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A preliminary study of the effects of working memory training on brain function in Attention-Deficit/Hyperactivity Disorder

Michael C. Stevens^{1,2}, Alexandra Gaynor¹, Katie L. Bessette¹, and Godfrey D. Pearlson^{1,2}

¹Olin Neuropsychiatry Research Center, The Institute of Living, Hartford, CT, USA

²Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Abstract

Working memory (WM) training improves WM ability in Attention-Deficit/Hyperactivity Disorder (ADHD), but its efficacy for non-cognitive ADHD impairments ADHD has been sharply debated. The purpose of this preliminary study was to characterize WM training-related changes in ADHD brain function and see if they were linked to clinical improvement. We examined 18 adolescents diagnosed with DSM-IV Combined-subtype ADHD before and after 25 sessions of WM training using a frequently employed approach (CogmedTM) using a nonverbal Sternberg WM fMRI task, neuropsychological tests, and participant- and parent-reports of ADHD symptom severity and associated functional impairment. Whole brain SPM8 analyses identified ADHD activation deficits compared to 18 non-ADHD control participants, then tested whether impaired ADHD frontoparietal brain activation would increase following WM training. *Post hoc* tests examined the relationships between neural changes and neurocognitive or clinical improvements. As predicted, WM training increased WM performance, ADHD clinical functioning, and WM-related ADHD brain activity in several frontal, parietal and temporal lobe regions. Increased left inferior frontal sulcus region activity was seen in all Encoding, Maintenance, and Retrieval Sternberg task phases. ADHD symptom severity improvements were most often positively correlated with activation gains in brain regions known to be engaged for WM-related executive processing; improvement of different symptom types had different neural correlates. The responsiveness of both amodal WM frontoparietal circuits and executive process-specific WM brain regions was altered by WM training. The latter might represent a promising, relatively unexplored treatment target for researchers seeking to optimize clinical response in ongoing ADHD WM training development efforts.

Keywords

ADHD; working memory; training; fMRI; brain

Corresponding Author: Michael C. Stevens, Ph.D., 200 Retreat Avenue, Whitehall Building, The Institute of Living/Hartford Hospital, Hartford, CT 06106, (860) 545-7552 (Office), (860) 545-7797 (Fax).

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Introduction

Working memory (WM) deficits are among the most prominent (Kasper et al., 2012; Martinussen et al., 2005; Willcutt et al., 2005) of the many cognitive impairments often found in patients diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) (Frazier et al., 2004; Willcutt et al., 2012). Although WM engages a complex, multi-component, dynamic set of cognitive processes, a useful and effective consensus definition describes WM as active maintenance and flexible updating of goal- or task-relevant information in a form that has limited capacity and resists interference (Baddeley, 1992; RDoC Workgroup, 2010). Poor WM task performance is correlated with symptoms of ADHD inattention (Burgess et al., 2010; Kofler et al., 2010), hyperactivity (Rapport et al., 2009), impulsivity (Raiker et al., 2012) and “real world” ADHD-like behaviors, including multi-tasking (Buhner et al., 2006; Hambrick et al., 2010), mind wandering (Kane et al., 2007), following directions (Engle et al., 1991; Gathercole et al., 2008), as well as indicators of ADHD-related functional deficits such as social problems (Kofler et al., 2011) and educational achievement (Burgess et al., 2010; Rapport et al., 2008; Rapport et al., 2009). This raises the possibility that treatments which improve WM might consequently improve ADHD behaviors.

Because first-line recommended ADHD treatments like stimulant medications (Pliszka, 2007) have inconsistent effects on WM (Bedard et al., 2007; Epstein et al., 2006; Kobel et al., 2009; Pietrzak et al., 2006; Rapport et al., 2013; Rhodes et al., 2006) – typically normalizing neither WM task performance deficits (Biederman et al., 2008; Everett et al., 1991; Gualtieri and Johnson, 2008; Kobel et al., 2009; Risser and Bowers, 1993) nor WM-related brain dysfunction (Kobel et al., 2009; Prehn-Kristensen et al., 2011; Rubia et al., 2014) (but see Cubillo et al., 2014) – the efficacy of other approaches to improve WM have been increasingly explored. WM training is a facilitative intervention (Rapport et al., 2013) that uses intensive repetition of exercises with consistently high WM demands (Morrison and Chein, 2011; Rapport et al., 2013) with an expectation that training alters the brain’s capacity to effectively represent or manipulate information. The most frequently studied WM training regimens involve 4–5 weeks of near daily, computerized WM training sessions that last 30–40 minutes. Using several different types of WM tasks in each session is a strategy believed to enhance a general WM capacity (Backman and Nyberg, 2013; Buschkuhl et al., 2012; Klingberg, 2010, 2012; Morrison and Chein, 2011; Qi and Constantinidis, 2013; Rutledge et al., 2012). This strategy is typical of WM training approaches, and has been the most frequently studied in ADHD (e.g., CogMed™).

Both qualitative (Chacko et al., 2014; Evans et al., 2013; Morrison and Chein, 2011; Rutledge et al., 2012; Shipstead et al., 2012a; Shipstead et al., 2012b; Toplak et al., 2008) and meta-analytic (Hodgson et al., 2014; Melby-Lervag and Hulme, 2013; Rapport et al., 2013; Sonuga-Barke et al., 2013) reviews find that WM training reliably enhances WM performance on trained and closely-related WM tasks for children, adolescents, and adults with different presentations/subtypes of ADHD. For instance, for Cogmed specifically 13 peer-reviewed clinical trials (including 8 randomized clinical trials) found ADHD patients’ WM ability improves after training (Beck et al., 2010; Chacko et al., 2013; Dahlin, 2013; Egeland et al., 2013; Gibson et al., 2011; Gray et al., 2012; Green et al., 2012; Gropper et

al., 2014; Holmes et al., 2010; Hovik et al., 2013; Klingberg et al., 2005; Klingberg et al., 2002; Mezzacappa and Buckner, 2010) and gains persist 2–8 months later (Gropper et al., 2014; Holmes et al., 2010; Hovik et al., 2013) (see also meta-analysis Melby-Lervag and Hulme, 2013). However, the evidence that WM training is effective in reducing ADHD symptom severity or associated clinical dysfunction is mixed. Among published studies measuring ADHD clinical function, 7 studies found improved parent-, teacher-, or self-rated ADHD severity (Beck et al., 2010; Gibson et al., 2011; Gropper et al., 2014; Klingberg et al., 2005; Mezzacappa and Buckner, 2010) or objectively-measured ADHD-like behavior (e.g., actigraph-measured motor restlessness or classroom time-on-task (Green et al., 2012; Klingberg et al., 2005), with evidence that gains persisted months (Beck et al., 2010; Klingberg et al., 2005). Two studies found Cogmed improved academic skills, which also lasted at least 7–8 months (Dahlin, 2013; Egeland et al., 2013). In contrast, some studies had no clinical improvements despite WM gains (Egeland et al., 2013; Gray et al., 2012), and two found ADHD symptom reductions did not surpass that seen with treatment-as-usual or active placebo (Chacko et al., 2013; Green et al., 2012). Several reviews of these trials have criticized the reliance on subjective reports of improvements (particularly in “open” trials without placebo-control). Indeed, the most recent meta-analysis of 6 WM training RCTs failed to find any changes in ratings of ADHD symptom severity (Cortese et al., 2015). Other criticisms that reduce confidence in WM training efficacy for ADHD clinical severity include the inconsistency of specific ADHD dysfunction-related gains across studies and methodological limitations such as failing to take into account psychiatric comorbidity, medication status, practice effects, of pre-training WM ability differences (Evans et al., 2013; Gathercole et al., 2012; Klingberg, 2010; Melby-Lervag and Hulme, 2013; Morrison and Chein, 2011; Rabipour and Raz, 2012; Redick et al., 2013; Shah et al., 2012; Shipstead et al., 2012b; Sonuga-Barke et al., 2013; Takeuchi et al., 2010; Toplak et al., 2008). At best, empirical support for using WM training in ADHD is currently mixed, with sometimes sharp disagreement on the basic question of whether this treatment approach reduces ADHD-associated clinical impairments outside the domain of WM. As a result, an emerging opinion in the field is that WM training ultimately might not be considered a “front-line” treatment for ADHD (Cortese et al., 2015).

Another way to inform the question of whether or not WM training could be effective for ADHD would be to show that any ADHD clinical improvements are linked to WM-induced changes in ADHD brain function during WM task performance. In non-ADHD samples, WM training has been found in several studies to alter brain structure and function, including grey and white matter volume, dopaminergic function, brain activation, and functional connectivity (see review (Buschkuehl et al., 2012). However, specific results differ across studies and WM training techniques. As yet, no single specific, common neurobiological “mechanism” has been identified to explain how WM gains are made (Buschkuehl et al., 2012; Takeuchi et al., 2010), in part likely due to the complexity of WM cognitive processes and their neural correlates. Moreover, neural changes are likely to vary according to disorder-specific pathophysiology in ways that have not yet been clearly characterized. Although some effort has been made to study brain changes following intensive cognitive training in ADHD (e.g., Hoekzema et al., 2011; Hoekzema et al., 2010), the effects of WM training has not yet been examined. Therefore, the neurobiological basis

of WM improvements in ADHD following WM training is not understood, despite the NIMH's recent programmatic emphasis on understanding the neurobiological basis of clinical change to help develop effective new treatments.

There is a need for studies that describe how WM training alters brain function in ADHD-diagnosed patients. This preliminary study sought to characterize for the first time how ADHD brain function is affected by a commonly-used WM training approach that targets WM capacity (Cogmed; Pearson, 2014) and to determine if such changes were associated with clinical improvements. fMRI meta-analyses describe a core frontoparietal WM neural circuit that is engaged across different types of WM tasks regardless of specific cognitive demands (Owen et al., 2005; Rottschy et al., 2012; Wager and Smith, 2003). We first compared ADHD to non-ADHD controls to localize any brain function deficits. Consistent with previous non-ADHD fMRI studies (Hempel et al., 2004; Jolles et al., 2010; Olesen et al., 2004), we predicted WM training would increase and possibly normalize ADHD WM task-related activation in some or most of these WM circuit regions, particularly left caudal superior frontal sulcus (SFS) and left inferior frontal sulcus (SFS) regions which most consistently show hypofunction in ADHD fMRI studies of short term WM storage (Fassbender et al., 2011; Hale et al., 2007; Prehn-Kristensen et al., 2011; Sheridan et al., 2007; Vance et al., 2007; Wolf et al., 2009) or WM updating (i.e., N-back tasks) (Bayerl et al., 2010; Cubillo et al., 2014; Ko et al., 2013; Kobel et al., 2009; Malisza et al., 2012; Massat et al., 2012; Passarotti et al., 2010; Valera et al., 2005). We also asked whether WM training preferentially altered ADHD brain function engaged during encoding, maintenance, or retrieval of information from WM and examined training effects on WM task difficulty. After identifying WM training effects, we conducted *post hoc* analyses to test the prediction that these neural changes would be associated with improvements in ADHD non-cognitive symptom severity or other, basic clinical characteristics, e.g., age, gender, use of psychostimulant medications.

Material and Methods

Participants

ADHD participants were recruited via community advertisements. Study procedures were explained to potential participants and at least one parent during an informed consent/assent protocol approved by Hartford Hospital's Institutional Review Board. Participants received monetary compensation for completing study procedures. Thirty-seven ADHD youth were consented, but 6 changed their minds after consent, and 13 were excluded: 5 did not meet diagnostic criteria; 1 had a positive drug urine toxicology result; 1 felt uncomfortable in the MRI; 1 had an MRI-detected brain cyst; and 5 were noncompliant with WM training. The final ADHD sample included 18 adolescents (6 females) ages 12–18. A comparison sample of 18 non-ADHD adolescents was recruited for comparison. This group did not statistically differ from the ADHD sample on sex, age, parental education/SES, WASI-measured IQ, reading level, or reported depression/anxiety-related complaints (Table 1).

Psychiatric diagnoses were evaluated using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) following its recommended interview format of both parent and child (Kaufman et al.,

1997), administered by experienced staff under the supervision of a licensed psychologist with over 14 years KSADS-PL clinical research experience. Diagnostic interview information was supplemented with both parent- and child-report ADHD symptom and dysfunction rating scales (see “Clinical Outcome Measures” below). None of the non-ADHD participants met criteria for any Axis I diagnoses. All ADHD participants met DSM-IV criteria for ADHD-Combined Hyperactive/Impulsive and Inattentive subtype (314.01). Their psychiatric comorbidities included: 1 with comorbid Oppositional Defiant Disorder (ODD) and 1 with both ODD and Conduct Disorder. Several participants met past criteria for other disorders that were in remission: 1 Generalized Anxiety Disorder, 1 Dysthymic Disorder, 1 Major Depressive Episode, and 1 Adjustment Disorder with Depressed Mood.

Thirteen of 18 ADHD participants were being prescribed short half-life “psychostimulant” medications: 6 sustained-release methylphenidate and 7 amphetamine-based drugs (5 amphetamine mixed salts, 2 lisdexamfetamine dimesylate). Non-ADHD medications did not preclude participation, as no prescriptions changed during the WM training trial, and participants served as their own controls. Of the medicated participants, 2 also took citalopram, 1 paroxetine, 1 clonidine, and 1 lamotrigine. The medication status for one participant was not reported.

Trial Design

This was an “open label” WM training trial (www.clinicaltrials.gov NCT02151396) using a commercially-available, computer-based program (Cogmed; Pearson, Inc.). Although a blinded, placebo-control study would have permitted stronger inferences about efficacy, the primary study goal was to determine whether any changes in WM brain function following WM training could be linked to neurocognitive and/or clinical improvement. As such, we used the same design as in most previous clinical trials, simply to ensure the WM training was rigorous and could be directly compared to published reports. ADHD participants completed 25 training sessions at home under parental supervision and weekly “coaching” phone calls by study staff to troubleshoot problems and provide motivational encouragement (Pearson, 2014). Performance data was uploaded regularly via internet so the training coach could closely track progress and identify treatment noncompliance. All WM training was completed within 5–6 continuous weeks by all participants. As per the standard Cogmed training approach, individual training item difficulty was adaptively adjusted on a trial-by-trial basis to continually challenge WM capacity throughout all trials. An assessment using fMRI, neuropsychological tests, and parent-/self-reports of ADHD clinical severity (Table 2) was done within 1 week before and within 2 weeks following WM training. Any participants who took psychostimulants underwent a 24-hour medication washout the day prior to these assessments to ensure medications did not influence brain function or cognitive performance during either fMRI/cognitive evaluation. Non-ADHD participants did not undergo WM training or re-assessment.

Clinical Outcome Measures

WM training progress was measured using Cogmed’s standard approach to calculating a Training Index, defined as the difference between final and initial training scores. The initial score was each patient’s average performance on two Cogmed exercises practiced during

days 2 and 3. The final score was the average of the best two trials throughout training. Although best performance theoretically could occur sporadically and not reflect true gains by treatment endpoint, inspection of patient performance levels throughout treatment showed steadily progressive gains and best task performance at end of training for all participants. Transfer of WM gains to non-trained WM tasks was evaluated using WM subtests of the Wechsler Intelligence Scale for Children (4th edition). Conner's Continuous Performance Test (2nd Edition; CPT-II) assessed whether WM training produced gains in non-WM cognitive domains. These tests were selected for both their proven construct validity as well as their frequent use in ADHD clinical evaluation and research. Because WM ability is multidimensional and the exact nature of ADHD WM deficits is a subject of ongoing research, it was not possible to predict in advance if any WM sub-factors might be found in the out-of-scanner WM neuropsychological measures examined. Therefore, exploratory principal component analysis (PCA) with Varimax rotation reduced WISC-IV WM treatment-related change scores to explore how training gains on possibly more easily interpretable aspects of WM related to patients' baseline characteristics.

ADHD symptom severity was evaluated before and after WM training using parent-reported DSM-IV symptoms rated on a 0–3 scale (Barkley and Murphy, 1998). Parent- and Adolescent self-report versions of Brown ADD Scales (Brown, 2001) measured ADHD-associated behavioral problems. The ADHD Home Situations Questionnaire (Barkley and Murphy, 1998) measured ADHD-related functional impairment, asking parents to rate on a 1–9 scale how ADHD symptoms disrupt 16 typical home situations (e.g., meal time or completing chores). Training effects were evaluated using paired *t* test on post- and pre-training scores. Across the entire sample, there were between 2–6 missing values for each ADHD symptom severity, Brown Parent ADD Scale, Brown Adolescent ADD Scale, and Home Situations scores due to failure for parents/participants to complete either pre- or post-training questionnaires. Little's MCAR test ($\chi^2(73)=71.244$, *ns*) showed these datapoints were missing randomly. Moreover, bivariate Pearson correlation analysis failed to find any meaningful relationship between missing vs. present status of any datapoint and other measures' change scores (i.e., only 1 of 33 possible associations was significant at $p=.037$; not sufficient to survive multiple comparisons correction).

fMRI Task

Stimuli for the nonverbal Sternberg WM fMRI task comprised either 2, 4, or 6 circles in a 4×4 grid which were briefly presented, followed by a cue to actively maintain the locations in WM, then a probe requiring a Yes/No response if it was in one of the locations held in WM (50% of probes were valid). Figure 1 shows a trial layout. Each span was given 6 times during two 7:50 minute sessions, for a total of 36 total trials. Pseudorandom jitter was inserted between trial onsets (5–8 sec) and the three trial periods (3–5 sec) so fMRI modeling could differentiate brain activity change during Encoding, Maintenance, and Retrieval information processing phases.

Imaging parameters

Imaging was done on a Siemens Allegra 3T system at the Olin Neuropsychiatry Research Center of the Institute of Living/Hartford Hospital in Hartford, CT. Functional image

volumes were collected in axial orientation to the anterior commissure-posterior commissure line using a gradient-echo sequence sensitive to the blood-oxygen-level-dependent (BOLD) signal (TR=1,500 msec, TE=28 msec, flip angle=65°, FOV=24×24 cm, 64×64 matrix, 3.4×3.4 mm in plane resolution, 5 mm slice thickness, 30 slices). Each session acquired 308 volumes. The first 6 volumes where T1 effects stabilized were discarded.

Image processing

Functional images were reconstructed offline and each run was separately realigned using INRIAlign (Freire and Mangin, 2001) and slice-timing corrected via interpolation as implemented in Statistical Parametric Mapping (SPM8). All participants had head motion <1 voxel length in any x,y,z plane. A mean functional image volume was constructed from the realigned image volumes for each session, used to determine parameters for spatial normalization into standardized Montreal Neurological Institute space. Normalized images were smoothed with an 8 mm³ full-width-at-half-maximum Gaussian filter.

fMRI Statistics

Brain activation was estimated using individual participant SPM8 GLM models. For ADHD, all 4 fMRI timeseries (2 pre-training, 2 post-training) were included in a single GLM for each participant. Regressors for each condition/session were derived by extracting stimulus onset timing for Encoding, Maintenance, and Retrieval stimuli and were convolved with a synthetic hemodynamic response function and its temporal derivative. Parametric interaction terms for each task phase identifying the 2, 4, or 6 stimulus conditions quantified greater or lesser brain function according to WM load. Six motion-correction parameter estimates (x, y, and z displacement and roll, pitch, and yaw rotations) were included as covariates-of-no-interest to isolate minor head motion BOLD signal variance. A high-pass filter (128 sec cutoff) removed low-frequency signals. GLM contrast coding produced maps quantifying overall activation, parametric effects of WM difficulty, and differences in activation between post- and pre-training for these effects, separately for Encoding, Maintenance, and Retrieval conditions. Simple activation to each condition was identified using SPM8 one-sample *t* tests, while non-ADHD vs ADHD differences were evaluated using SPM8 two-sample *t* tests on activation maps. ADHD treatment effects were evaluated using one-sample *t* tests on the difference maps constructed via contrast coding across the pre- and post-treatment fMRI sessions. For all group-level tests, “whole brain” statistical significance was evaluated using Monte Carlo simulation ($p < .01$ entry threshold, $p < .05$ clusterwise significance).

Supplemental *Post Hoc* Analyses

In order to determine if ADHD brain dysfunction was still detectable following WM training, we used an ROI analysis. 5 mm spheres centered on the peak xyz coordinate where pre-training ADHD differed from non-ADHD were interrogated using SPM small volume-corrected (SVC) analyses ($p < .05$ FWE SVC). Other *post hoc* analyses included SPM8 correlation to examine the association of condition main effect and parametric activity change maps with the Training Index scores and parent-reported ADHD symptom severity. First, we tested whether any voxels within 5 mm of peak training effects were correlated ($p < .05$ uncorrected), then examined the whole brain using Monte Carlo multiple comparisons corrections. Because the main effects of task activation to Encoding,

Maintenance and Retrieval were not part of the hypothesis-testing but are relevant for fully understanding how the task engaged WM-related brain activity, we included these activation maps for the entire sample in Supplemental Material. Figure S1 shows Sternberg activation to Encoding, Maintenance, and Retrieval conditions. Figure S2 depicts the parametric effect of WM load on activation in each condition.

Results

Neuropsychological Training Effects

ADHD participants' initial working memory Training scores varied from 67 to 102, indicating some participants had marked impairment, while others had near-typical Cogmed trial performance at training start. This was paralleled by non-trained WM test performance, where most patients (12 of 18) had at least a 1 SD weakness (i.e., scaled-score of 7 or less) on one or more WISC-IV WM subtests before WM training. Table 2 shows that ADHD participants' Cogmed training scores significantly improved after WM training. Relative to normative training scores in youth ages 7–17 (mean start/max scores = 73/100, SD=13; (Pearson, 2014), all ADHD participants improved at least 1 normative SD in WM trial difficulty (range 1–5 SDs, mean 2.3). *Post hoc* Pearson correlation showed the magnitude of WM training gains were unrelated to baseline Training score, participant age, or use of psychostimulants during the trial. Although ADHD girls on average achieved a slightly higher Training score by trial endpoint ($t=2.43$, $p=.027$), intra-individual improvement was not significantly greater than that seen in males.

ADHD performance on all non-trained WM tests significantly improved (Table 2). PCA on these change scores identified two factors with eigenvalues >1.0 , accounting for 67% of the variance. Factor loadings $>.400$ (Table S1 in Supplemental Material) reflected two factors: Factor 1 depicted improvements on tests requiring executive manipulation of WM contents (e.g., Letter-Number Sequencing and Spatial Span Backwards), and Factor 2 showed training-related changes in simple storage WM tests (e.g., Digit Span Forwards and Spatial Span Forwards). Gains in simple WM storage (PCA-derived Factor 2) were inversely correlated with BDI-II and MASC-scores ($r=-.506$, $p=0.077$ and $r=-.698$, $p=.003$, respectively), suggesting mild mood and anxiety problems constrained these WM gains.

None of the CPT-II indices showed any significant changes with WM training.

Clinical Training Effects

Table 2 also shows that ADHD patients improved on most subjective reports of ADHD symptom severity, ADHD-related problems, and severity of functional impairment at home. Because the handful of missing clinical datapoints was random, these analyses were re-run after replacing missing values with each variable's mean to ensure information from cases with only a single missing value were utilized in outcome evaluation. Findings were unchanged, except that significant group difference p values were even lower (ranged from $p=.003$ to $.00001$), likely due to the increased statistical power. Closer inspection of individual change scores showed a range of clinical responsiveness, with a few patients showing no ADHD symptom severity change or in one case even modestly worse parent-

reported symptoms, a larger handful showing modest improvement, and at least half the sample showing marked symptom improvement. Additional *post hoc* correlations showed clinical changes were unrelated to age or gender. Participants not taking psychostimulants showed significantly greater parent-rated symptom improvement ($t=2.91$, $p=.014$; mean/SD 31.3/10.7 vs 10.7/11.5).

The difference in Cogmed Training scores before and after training strongly predicted parent-reported ADHD symptom severity reductions (Inattentive symptoms $r = -.913$, $p=0.000035$; Hyperactive/Impulsive symptoms $r = -.795$, $p=.003$).

ADHD Deficits in WM-Related Brain Activation

Table 3 lists differences between ADHD and non-ADHD control participants; Figure 2 depicts ADHD activation deficits across the whole brain ($p<.05$ clusterwise corrected). Significantly lower ADHD activation was found for Maintenance and Retrieval conditions in numerous lateral prefrontal cortex and parietal lobe regions, including in areas within inferior frontal sulcus. No ADHD frontoparietal deficits were found for Encoding, but exploratory analysis at uncorrected statistical thresholds noted left ($x,y,z = -39, 17, 22$; $t=2.39$) and right ($x,y,z = 27, 47, 22$; $t=2.10$) middle frontal gyri activation deficits in ADHD. There also were regions in each condition where ADHD participants had greater activation than non-ADHD. During Encoding these were found in ventrolateral prefrontal/insular cortex, posterior parietal, putamen and cerebellum. During Maintenance, only insula, right parahippocampal gyrus/amygdala, and a large area of primary visual cortex were greater in ADHD. For information Retrieval, ADHD participants engaged several ventrolateral/ventromedial prefrontal, posterior parietal and cerebellar regions more than non-ADHD.

WM Training Effects on WM-Related Brain Activation

Brain regions with significantly altered activation after WM training are shown in Figure 3 and listed in Table 4. Changes were almost exclusively activation increases. Normal task-elicited activity increased in IFS, caudal SFS, and medial PFC during Encoding and Maintenance. Training effects were predominantly, though not entirely, seen in the left hemisphere. In particular, Maintenance activation was greater after WM training in homologous right PFC structures not engaged in these ADHD participants by this task (refer to Figure S1 for visual comparison). Left IFS regions (i.e., middle/inferior frontal gyri) showed greater activity regardless of Sternberg task phase, although WM training effects were localized to BA 45 for Encoding and Maintenance, but had a slightly more dorsal peak (i.e., including some aspects of BA 9/46) for Retrieval. In the parietal lobe, WM training-related increases were localized to different regions in each hemisphere. Both parietal and posterior temporal lobe changes were only observed during Encoding of stimuli into WM, and comparison to activation main effects (Figure S1) indicates they also represented recruitment of brain regions not normally engaged for task completion. *Post hoc* ROI analyses examined whether any of these changes normalized ADHD activation abnormalities listed in Table 3. Although there was evidence that some of the occipital lobe ADHD hypoactivation during Encoding changed, in general none of these deficits or ADHD over-activation in frontal, parietal, basal ganglia or cerebellar over-activation resolved. These

Encoding differences either still significantly differed, or were detectable as “trend” levels of difference. In contrast, the majority of ADHD activation abnormalities during Maintenance and many during Retrieval Sternberg task phases were non-significantly different from non-ADHD following WM training.

Figure 4 and Table 5 report altered parametric effects of WM task difficulty on brain activation after training. The most notable effect was lesser recruitment of several dlPFC and vlPFC regions at greater WM loads during Maintenance. Visual comparison to parametric main effects (Figure S2) localizes most of these effects to activated regions (note, in right vlPFC, change was found at $p < .01$ that did not survive clusterwise corrections). Midline superior/medial frontal gyri activation was the only parametric WM load effect showing greater activity in a region that did not show a main or parametric effect for Maintenance in this sample.

All fMRI analyses were repeated using either age, gender, or both age and gender together as covariates-of-no-interest. Results remained essentially unchanged.

Relationship of Brain Function Changes to Clinical Improvements

Post hoc analyses examined the relationship of neural change to various cognitive and clinical changes. Table 4 shows that several of the specific peak prefrontal and parietal WM training effects also correlated with WM or clinical gains at trend significance levels or better.

Figure 5 and Table 6 list other brain regions from supplemental analyses where the activation changes following WM training were correlated at a “whole brain” significance threshold with Cogmed Training change score. Greater Maintenance-elicited activity with greater WM change was seen in right IFS and left mid-lateral PFC.

Figures 6 and 7 and Table 7 report other regions where training-related changes to brain activity correlated with parent-rated ADHD-Inattentive or ADHD-Hyperactive/Impulsive symptom improvements. Different brain region change were linked to improvement of symptom severity in each symptom domain. Neural change in caudal SFS (bilateral middle frontal gyrus; BA 6) and cingulate/medial frontal gyri during Maintenance were the only associations found for both Inattentive and Hyperactivity symptom change.

Several additional *post hoc* analyses of potential interest were included as Supplemental Material. Table S3 lists brain regions where training-related changes in the brain’s response to task difficulty (i.e., parametric effect of WM load) correlated with improvement in the Cogmed Training change score. Table S3 lists regions where training-related change to Encoding, Maintenance, and Retrieval correlated with the PCA-derived Factor 1 (executive WM) or Factor 2 (short term WM storage).

Discussion

The dual purposes of this preliminary study were to characterize WM brain function change after 5 weeks of WM training in ADHD for the first time, and to determine if brain changes were associated with any clinical improvements. ADHD WM training was generally

successful and cognitive gains were WM-specific. Gains did not occur for sustained attention, response inhibition or response speed. WM training resulted in greater ADHD activation in several WM-linked frontoparietal brain regions, with the magnitude of neural change in posterior brain regions predicting degree of WM gains. Many of these changes coincided closely with frontoparietal activation deficits localized by comparison to non-ADHD controls, and which were consistent with previous ADHD fMRI WM studies. Indeed, ROI analysis showed many of the ADHD brain activation abnormalities detected before WM training were no longer significantly different after treatment, particularly during Sternberg task Maintenance and many prefrontal regions engaged for Retrieval. This suggests that WM training is normalizing some aspects of ADHD WM-related brain dysfunction. However, it is important to note that many effect sizes of ADHD vs. non-ADHD differences remained meaningful, despite the lack of statistical significance. So it would be misleading to conclude full brain function normalization occurs following a standard course of WM training. Despite some evidence for specificity of brain function benefit, neural changes were seen throughout fMRI task phases in numerous regions, consistent with the assumption that core WM training approaches have a broad, generalized effect (Morrison and Chein, 2011). Importantly, *post hoc* analyses showed that clinically-meaningful improvement ADHD clinical functioning not only was linked to WM training gains, but also, as hypothesized was linked to neurobiological change in WM-linked brain regions when ADHD-diagnosed participants engaged in WM processing. Interestingly, the training-induced activation increases seen in SMA, cingulate, and parietal lobe regions across all task phases were correlated with improvement in ADHD Inattentive symptoms, while Hyperactive/Impulsive symptom reduction was associated with greater activity in premotor/motor, cerebellar, cingulo-opercular, and caudate regions. The latter finding is consistent with proposals that transfer of WM training benefits to other functions might require intact basal ganglia function (Dahlin et al., 2009; Dahlin et al., 2008). It is possible that individual ADHD patient differences in striatal dysfunction might explain inconsistent clinical improvement in previous ADHD WM training clinical trials (Beck et al., 2010; Chacko et al., 2013; Dahlin, 2013; Egeland et al., 2013; Gibson et al., 2011; Gray et al., 2012; Green et al., 2012; Gropper et al., 2014; Klingberg et al., 2005; Mezzacappa and Buckner, 2010). The lack of corrections for multiple comparisons on these *post hoc* analyses should be taken into account when evaluating the relevance of these latter findings.

ADHD brain activation changes in this study did not coincide with those found in the one previous fMRI study of ADHD after cognitive training, but this is unsurprising as that study trained neither WM nor evaluated ADHD brain function using a WM task (Hoekzema et al., 2010). The greater activation of ADHD middle/inferior frontal gyri and superior/inferior parietal lobe regions – two well-described WM network regions (Owen et al., 2005; Rottschy et al., 2012; Wager and Smith, 2003) – after WM training overlap with brain function change findings in previous non-ADHD WM training fMRI studies (Hempel et al., 2004; Jolles et al., 2010; Olesen et al., 2004). We also found that WM training increased ADHD activation in other frontoparietal regions linked to WM, particularly left IFS and bilateral IPS regions. This supports the idea that continual, intensive practice of WM tasks in ADHD potentiates activation within a broader network of WM task-specialized brain regions than previously observed in non-ADHD. This observation is tempered by the

recognition that most previous ADHD WM fMRI studies employed N-back or simple storage retrieval tasks, not specifically the Sternberg paradigm. Specifically, WM training increased activation in IFS and caudal SFS prefrontal regions that were impaired for ADHD at pre-treatment, suggesting WM training at least partially normalizes some neural deficits. Also, although temporal lobe, angular gyrus, and other TPO junction regions were not normally engaged by ADHD patients while performing this WM task, they were among the only regions both to increase activation following WM training and to correlate with Cogmed task performance. This raises the possibility that in ADHD, WM performance gains might also involve some form of neural compensation. The angular gyrus is a heteromodal information processing hub that supports attention reorientation, semantic concept retrieval, and mental information manipulation (Seghier, 2013), and is directly connected with both dlPFC and vlPFC via superior longitudinal fasciculi (Frey et al., 2008; Makris et al., 2005). The posterior aspects of middle temporal gyrus also are believed to contribute semantic knowledge relevant to current goal-directed behavior (Jefferies, 2013). Therefore, WM training might not simply remediate ADHD neural deficits, but also improve local processing in other brain regions to overcome ADHD neurobiological abnormalities.

Interestingly, WM training effects appear categorically different from published descriptions of ADHD psychostimulant medication effects. Although there is some evidence that drugs like methylphenidate improve WM in ADHD (Mehta et al., 2004), its behavioral effects are minimal or inconsistent at best, mirroring the results of fMRI studies of how such medications alter ADHD WM-related brain dysfunction (Rubia et al., 2014). In pediatric ADHD, methylphenidate generally increases right inferior frontal cortex, insula, superior temporal lobe and putamen activation (Rubia et al., 2014; Schweren et al., 2013). Previous WM fMRI comparisons of medicated and non-medicated ADHD have had mixed results, variably finding PFC decreases (Sheridan et al., 2007), no differences (Kobel et al., 2009; Rubia et al., 2014), effects in some but not all WM contexts (Cubillo et al., 2014; Prehn-Kristensen et al., 2011), or WM-related functional connectivity effects only (Wong and Stevens, 2012). In contrast, WM training clearly targeted ADHD bilateral dlPFC and bilateral parietal cortex in different functional contexts, reflecting alteration to the responsiveness of domain-general, sensory amodal components of the WM circuit (Shallice, 1994, 2004; Stuss, 2006; Stuss and Alexander, 2000) and to posterior temporal lobe regions. Such differences between treatment approaches might be because neural changes induced through WM training are hypothesized to involve microstructural synaptic connectivity alterations induced by neuroplastic mechanisms (Willis and Schaie, 2009), instead of the short-term, neurotransmitter availability-dependent alterations to cellular function seen with medications. Only left mid-lateral PFC (BA 9/46) consistently showed increased activation during encoding, maintenance and retrieval, suggesting it might be a key focus of putatively neuroplastic WM training effects in ADHD. This IFS region not only is robustly engaged for WM (Owen et al., 2005; Rottschy et al., 2012; Wager and Smith, 2003), but also hypofunctional in ADHD across different tasks (Cortese et al., 2012). It is involved in configuring information processing in response to changing task demands, integrating external and internal information, and flexibility in adjusting ongoing cognition or behavior. This brain region also was one of the few affected by WM task difficulty. As seen in Supplemental Figure S2, a greater parametric effect of WM load was found before WM

training, which could indicate either reduced need to engage this region at higher loads after training (e.g., greater “efficiency” (Haier et al., 1992; Neubauer and Fink, 2009), or consistently greater activation after training, regardless of task demands.

Although we found clear evidence that WM training was linked to improved ADHD clinical and cognitive functioning in the majority of patients in our sample, we note our findings were somewhat more positive, and cognitive gains more specific to WM than seen in many previous non-fMRI clinical trials of the Cogmed WM training approach. It is possible that clinical outcome was related to expectancy effects, which are especially problematic in open-label, WM training trials when placebo control is not used. It also is possible that outcome was better because our sample was more clinically homogenous than previous studies (all Combined-subtype ADHD, post-pubertal development, minimal comorbid psychiatric symptoms, most with pre-existing WM weaknesses). Alternatively, outcome might reflect greater motivation typical in those who participate in an MRI study, or another uncontrolled sampling characteristic. Several factors argue against (but cannot eliminate without a randomized trial) the idea that the generally positive outcome was due to expectancy effects. First, neuropsychological and brain function changes are objectively measured, and as such, far less likely than subjective symptom severity ratings to be the result of patients’ or their parents’ wishful thinking about treatment success. WM training had a demonstrable effect on both. Second, WM training-related brain function changes did not occur in regions identified by an emerging literature on placebo and expectancy effects (Beauregard, 2009; Wager et al., 2011). Third, clinical and cognitive outcome was generally consistent with prior WM training trials, in that WM performance improved on both trained and untrained tasks, transfer of gains to other cognitive domains typically was limited, and patients showed a range of overall clinical responsiveness (i.e., not everyone improved). Fourth, specific brain function changes following WM training that were linked to symptom reduction were found in many regions that already have been linked to ADHD symptom severity in previous fMRI WM reports (Passarotti et al., 2010; Valera et al., 2005). Finally, many WM training-induced changes occurred in regions that were impaired relative to non-ADHD prior to training, particularly in prefrontal cortex. The latter is taken as evidence that WM training helps to normalize some aspects of abnormal ADHD brain function. It is important to emphasize that this study was not conducted as another test of Cogmed WM training efficacy in ADHD, but rather to show that non-cognitive improvement –when it does occur – is related to the degree of neurobiological improvements in WM brain function. That said, we emphasize the importance of conducting a future randomized-clinical trial to re-examine the questions we ask in this study. We not only need to replicate our preliminary findings, but also provide the strongest possible evidence that they are not due to uncontrolled sampling factors, varying participant expectancies, or other such hazards to experimental inference in the absence of placebo control. Mitigating the study limitations, the sample’s psychiatric comorbidity was reasonably well-controlled, its ADHD sampling clinical homogeneity lowers the likelihood that ADHD clinical or putative etiological diversity obscured meaningful findings, and factors such as minor mood/anxiety symptoms, age, or gender were found to be unrelated to fMRI-measured neural change. Medication status did seem to curtail parent-rated ADHD symptom change scores, but this also could

reflect that unmedicated patients had greater room for improvement. Medication status was unrelated to brain activity change.

This initial study leaves several interesting clinical and neuroscientific questions unaddressed. For this reason, it should be viewed as only an initial step in this line of research. It will be important to determine whether ADHD brain changes following WM training predict long-term maintenance of clinical gains. Future studies also should attempt to better describe which brain regions and what precise types of neural activity changes are associated with optimal ADHD symptom reductions by studying larger samples, using different types of WM fMRI paradigms. Given the suspected heterogenous nature of ADHD pathophysiology (Castellanos and Proal, 2012; Cortese et al., 2012; Makris et al., 2009), it also is important to learn if pre-training profiles of ADHD brain dysfunction could predict whether a patient is more or less likely to benefit from treatment. We have taken one step towards this goal by finding that ADHD adolescent cognitive, clinical, and neurobiological outcomes after Cogmed WM training were unrelated to patient age or gender. This suggests inquiry should turn to finding whether neurobiological factors dictate treatment success. However, there might exist other clinical features that predict WM training outcome (e.g., types or severities of WM deficits) that could be easily assessed by paper-and-pencil measures in the clinical setting.

It has been proposed that WM training exercises could be re-developed to more optimally target the brain systems known to be specifically impaired in ADHD, or the various circuits engaged for WM. Although Cogmed exercises do not focus on improving executive WM, we observed that ADHD patients nonetheless showed increased activation after WM training in brain regions known to contribute to executive control, such as bilateral caudal SFS. Indeed, caudal SFS was the only region to show increased engagement in all three Sternberg task conditions, suggesting it had the most generalized contribution to WM improvements. Caudal SFS underlies diverse WM executive demands, including distractor resistance, susceptibility to interference, updating WM, and shifting attention among elements within WM (Nee et al., 2013). During Sternberg retrieval, brain activity changes also were seen in ventral attention network regions, linked to other putatively “executive” WM processing, such as selection of information for WM recall (Badre and Wagner, 2005), resolving proactive interference (Jonides and Nee, 2006), and selective attention. One of the few activation decreases after training was found during Encoding in midline pre-SMA (medial/superior frontal gyri) – a region linked to filtering external distraction during WM stimulus encoding (Nee et al., 2013). The involvement of so many executive WM-linked regions in Cogmed WM training, despite its theoretical focus on simple storage capacity, raises the possibility that directly training executive aspects of WM might produce greater or more consistent clinical effects in ADHD. Moreover, numerous executive WM brain regions were linked with transfer of WM training benefits to the clinical symptom domain. Just as some studies (Gibson et al., 2014; Gibson et al., 2012; Gibson et al., 2013) have criticized WM training for only targeting short-term storage and not “secondary memory” (e.g., a cue-based controlled/strategic search of medial temporal lobe long-term memory stores (Chein et al., 2011) to access information displaced from primary WM) important to dual-process WM theories (Unsworth and Engle, 2007a, b), our results suggest that executive WM processes might also be good targets for WM training. Interestingly, our PCA analyses of WM test

performance found that ADHD gains in “executive” WM were not related to anxiety or mood symptoms, thus possibly representing a clearer pathway towards WM ability improvement. Although several studies have attempted to train different types of executive functions in both ADHD and non-ADHD with some encouraging initial success^{171, 172}, none so far has specifically focused on exercises designed to train the executive aspects of WM (Nee et al., 2013). To guide future model building and neuroimaging research for WM training development, the supplemental material further details which brain regions were specifically associated with the PCA-derived “executive” WM change scores.

Conclusions

This study takes a meaningful step towards understanding the basis of WM training in ADHD. WM gains and non-cognitive clinical improvement are linked to ADHD brain activity augmentation in regions showing activation deficits and possible compensation-like neurobiological changes. The study sets the stage for future research to more conclusively determine whether clinical improvement not only is directly mediated through WM neural circuit change, but also if improved WM ability is the proximate cause of reduced clinical impairment. Alternatively, WM training might exert its effects on clinical functioning via changes in non-WM systems that might contribute to WM processing, but in actuality improve ADHD symptoms and disorder-related functional impairment in a coincidental fashion. While this might seem a minor, subtle distinction, it actually goes to the heart of WM training efficacy – Are clinical gains the product of having better WM itself, or does WM training somehow provide a means to alter dysfunctional neural systems more directly linked to disorder expression? The current findings also point towards the potential value in training specific executive aspects of WM processes as a likely avenue forward for optimizing outcome or achieving a mechanistic understanding of the neural basis of WM training effects in ADHD. The identification of specific neural correlates of ADHD clinical benefits help to validate WM training as a viable treatment approach, and exemplifies the potential utility of future clinical trials that integrate fMRI measurement as an informative clinical trial outcome measure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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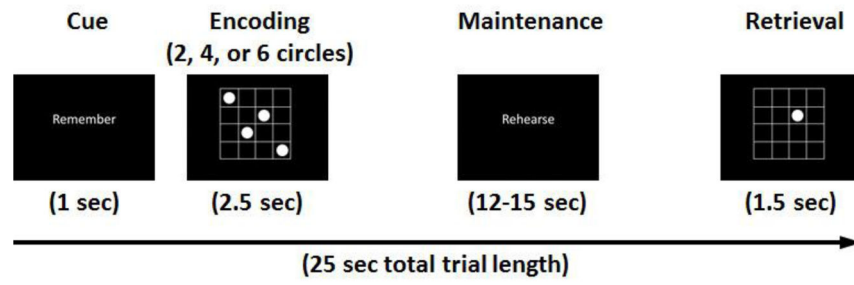


Figure 1.
Layout of a Sternberg working memory fMRI task trial.

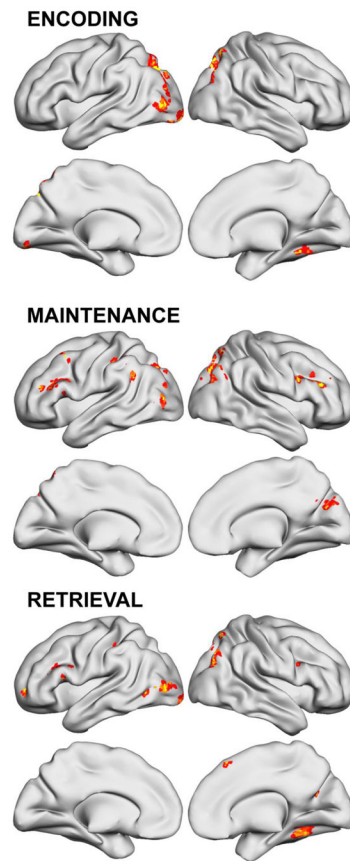


Figure 2. ADHD working memory brain activation deficits before working memory training compared to non-ADHD control participants ($p < .05$ clusterwise significance threshold).

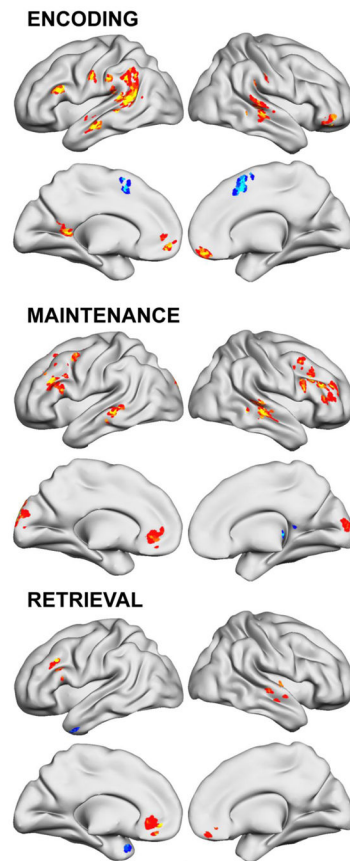


Figure 3. Working memory brain activation changes after 5 weeks of working memory training ($p < .05$ clusterwise significance threshold).

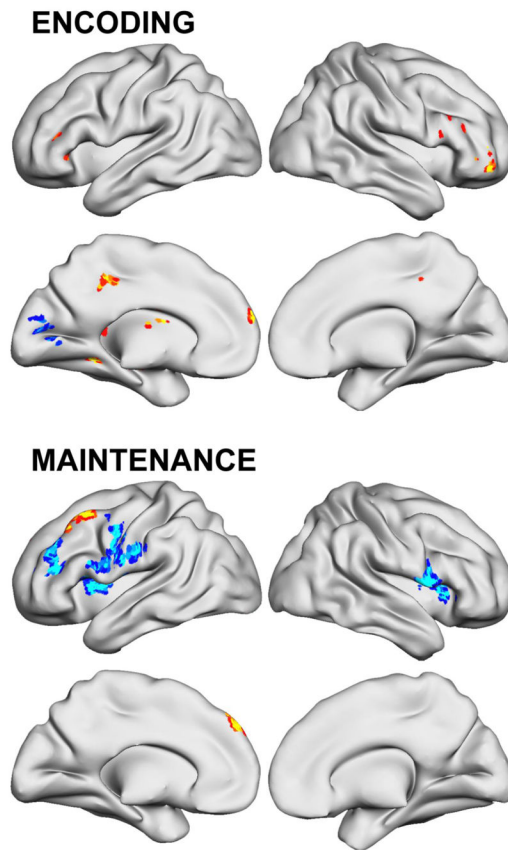


Figure 4. Changes to the parametric effect of working memory load on brain activation after 5 weeks of working memory training ($p < .05$ clusterwise significance threshold).

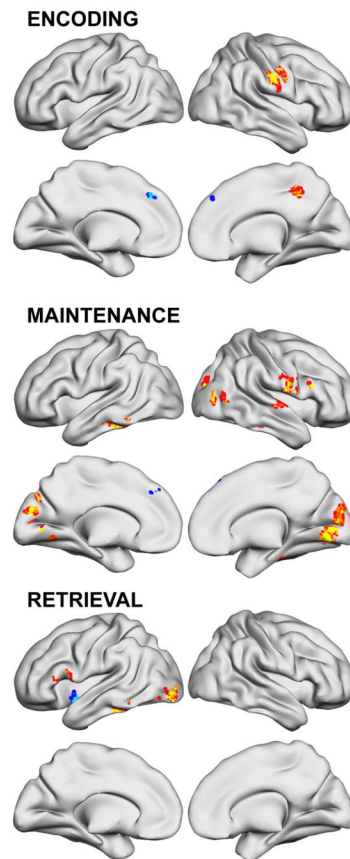


Figure 5. Brain regions where working memory brain activation changes after 5 weeks of working memory training correlated with Cogmed's Training Index working memory performance improvement score ($p < .05$ clusterwise significance threshold).

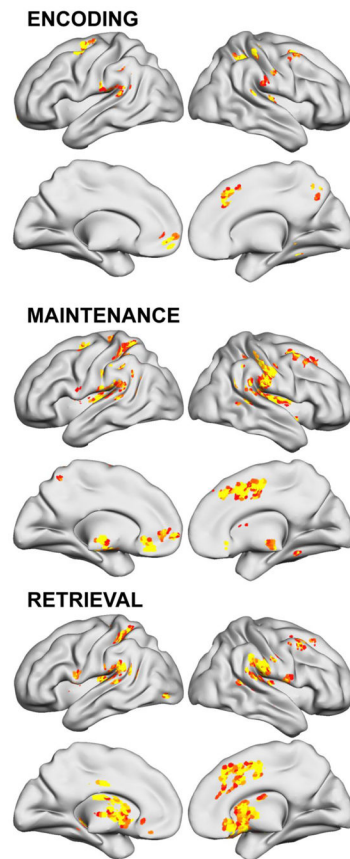


Figure 6. Regions where training-related changes to ADHD brain activity correlated with parent-rated ADHD-Inattentive symptom improvements after 5 weeks of working memory training ($p < .05$ clusterwise significance threshold).

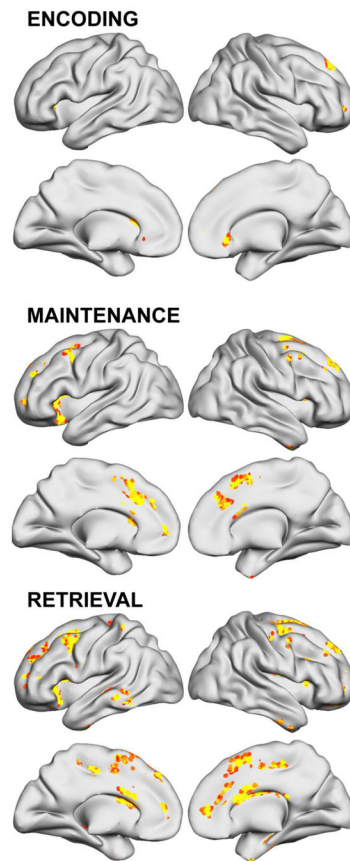


Figure 7. Regions where training-related changes to ADHD brain activity correlated with parent-rated ADHD-Hyperactive/Impulsive symptom improvements after 5 weeks of working memory training ($p < .05$ clusterwise significance threshold).

Table 1

Demographic and clinical characteristics of non-ADHD and in ADHD adolescents.

	ADHD	Non-ADHD	
	Mean (SD)	Mean (SD)	<i>p</i>
Age	15.2 (1.91)	15.8 (1.40)	<i>ns</i>
Sex	11M/6F	11M/6F	<i>ns</i>
Mean Years of Parental Education	15.5 (1.84)	16.0 (2.75)	<i>ns</i>
WASI Full Scale IQ Estimate	108.7 (11.70)	103.3 (9.51)	<i>ns</i>
Wide Range Achievement Test Reading SS	102.8 (9.33)	104.8 (9.88)	<i>ns</i>
Beck Depression Scale II Total Score	6.9 (5.31)	4.6 (3.76)	<i>ns</i>
Multidimensional Anxiety Scale for Children Total Score	30.7 (14.57)	31.5 (12.55)	<i>ns</i>
Brown ADD Scales Total Score (Self-Report)	65.3 (12.50)	50.7 (1.61)	<.001
Brown ADD Scales Total Score (Parent-Report)	67.7 (12.66)	50.3 (0.97)	<.001

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Table 2

Neuropsychological test performance in non-ADHD and in ADHD adolescents before and after 5 weeks of working memory training.

	ADHD Pre-Training	ADHD Post-Training	ADHD Pre- vs Post-Training
	Mean (SD)	Mean (SD)	<i>p</i>
<i>Trained WM Tests</i>			
Cogmed Training Index	85.5 (10.9)	115.3 (16.4)	0.0000001
<i>Non-Trained WM Tests</i>			
WISC-IV Digit Span Forwards Scaled Score	8.4 (2.8)	11.1 (3.5)	0.00001
WISC-IV Digit Span Backwards Scaled Score	8.7 (2.8)	12.3 (3.2)	0.0007
WISC-IV Letter-Number Sequencing Scaled Score	9.3 (2.3)	11.1 (2.0)	0.0005
WISC-IV Spatial Span Forwards Scaled Score	11.2 (2.5)	13.4 (2.9)	0.002
WISC-IV Spatial Span Backwards Scaled Score	10.3 (1.9)	13.3 (1.9)	0.0002
<i>Cognitive "Far Transfer" Tests</i>			
Conner's CPT-II Omissions T-score	52.5 (13.0)	50.0 (12.0)	<i>ns</i>
Conner's CPT-II Commissions T-score	56.9 (10.7)	58.1 (7.9)	<i>ns</i>
Conner's CPT-II Hit Rate T-score	46.4 (12.0)	43.0 (12.2)	<i>ns</i>
<i>ADHD Clinical Severity Indicators</i>			
Hyperactive/Impulsive symptom severity (max 27)	17.9 (7.3)	11.4 (6.7)	.002
Inattentive symptom severity (max 27)	21.7 (5.5)	15.2 (6.5)	.017
Brown ADD Scales Total T (Child)	65.5 (12.5)	57.4 (12.3)	.023
Brown ADD Scales Total T (Parent)	67.7 (12.4)	62.2 (11.9)	<i>ns</i>
Home Situations Questionnaire problem severity	5.4 (1.3)	4.1 (1.6)	.015

Significant differences between ADHD and non-ADHD participant's brain function, using Monte Carlo simulations to set clusterwise control over false positives across the whole brain at $p < .05$. The Table also lists effect sizes quantifying the magnitude of ADHD Pre-Training and Post-Training differences from non-ADHD controls.

Table 3

	Non-ADHD vs ADHD Pre-Training			Post-Training Region-of-Interest Analysis		
	x, y, z	t	Cohen's d	t	p	Cohen's d
Encoding						
<i>Non-ADHD > ADHD</i>						
Left middle occipital gyrus/precuneus	-24, -82, 40	4.72	1.60	2.86	✓	0.97
Right superior parietal lobule/precuneus	36, -76, 40	4.30	1.45	2.73	✓	0.92
Left lingual/inferior occipital gyri	-15, -100, -11	3.64	1.23	3.12	0.031	1.05
Right parahippocampal gyrus	21, -46, -14	3.35	1.13	2.81	✓	0.95
<i>Non-ADHD < ADHD</i>						
Left middle frontal gyrus (BA 8/9)	-36, 32, 43	4.02	1.36	3.86	0.006	1.30
Midline superior frontal gyrus (BA 8)	0, 35, 55	4.64	1.57	3.41	0.017	1.15
Medial frontal gyrus (BA 9)	-3, 44, 31	3.13	1.06	4.76	0.001	1.61
Left inferior frontal gyrus (BA 45)	-54, 38, 4	3.62	1.22	4.24	0.001	1.43
Left inferior frontal gyrus (BA 47)	-36, 32, -20	3.36	1.14	2.98	0.041	1.01
Right insular cortex (BA 13/47)	30, 17, -5	2.44	0.82	2.81	✓	0.95
Left insular cortex (posterior BA 13)	-42, -13, 1	3.96	1.34	3.83	0.007	1.29
Right sensorimotor cortex (pre/postcentral gyri)	18, -19, 58	4.07	1.38	3.81	0.007	1.29
Right supramarginal gyrus (BA 40)	57, -28, 34	3.25	1.10	4.41	0.002	1.49
Right fronto-temporal space (BA 45)	60, 11, 7	3.65	1.23	3.10	0.032	1.05
Right putamen	27, -7, -8	3.52	1.19	3.42	0.017	1.16
Left cerebellum (posterior lobe)	-12, -70, -17	3.99	1.35	3.51	0.014	1.19
Maintenance						
<i>Non-ADHD > ADHD</i>						
Left middle frontal gyrus (BA 8)	-30, 17, 52	3.86	1.30	1.45	ns	0.49
Left middle/inferior frontal gyri (BA 46)	-42, 14, 22	3.38	1.14	1.55	ns	0.52
Right middle/inferior frontal gyri (BA 46)	42, 32, 25	3.96	1.34	2.69	✓	0.91

	Non-ADHD vs ADHD Pre-Training			Post-Training Region-of-Interest Analysis		
	X, Y, Z	t	Cohen's d	t	p	Cohen's d
Left inferior parietal lobule (BA 40)	-36, -37, 43	3.53	1.19	2.05	ns	0.69
Left precuneus	-24, -85, 40	3.73	1.26	2.32	ns	0.78
Right precuneus/superior parietal lobule	33, -79, 37	4.33	1.46	1.44	ns	0.49
Left middle occipital gyrus (BA 19)	-42, -88, 10	3.37	1.14	1.68	ns	0.57
<i>Non-ADHD < ADHD</i>						
Left insular cortex (BA 13)	-39, 11, 1	3.01	1.02	2.22	ns	0.75
Primary visual cortex (L/R cuneus/lingual)	15, -100, 19	4.69	1.59	4.74	<0.001	1.60
Right parahippocampal gyrus/amygdala	18, 5, -23	4.01	1.36	2.59	†	0.88
Retrieval						
<i>Non-ADHD > ADHD</i>						
Midline superior/medial frontal gyri (BA 8)	3, 26, 52	3.31	1.12	3.48	0.015	1.18
Left inferior/middle frontal gyri (BA 46)	-48, 17, 19	3.17	1.07	1.76	ns	0.59
Right inferior frontal gyrus	42, 11, 22	3.02	1.02	2.32	ns	0.78
Left middle frontal gyrus (BA 10)	-27, 47, -5	3.53	1.19	2.44	ns	0.82
Left inferior parietal lobule (BA 40)	-36, -40, 40	3.43	1.16	2.55	†	0.86
Right precuneus	36, -73, 31	3.29	1.11	2.70	†	0.91
Left middle occipital gyrus (BA 19)	-42, -88, 4	3.35	1.13	2.78	†	0.94
Right parahippocampal/fusiform gyri (BA 37)	30, -52, -11	3.37	1.14	2.32	ns	0.78
<i>Non-ADHD < ADHD</i>						
Midline superior/medial frontal gyri (BA 9)	3, 53, 31	3.51	1.19	3.76	0.008	1.27
Right precentral/inferior frontal gyri (BA 44)	60, 11, 7	3.64	1.23	2.75	†	0.93
Orbital/medial frontal gyri (BA 11)	3, 44, -23	2.88	0.97	3.23	0.022	1.09
Right inferior frontal gyrus (BA 47)	24, 23, -23	3.82	1.29	2.50	ns	0.85
Right paracentral lobule	6, -28, 52	4.22	1.43	4.80	0.001	1.62
Left inferior parietal lobule (BA 40)	-57, -40, 52	4.45	1.50	2.01	ns	0.68
Right inferior parietal lobule (BA 40)	48, -25, 28	3.24	1.10	3.88	0.006	1.31
Left superior temporal gyrus (BA 22)	-51, 11, -14	3.09	1.04	2.40	ns	0.81
Left cerebellum (posterior lobe)	-18, -67, -23	5.26	1.78	2.57	†	0.87
Right cerebellum (posterior lobe)	18, -70, -23	3.74	1.26	2.26	ns	0.76

represents a trend level of FWE small-volume corrected significance ($> .05$ but $< .10$). This was included because the p values from the ROI analysis results are not directly comparable to Monte Carlo "whole brain" corrections (although the t statistics at the peak voxel of study group difference are equivalent for head-to-head comparison).

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Table 4

Main effect of 5 weeks of working memory training on brain activation during different phases of the Sternberg fMRI task. Analyses are repeated-measures t tests comparing fMRI assessment of Encoding, Maintenance, and Retrieval brain activation at study endpoint to pre-training baseline fMRI, using Monte Carlo simulations to set clusterwise control over false positives across the whole brain at $p < .05$. For each region showing significant differences, *post hoc* tests evaluated the Pearson correlation of brain function within 5 mm of the peak and either Cogmed WM task performance improvement, or change in parent-reported ADHD symptom severity separately for Inattentive versus Hyperactive/Impulsive symptoms.

Brain region	Peak x, y, z	Peak t	Cogmed Training Index Change r	Inattentive Symptom Change r	Hyperactive/Impulsive Symptom Change r
Encoding					
<i>Post-Training Increases</i>					
Left inferior frontal gyrus (BA 46/45/9)	-57, 23, 22	3.44	ns	ns	ns
Medial frontal gyrus	-6, 50, -5	3.90	ns	ns	ns
Left postcentral gyrus	-60, -13, 37	4.12	ns	ns	ns
Left supramarginal gyrus/inferior parietal lobule	-63, -25, 34	3.46	0.07	ns	ns
Right inferior parietal lobule	45, -31, 31	4.12	ns	ns	ns
Left angular/superior temporal gyri (posterior)	-60, -49, 37	3.68	0.02	ns	ns
Left middle temporal gyrus	-63, -16, -14	4.69	ns	ns	ns
Right middle/superior temporal gyri	54, -31, 4	3.56	ns	0.03	ns
Right posterior cingulate	-15, -52, 13	3.37	ns	ns	ns
Brainstem	-6, -31, -38	3.90	ns	ns	0.05
<i>Post-Training Decreases</i>					
Superior frontal/medial frontal gyri (pre-SMA)	6, 11, 46	3.64	0.06	0.01	ns
Maintenance					
<i>Post-Training Increases</i>					
Left middle/inferior frontal gyri (BA 9/8/46/45)	-27, 17, 52	3.45	ns	ns	ns
Right middle/inferior frontal gyri (BA 46/9)	42, 23, 25	5.29	ns	ns	0.08
Anterior cingulate/Medial frontal gyrus (BA 32/10)	-6, 35, -8	2.91	ns	ns	ns
Left middle temporal gyrus	-63, -37, -2	3.62	0.006	0.01	ns
Right middle/superior temporal gyri	54, -31, 1	4.21	0.10	0.10	ns

Brain region	Peak x, y, z	Peak t	Cogmed Training Index Change r	Inattentive Symptom Change r	Hyperactive/Impulsive Symptom Change r
Bilateral cuneus (BA 18/19)	3, -97, 16	2.95	<i>ns</i>	0.001	0.02
Retrieval					
<i>Post-Training Increases</i>					
Left middle/inferior frontal gyri (BA 9/46)	-51, 20, 25	3.74	<i>ns</i>	0.08	<i>ns</i>
Anterior cingulate/medial frontal gyri (BA 32)	-3, 35, -11	3.48	<i>ns</i>	<i>ns</i>	<i>ns</i>
Right superior temporal gyrus	54, -10, -2	3.33	<i>ns</i>	<i>ns</i>	0.03
<i>Post-Training Decreases</i>					
Left cerebellum	-36, -55, -38	5.29	<i>ns</i>	<i>ns</i>	0.004
Right cerebellum	42, -55, 38	4.31	<i>ns</i>	0.02	<i>ns</i>

Table 5

Main effect of 5 weeks of working memory training on the brain's response to task difficulty. Analyses are repeated-measures *t* tests of the parametric effect of working memory load (2, 4, or 6 stimuli to be remembered) comparing study endpoint fMRI and pre-training baseline fMRI. Increases represent a brain region that showed a greater relationship between difficulty and activation amplitude at baseline.

Brain region	Peak x, y, z	Peak <i>t</i>	Cluster extent
Encoding Parametric			
<i>Post-Training Increases</i>			
Medial frontal gyrus (BA 10)	0, 65, 22	4.93	25
Right inferior frontal gyrus	48, 20, 19	3.58	26
Left inferior frontal gyrus (anterior insula)	-42, 32, -2	3.10	37
Right middle frontal gyrus (BA 10/47)	45, 50, -5	4.01	33
Precuneus/paracentral lobule (BA 31)	0, -40, 43	3.05	57
<i>Post-Training Decreases</i>			
Left cuneus (BA 17/18/23)	-3, -85, 16	3.43	44
Maintenance Parametric			
<i>Post-Training Increases</i>			
Left middle/superior frontal gyri (BA 8/6)	-33, 26, 52	3.16	42
Midline superior/medial frontal gyri (BA 9/8)	-6, 56, 37	4.06	37
<i>Post-Training Decreases</i>			
Left middle/inferior frontal gyri (BA 44)	-42, 38, 31	3.71	484
Left insula	-36, 11, 10	4.36	
Left precentral gyrus	-54, 2, 19	3.44	
Left postcentral gyrus	-57, -16, 28	3.54	
Right insula	33, 17, 7	4.47	181
Retrieval Parametric			
None			

Table 6

Supplemental analysis showing additional brain regions where post-training versus pre-training fMRI measurements significantly correlated with changes in the Cogmed Training Index score of WM exercise performance. The analysis used using Monte Carlo simulations to set clusterwise control over false positives across the whole brain at $p < .05$.

Brain region	Peak x, y, z	Peak <i>t</i>	Cluster extent
Encoding			
<i>Post-Training Increases</i>			
Right pre/postcentral gyri (sensorimotor cortex)	54, -16, 34	5.43	119
Left cerebellum	-15, -52, -32	4.57	388
<i>Post-Training Decreases</i>			
Medial frontal gyrus (BA 6/9/8)	0, 38, 40	3.98	32
Maintenance			
<i>Post-Training Increases</i>			
Right inferior frontal gyrus (BA 45/9)	63, 17, 22	3.63	39
Right pre/postcentral gyrus (sensorimotor cortex)	63, -7, 13	3.81	79
Left middle/inferior temporal gyri	-51, -37, -17	3.97	44
Bilateral cuneus (BA 18/19/17)	0, -88, 13	3.49	381
Right middle temporal/middle occipital gyri	45, -79, 10	3.82	41
Bilateral cerebellum (anterior lobe)	-9, -52, -26	5.07	567
<i>Post-Training Decreases</i>			
Medial frontal gyrus (BA 6/9/8)	3, 41, 43	3.65	34
Retrieval			
<i>Post-Training Increases</i>			
Left inferior frontal gyrus (BA 44/45)	-60, 14, 7	2.97	32
Left middle temporal/fusiform gyri	-48, -37, -20	4.27	42
Left middle/inferior occipital gyri (BA 18)	-30, -97, -8	3.82	70
Cerebellum	6, -58, -23	3.78	41
Brainstem (pons/midbrain)	-6, -28, -23	3.31	63
<i>Post-Training Decreases</i>			
Left superior temporal gyrus/insula	-36, 2, -14	3.75	32

Table 7

Supplemental analysis showing additional brain regions where post-training versus pre-training fMRI measurements significantly correlated with changes in parent-rated DSM-IV ADHD symptom severity. The analysis used using Monte Carlo simulations to set clusterwise control over false positives across the whole brain at $p < .05$.

Brain region	Inattentive Symptom Change Correlation		Hyperactive/Impulsive Symptom Change Correlation	
	Peak x, y, z	Peak t	Peak x, y, z	Peak t
Encoding				
<i>Post-Training Increases</i>				
Left middle frontal gyrus (BA 6)	-36, -1, 58	6.49		
Right middle frontal gyrus (BA 6)	36, 11, 58	3.26		
Right superior frontal gyrus (BA 8)			15, 44, 49	4.98
Right cingulate/medial frontal gyri (BA 32,8)	12, 23, 40	4.41		
Right anterior cingulate (rostral BA 24)			3, 23, -2	3.93
Right superior frontal gyrus (BA 10)			18, 53, 4	4.37
Left Medial frontal gyrus	-12, 53, -8	5.37		
Right inferior parietal lobule (BA 40)	42, -37, 55	4.92		
Right precuneus (BA 7)	15, -64, 46	4.45		
Left supramarginal gyrus/inferior parietal lobule/posterior insula	-45, -22, 19	5.41		
Right inferior parietal lobule/postcentral gyrus	69, -34, 19	5.04		
Right putamen/lentiform nucleus	30, -22, 1	3.96		
Anterior cerebellum	18, -46, -14	5.14		
Right posterior cerebellum			33, -76, -35	4.50
Maintenance				
<i>Post-Training Increases</i>				
Left middle frontal gyrus (BA 6)	-21, -7, 55	5.49	-12, 2, 58	3.92
Left middle frontal gyrus (BA 6/8)			-36, 8, 55	7.78
Right middle frontal gyrus (BA 6)	33, 8, 55	3.52	48, 8, 49	4.19
Right cingulate/medial frontal gyri (BA 32/24/8)	9, 11, 49	5.26	6, 17, 49	3.89
Right medial/superior frontal gyri (BA 6)			15, 8, 49	4.02
Right superior frontal gyrus (BA 8/9)			15, 47, 46	4.86
Right cingulate/medial frontal gyri			-12, 26, 40	4.81
Right anterior cingulate gyrus (BA 32)			9, 29, 28	3.40
Left medial/superior frontal gyri (BA 10)	-9, 56, 1	6.22	-15, 50, 4	3.70
Left anterior cingulate (rostral)	-6, 29, -14	5.63		
Left insula (BA 13)			39, 5, 13	4.28
Right anterior insula (BA 47)			-30, 23, -14	5.17
Left postcentral gyrus	-18, -34, 61	4.40		
Left superior parietal lobule/precuneus	-18, -55, 61	4.18		
Right postcentral gyrus/inferior parietal lobule	45, -40, 49	5.01		

Brain region	Inattentive Symptom Change Correlation		Hyperactive/Impulsive Symptom Change Correlation	
	Peak x, y, z	Peak t	Peak x, y, z	Peak t
Left supramarginal gyrus/inferior parietal lobule	-45, -43, 34	3.56		
Left posterior insula/lentiform nucleus	-45, -19, 13	3.41		
Right posterior insula/lentiform nucleus	45, -31, 16	4.64		
Midbrain	-3, -22, -17	6.32		
Anterior cerebellum	-9, -49, -14	4.66		
Retrieval				
<i>Post-Training Increases</i>				
Left middle frontal gyrus (BA 6)			-36, 5, 49	11.85
Right middle/superior frontal gyri (BA 8)	33, 17, 58	4.03		
Left medial frontal/cingulate gyri			-15, 5, 55	6.16
Right cingulate/medial frontal gyri (BA 24/32)	9, 14, 49	4.51	12, 20, 49	4.32
Right precentral gyrus			51, 2, 49	4.23
Right precentral gyrus			36, -10, 55	8.55
Left medial/superior frontal gyri			-12, 32, 43	7.41
Right insula (BA 13)			39, 14, 13	4.29
Left inferior frontal gyrus			-33, 32, 4	6.70
Right pregenual cingulate (BA 25)	6, 20, -11	5.40		
Left inferior parietal lobule (BA 40)/superior temporal gyrus	-63, -46, 22	4.65		
Left middle temporal gyrus			-60, -40, -8	5.22
Right inferior parietal lobule (BA 40)/superior temporal gyrus	63, -37, 34	5.49		
Left middle occipital gyrus	-30, -85, 1	4.62		
Left caudate			-15, 17, 16	2.83
Right caudate	18, 11, 13	3.65		
Right claustrum			30, 14, 16	8.18
Right globus pallidus	21, -13, -2	8.09		
Left thalamus	-15, -13, 13	5.36		
Left anterior cerebellum	-18, -43, -23	3.24		
Pons			-6, -31, -44	4.66