$. Tests yielding $p < 0.10$ were examined to determine those additional measures which might have risen to statistical significance with a larger sample size. For the primary outcome variables, the MAAT/Placebo group showed higher CVLT performance (**Figure 2a**) relative to the ABT/MPH ($p=0.063$) and MAAT/MPH ($p=0.070$) groups. For the secondary outcome variables, the MAAT/MPH group showed higher performance than the ABT/placebo group on BLT ($p=0.078$, **Figure 2c**) and CRAFT ($p=0.055$, **Figure 2d**).

Discussion

Persistent cognitive changes are among the most problematic symptoms after TBI, with potential negative effects on quality of life across multiple domains. Consistent with findings from prior studies, the current results suggest that cognitive rehabilitation (MAAT) and pharmacotherapy (MPH) may improve cognitive performance in individuals with chronic cognitive impairments and/or complaints after TBI. To our knowledge, this is the first study to examine the utility of cognitive rehabilitation and pharmacotherapy in combination; our results suggest that combining pharmacotherapy and cognitive rehabilitation treatments may achieve greater improvement in cognitive functioning after TBI than either treatment alone.

For two of the outcomes examined (PASAT and BLT), patients who received a compensatory training intervention and MPH (the MAAT/MPH group) showed significantly stronger performance than other treatment groups, demonstrating a benefit for combined treatment in terms of performance on objective measures of learning, working memory, and divided attention. This finding is particularly important given that these domains are among those most commonly affected after TBI. On a measure of verbal learning (CVLT), the MAAT/placebo group showed significantly stronger performance than the ABT/placebo group. This finding offers evidence that a metacognitive (compensatory training) cognitive rehabilitation intervention is more beneficial for verbal encoding deficits than is a repetitive practice (remediation) treatment approach.

The present observations also suggest a possible synergistic effect of catecholaminergic augmentation and a metacognitive rehabilitation approach. Westbrook and Braver (Westbrook and Braver, 2016) summarize the role of dopamine in multiple aspects of cognition, including motivation, learning, working memory, and decision-making, and propose that dopamine's role in regulating working memory has direct relevance for cognitive effort, due to involvement of the dopamine system in incentive (reward) processing. MPH works directly on the dopaminergic system by inhibiting dopamine reuptake. The metacognitive approach of MAAT emphasizes improving behavioral aspects of executive functioning. As metacognition is sensitive to dopaminergic modulation (Joensuu *et al*, 2015), and metacognitive tasks also increase prefrontal dopamine (Westbrook *et al*, 2016), this may explain the relatively greater improvements seen in patients receiving both MPH and MAAT relative to metacognitive rehabilitation without MPH or repetitive practice treatment (i.e., ABT) with MPH.

Among the strengths of the study are its design, the representativeness of the sample of individuals with persistent post-traumatic cognitive impairments residing in the community, and demonstration of treatment feasibility and acceptability. This double-blind, placebo-controlled study incorporated comparison conditions for both its pharmacotherapeutic (i.e., methylphenidate vs. placebo) and cognitive rehabilitation (i.e., MAAT vs. ABT) components. Our data suggest that the active cognitive-behavioral component of MAAT was more effective in generating gains in cognition than the repetitive practice approach of ABT, although the concurrent administration of placebo with both limits inferences that can be drawn about the relative intrinsic efficacies of these very different approaches to cognitive rehabilitation.

Participants were representative of individuals with TBI residing in three geographically distinct areas of the country (Northern New England, Midwest, Rocky Mountain Region). Inclusion criteria were relatively broad, and potential participants were only excluded for conditions likely to confound outcome measures or to present a potential safety risk. In addition, while the majority (59%) of participants experienced mild or complicated mild TBI, generally consistent with the preponderance of mild TBI in terms of overall incidence of injury severity, the study sample included good representation of moderate (11%) and severe (31%) injury as well. These factors increase the generalizability of the findings.

We also demonstrated acceptable tolerability, safety, and treatment adherence (>90% on average, as noted above), with minimal attrition (5%) over the course of the trial. This suggests that the types of pharmacologically facilitated cognitive rehabilitation employed in this study are sufficiently acceptable to those with persistent post-traumatic cognitive impairments to merit further study in larger-scale efficacy and effectiveness trials.

The principal limitation of the study is the small sample size. As has been noted in related literature, despite the need for interventional studies to address cognitive problems after TBI, recruitment for this and similar studies is extremely challenging (McAllister *et al*, 2015). The initial target for this study was to recruit 50 patients into each treatment group, for a total of 200 participants. As reflected in the CONSORT diagram (**Figure 1**), 101 individuals were screened in person for this study. That number represents only about 10% of the total pool of individuals screened, the majority of whom were found to be ineligible after an initial phone screen. Of those who completed in-person screening, some otherwise eligible individuals were unwilling to

consider taking MPH, or unable to make the commitment required to participate in cognitive therapy.

In the context of small sample size, the population heterogeneity mentioned above as a strength with regard to representativeness could also be considered a weakness in terms of factors which may influence effectiveness of treatment, such as injury severity, injury to treatment interval, and other such metrics. The sample also had very limited racial/ethnic diversity. We therefore are unable to comment on whether there are subgroups for whom individual treatments may be more effective than others, and whether or not duration of time since injury significantly impacts on improvement after intervention.

Challenges in identifying and recruiting participants to treatment trials are unfortunately common in the field, making it extremely difficult to conduct definitive, appropriately powered trials to determine the efficacy of a given intervention. This study was initially designed as a single-center trial, but was expanded to be a multicenter study given the recruitment challenges. This was an early phase study with a targeted directional hypothesis, and we wanted to discover possible sensitive candidate outcomes. Therefore, no adjustments were made for multiple comparisons, and differences with an associated p value <0.05 were considered statistically significant. Additional studies replicating the present findings are needed, and such studies will likely also need to be multicenter trials in order to accrue sufficient numbers of participants. However, the presence of significant results and medium to large effect sizes in the current modest sample showing positive effects of combined cognitive rehabilitation and pharmacotherapy treatment for cognitive changes after TBI is highly encouraging, and suggests

that additional findings may have risen to statistical significance had the study been powered as initially intended.

In summary, we demonstrated that combined treatment with a manualized cognitive rehabilitation approach and MPH resulted in modest but statistically significant improvements in cognitive functioning on measures of verbal and nonverbal learning, working memory, and divided attention in adults with persistent cognitive symptoms after TBI. While additional research is needed to replicate these promising initial findings, the current results provide support for multimodality treatment approaches to improve cognitive functioning even months to years after TBI.

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Figure Legends

Figure 1. CONSORT diagram of study subject flow. CONSORT flow diagram showing disposition of patients assessed for study eligibility. ABT=Attention Builders Training; MAAT=Memory and Attention Adaptation Training; MPH=methylphenidate

Figure 2. Treatment group comparisons. Outcome variables showing between-group differences from pre- to post-treatment for: 2a) CVLT, 2b) PASAT, 2c) BLT, and 2d) CRAFT. Predicted Post-Treatment Scores are post-treatment performance adjusted for pre-treatment performance, study site, time since injury, and treatment adherence. CVLT=California Verbal Learning Test-II; PASAT=Paced Auditory Serial Addition Test; BLT=Brown Location Test; ABT=Attention Builders Training; MAAT=Memory and Attention Adaptation Training; MPH=methylphenidate

Supplemental Figure 1. Outline of participant flow through study visits, from screening procedures to assess eligibility through active treatment. ABT=Attention Builders Training; EKG=electrocardiogram; MAAT=Memory and Attention Adaptation Training; MPH=methylphenidate

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Table 1. Demographic and Injury Characteristics

	MAAT/MPH Mean (SD) or N (%)	ABT/MPH Mean (SD) or N (%)	MAAT/Placebo Mean (SD) or N (%)	ABT/Placebo Mean (SD) or N (%)	p
Number Enrolled	18	20	18	19	
Age	43.1 (12.3)	43.0 (15.0)	37.2 (12.0)	37.3 (14.2)	0.33
Education (years)	15.1 (2.4)	15.4 (2.4)	14.7 (2.1)	14.1 (2.1)	0.30
Years Post Injury	9.0 (8.5)	7.6 (10.3)	5.4 (7.5)	8.2 (10.1)	0.68
Race					0.52
American Indian/ Alaska Native	0 (0%)	0 (0%)	1 (5.6%)	0 (0%)	
African American	1 (5.6%)	1 (5.0%)	0 (0%)	0 (0%)	
White	17 (94.4%)	19 (95.0%)	17 (94.4%)	19 (100%)	
Not Hispanic or Latino	17 (94.4%)	20 (100%)	18 (100%)	18 (94.7%)	0.55
Right-handed	17 (94.4%)	15 (75.0%)	16 (88.9%)	18 (94.7%)	0.19
Male	8 (44.4%)	14 (70.0%)	14 (77.8%)	13 (68.4%)	0.17
TBI severity					0.42
Mild	9 (50.0%)	10 (50.0%)	10 (55.6%)	7 (36.8%)	
Complicated Mild	4 (22.2%)	2 (10.0%)	1 (5.6%)	1 (5.3%)	
Moderate	2 (11.1%)	3 (15.0%)	2 (11.1%)	1 (5.3%)	
Severe	3 (16.7%)	5 (25.0%)	5 (27.8%)	10 (52.6%)	

p values are from ANOVA or chi-square tests as appropriate

Table 2. Predicted Post-Treatment Cognitive Performance Scores

	MAAT/MPH	ABT/MPH	MAAT/Placebo	ABT/Placebo
Sample Size (N)	17	19	17	18
CVLT-II Total Score Trials 1-5	51.8 (2.1)	51.9 (1.9)	57.2 (2.0)	51.3 (1.9)
CPT Distractibility Trial Reaction Time (msec)	394.7 (17.3) ^a	416.6 (15.9) ^a	413.0 (17.3) ^a	426.4 (15.3)
PASAT 1.6" Pacing Number Correct	40.2 (1.4) ^c	35.7 (1.2) ^a	37.6 (1.3) ^b	38.6 (1.2) ^b
WAIS-III Digit Symbol- Coding Raw Score	71.7 (2.5)	73.5 (2.4)	71.2 (2.5)	75.7 (2.4)
D-KEFS Trail Making Number Sequencing Trial Time (sec)	33.4 (2.3)	30.8 (2.2)	32.5 (2.3)	30.5 (2.2)
MASQ Total Score	120.5 (4.8)	114.1 (4.5)	118.1 (4.8)	116.4 (4.5)
Craft Stories Immediate Recall Total Score	51.4 (2.1)	48.6 (2.1) ^b	48.7 (2.2) ^a	45.4 (2.1) ^a
BLT Total Score Trials 1-5	41.1 (2.1)	34.9 (1.9)	34.3 (2.0)	36.0 (1.9)
D-KEFS Sorting Test Free Sorting Description Score	38.2 (2.1)	40.0 (2.0) ^a	37.9 (2.2) ^a	38.7 (2.0) ^a

Values are Predicted Score (SE). CVLT-II=California Verbal Learning Test-II; CPT=Gordon Diagnostic System Continuous Performance Test; PASAT=Paced Auditory Serial Addition Test; WAIS-III=Wechsler Adult Intelligence Scale-III; D-KEFS=Delis-Kaplan Executive Function System; MASQ=Multiple Abilities Self-Report Questionnaire; BLT=Brown Location Test

^a Data were missing for 1 participant

^b Data were missing for 2 participants

^c Data were missing for 3 participants

Table 3. Between-Group Treatment-Related Comparison Data

	Adjusted R²	p	Standardized Coefficient	Cohen's d Effect Size
CVLT	0.548			
MAAT/Placebo-ABT/Placebo		0.040	0.491	0.792
MAAT/Placebo-ABT/MPH		0.063	0.439	0.752
MAAT/Placebo-MAAT/MPH		0.070	0.449	0.828
PASAT	0.814			
MAAT/MPH-ABT/MPH		0.021	0.392	0.301
CRAFT	0.496			
MAAT/MPH-ABT/Placebo		0.055	0.511	0.789
BLT	0.517			
MAAT/MPH-ABT/Placebo		0.078	0.447	0.719
MAAT/MPH-MAAT/Placebo		0.021	0.603	0.745
MAAT/MPH-ABT/MPH		0.030	0.550	0.680

Figure 1. CONSORT diagram of subject study flow

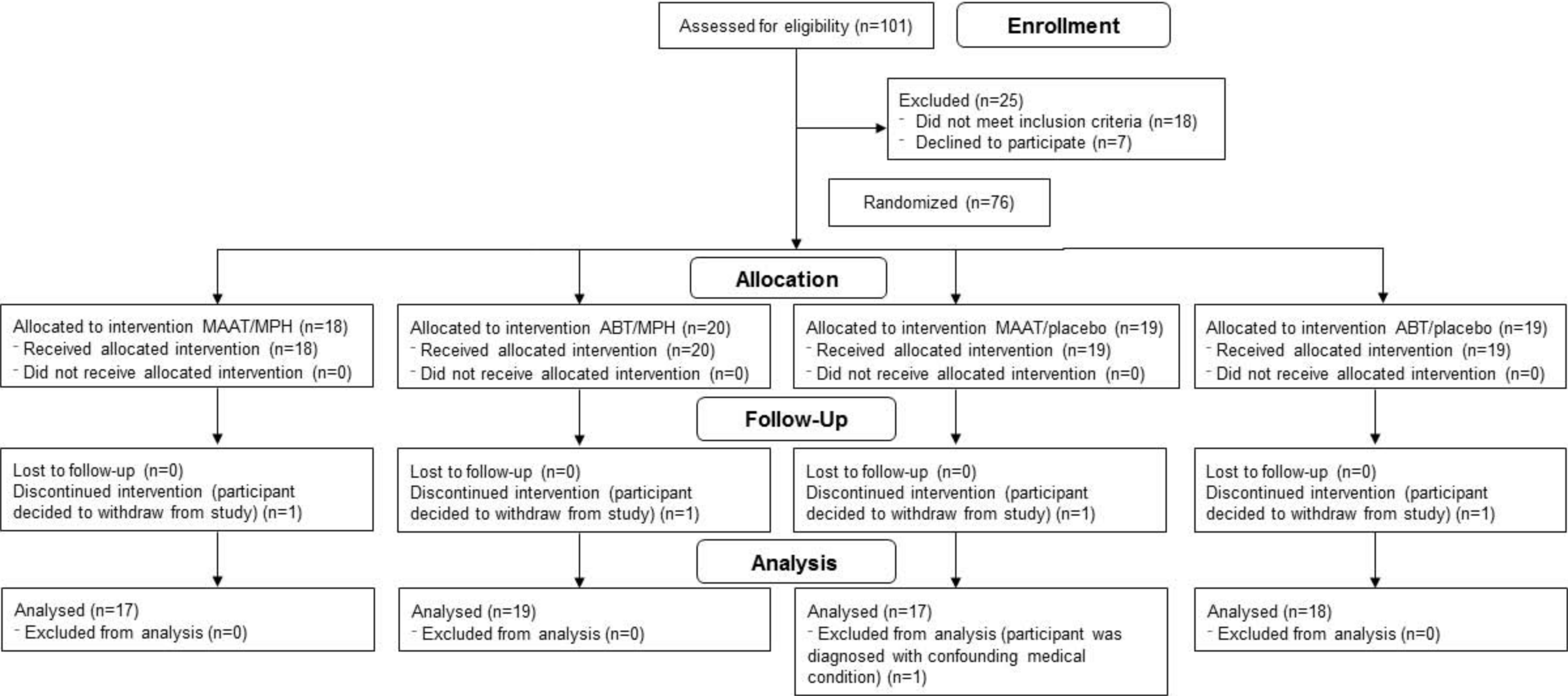


Figure 2. Treatment Group Comparisons

