Target ADHD Executive Working Memory Training Replication Study

Study Protocol

IRB Approval Date: 9/22/2023

Behavioral and Neural Target Engagement for ADHD Executive Working Memory Training

Phase II

This proposal is based on converging evidence that suggests prior ADHD working memory training studies might have produced lackluster clinical outcomes because they focused on enhancing the wrong cognitive and neurobiological targets. The proposed study will replicate target engagement as assessed in the first phase while also determining if it correlates with clinically meaningful improvements in ADHD dysfunction. The full project was designed so that if these study aims are successful, the data we obtain will be adequate to support a future preliminary efficacy clinical trial.

Many investigators have attempted to show that using intensive cognitive training to increase Attention-Deficit/Hyperactivity Disorder (ADHD) patients' capacity to store information within WM might also reduce symptom severity or functional impairment. Those studies were based on strong evidence for WM behavioral and neural dysfunction in ADHD, a widely-held belief that WM-related brain dysfunction is etiologically significant, and arguments that impaired WM contributes to the maintenance of the disorder. But despite promising early evidence for WM storage training potential efficacy, a decade of equivocal and negative outcomes from several well-designed randomized clinical trials have left investigators wondering why meaningful, replicable ADHD clinical improvements are not always achieved when WM storage capacity is reliably enhanced. Because few investigators want to mistakenly abandon such a promising intervention premise, there is a search for novel working memory-related treatment targets that focus on something other than simple WM storage capacity. In this proposal, we synthesize published findings and provide our own pilot neuroimaging evidence to argue that a better WM training target might be brain regions that specifically underlie the executive aspects of WM. Such executive working (EWM) memory operations represent patients' ability to effectively use the information represented in WM for behavioral and cognitive control. These abilities likely are more meaningful to ADHD behavioral impairment than merely how large patients' general WM storage capacity is. An extensive theoretical framework supports that the 'working' part of WM involves a small handful of discrete cognitive operations that flexibly manipulate information within WM, or stabilize WM representations in the face of different types of environmental distraction. Dozens of prior fMRI studies reliably link the four primary types of these EWM operations to activity within specific brain regions – the superior frontal sulcus and mid-lateral prefrontal cortex. Converging evidence including our pilot evidence shows these regions function abnormally in ADHD, predict ADHD symptom severity, and can be enhanced by practicing EWM tasks. NIMH's R61/R33 experimental therapeutics mechanism is ideal to learn if a typical 5-week, course of intensive training that uses these EWM exercises can engage the proposed brain targets linked to both EWM ability and to ADHD dysfunction. As the neuroscience-guided, initial 2-year R61 study phase achieved its milestones, this R33 study phase will seek to replicate, and then show the relevance of target engagement to ADHD clinical function. If both R61/R33 aims are achieved, a series of secondary analyses will re-examine the trial outcome data. These efforts will inform the design of any subsequent preliminary efficacy study, facilitating a rapid transition into larger-scale efficacy testing.

Over a decade ago, considerable interest emerged in whether intensive practice of working memory (WM) tasks designed to expand one's overall capacity to store information briefly in mind might benefit patients with Attention-Deficit/Hyperactivity Disorder (ADHD). WM training has a convincing neuroscientific foundation and there was exciting preliminary evidence that prompted WM training intervention development. Nearly all clinical trials to date that have focused on increasing simple short-term WM storage capacity have been disappointing. Investigators remain perplexed why ADHD patients make very reliable, usually persistent WM gains, but simply having a larger WM capacity does not convincingly result in ADHD symptom improvements. Our pilot studies suggest WM training might live up to early expectations if investigators switch focus to a new training target – 'executive working memory' (EWM). EWM refers to a few selective attention-based cognitive processes that operate within WM either to flexibly allow information to be manipulated, or to stabilize and protect mental representations when they are needed to guide behavior. Converging evidence supports EWM as a potentially better training target than WM storage capacity. Importantly, our pilot data also show EWM practice alters ADHD brain function in regions linked to ADHD symptom severity in our prior research. This proposal includes a 2-year milestone-driven R61 initial test of target engagement using a new EWM training intervention in *n*=62 ADHD-diagnosed adolescents randomized to a 'sham training' placebo or to train on 4 different EWM tasks per session 4 times each week. Exercise difficulty levels in the active intervention increased across 5 weeks to continually challenge EWM ability. EWM training used a novel, remotely-supervised 'at home' computerized training approach. Since the R 61 EWM training target engagement milestones were met, a 3-year R33 phase will begin. The R33 will replicate target engagement in another randomized placebo-controlled trial of *n*=90 new ADHD adolescents and attempt to establish a convincing link between the hypothesized targets and ADHD symptom expression. It also will characterize ADHD brain activity or EWM ability changes relative to typical levels seen in an *n*=40 non-ADHD control group.

R33 AIM 1 Replicate and Extend ADHD EWM Training Target Engagement Relative to Placebo

Another randomized, placebo-controlled trial of *n*=90 new ADHD adolescents will provide evidence needed to support a subsequent efficacy trial – replication of target engagement and confirmation of clinical relevance.

R33 Hypotheses 1-2 Compared to a 'sham training' placebo for which we expect no EWM target change:

1) We will replicate both SFS/mid-latPFC brain activity/connectivity and behavioral changes seen in the R61.
2) We will see evidence of 'near transfer' of EWM behavioral training gains to non-trained EWM tests.

R33 AIM 2 Establish a Link Between Target Engagement and ADHD Symptom Expression

Data will be used to test assumptions the proposed neural targets are relevant to ADHD clinical impairment.

R33 Hypotheses 3-4 There will be a significant association between EWM engagement and ADHD symptoms:

3) Before training, ADHD symptom severity will correlate with EWM brain function and behavior (r>.35).
4) The degree of fMRI-measured EWM training target engagement will significantly correlate with ADHD outcome measured by ADHD symptom severity rating scales and secondary functional inventories.

Unmet ADHD Treatment Need DSM 5 Attention-Deficit/Hyperactivity Disorder (ADHD) [1] affects 5-7% of children and adolescents [2-4]. It is marked by excessive impulsivity/hyperactivity and inattention causing significant academic [5-11], employment, legal or psychosocial problems and risk for other psychopathology and substance disorder [7, 12, 13] despite the best-supported treatments [14-16]. Stimulant-based medications are first-line recommended ADHD treatments [17], but have meaningful limitations. Medications manage immediate problem behavior, but do not prevent poorer ADHD long-term educational, vocational, or social outcomes [18-24]. Roughly ¼ of ADHD patients fail to show any beneficial response [25]. Medications can be very unpopular with some patients and their parents [26, 27] due to intolerance of side effects [28, 29] or parental concerns of misuse [30-33] from a high abuse potential [30-32, 34] and fears about growth and health risks [35, 36]. Only about half of ADHD-diagnosed children [37] and adolescents [38] use medications. As such, at least half of ADHD patients could benefit from an effective alternative, non-pharmacological treatment to help reduce the $143-266 billion annual estimated economic burden of ADHD in the U.S. from healthcare costs, lost workforce productivity, and similar factors [39]. An effective alternative ideally would not be another temporary palliative, but instead offer sustained benefits.

Why Train Working Memory to Treat ADHD? Over the past decade, considerable effort has been poured into studying a non-pharmacological cognitive training approach for ADHD that seeks to improve working memory (WM) through weeks of continually challenging training sessions. Such approaches are based upon a well-supported premise that intensive practice reliably induces long-term synaptic connectivity and brain structure changes [40-42] (i.e., experience-dependent 'neuroplasticity') in networks that underlie the specific ability that has been trained [43-51]. A strong appeal of cognitive training is that it might offer enduring therapeutic benefits for ADHD patients from neuroplastic changes – particularly if those changes occur early to optimize neurodevelopmental trajectories into adulthood. The ultimate goal of these intervention development efforts has always been to reduce ADHD symptom severity and associated clinical dysfunction. The premise of WM training for ADHD rests on a reasonable conceptual foundation that links WM performance on brief WM information storage tasks to attention abilities [40, 52, 53], general aptitude (IQ [54-56], reasoning ability [57], or SAT performance [58]), and academic achievement [54, 58-64]. Moreover, ADHD patients' performance on some WM tasks predicts 'real world' ADHD-like behaviors in non-ADHD persons [65, 66], e.g., multi-tasking [67, 68], mind wandering [69], and following directions [70, 71]. Meta-analyses of neuropsychological studies also show WM deficits are among the most consistently found cognitive impairments in ADHD [72-75]. It has been proposed that WM training might work by directly remediating WM-related ADHD brain dysfunction believed to be etiologically-significant for the disorder [72, 76-84]. Not only is WM a proposed endophenotype for common genetic risk in ADHD [85, 86], recent studies have begun to demonstrate WM's etiological importance by showing ADHD patients' WM ability levels mediate links between ADHD polygenic risk scores and ADHD symptom expression [85, 87] in ways not found for other cognitive deficits [88]. In the WM training earliest studies, pioneering approaches (e.g., Cogmed™) were found not only to increase ADHD WM storage capacity on behavioral tests, but in non-ADHD also to alter grey and white matter brain structure, dopaminergic function, and brain activity [89]. Indeed, numerous fMRI studies of young [90-94] and older adults [90, 95], and fMRI [91, 96, 97] and EEG [98] functional connectivity studies done after WM training show brain network [99-102] connectivity reconfiguration and strengthening within the frontoparietal system engaged for WM, and with key WM-specialized regions in other parts of the brain. As such, there was great excitement we ultimately might find these neural effects converged with evidence for WM-related brain dysfunction that has been found in ADHD in over a dozen fMRI studies [103-106].

WM Storage Training Fails Expectations Nearly all ADHD WM training research to date has focused on increasing WM storage capacity. These efforts have fallen short of expectations. On the one hand, qualitative [107-113] and meta-analytic [114-117] reviews conclude WM training reliably improves ADHD WM capacity, with gains that persist over time [118-120]. Disappointingly however, the evidence these WM capacity gains translate into improved ADHD symptom severity or better functioning is marginal and inconsistent. The earliest clinical trials found improved parent-, teacher-, or self-rated ADHD severity [53, 121-125] or objectively-measured ADHD behavior (e.g., actigraph-measured motor restlessness or classroom time-on-task [53, 126]), with some evidence that gains might persist for months [53, 123, 125]. However, this evidence came almost entirely from 'open label' trials where expectancy effects typically inflate perception of clinical benefit. Subsequent, better-designed randomized clinical trials (RCTs) have not strongly supported WM storage training efficacy in ADHD. While several RCTs found WM training can produce modest clinical improvement, WM training groups typically do not outperform active treatment control groups. A recent meta-analysis has concluded RCT blinding reduces the promising effects seen in the earlier open label trials to clinically insignificant levels [127]. Perplexingly, those RCTs often failed to replicate the same small positive outcomes [107, 125, 126, 128]. By and large, efforts to train other executive

abilities (e.g., response inhibition, sustained attention, etc.) (e.g., [129, 130]; see meta-analysis [116]), or to train several executive abilities together [131], or to individualize training exercises to ADHD patients' pre-existing executive deficits [132] also have not held up against placebo control. Most reviewers of this literature have concluded WM training still holds considerable promise in ADHD [108, 109, 112, 113, 115, 117, 133-138]. But they also make it clear new ideas are needed for how to modify training to have stronger and more reliable benefits for ADHD symptoms. We believe meaningful ADHD clinical improvement will require not only an entirely new cognitive training focus, but also a neuroscience-informed research formulation that identifies brain-based training targets that have been empirically shown to predict ADHD symptom expression.

Executive Working Memory This proposal builds on converging theory and evidence that 'executive working memory' (EWM) likely represents a better context for ADHD WM training than WM storage capacity, with highly specific brain-based training targets of clear relevance to ADHD. EWM describes cognitive operations that account for what Baddeley's seminal WM theory described as the 'central executive' – a system that controls information flow within WM. Although early WM studies tended to conceptualize WM's central executive as a single construct, neuroscience evidence suggests that instead there likely are a small number of behaviorally dissociable basic EWM operations supported by partially overlapping brain systems. Bledowski et al. [139] has proposed some of these EWM operations promote *flexibility* of selective attention to WM contents (e.g., measured by tasks that require attention *Shifting* among information held briefly in WM or *Updating* WM content with new information). Others lend *stability* to WM representations (e.g., *Filtering* any extraneous distracting information during WM maintenance, or *Suppression* of proactive interference from uninformative information during retrieval of information from WM) [140]. These attention-based EWM basic operations emerge directly from Cowan's [54], Oberauer's [141], and Engle's [142, 143] current theories about WM's central executive and reflect a basic, well-supported dichotomy between maintenance vs. disengagement via selective attention processes [144]. Each of these EWM operations seem to be suitable candidates for cognitive training exercises. To justify combining them all into a unified EWM training intervention, we examined their relationship to each other in *N*=160 adults who completed online EWM tasks on Amazon's mTurk internet worker platform [145, 146], and whose data met rigorous sampling and data quality control criteria [147-149]. These participants completed the same verbal and nonverbal versions of the EWM *Updating*, *Shifting* and *Distractor Filtering/ Suppression* tasks we propose to use in this project (See **Approach**). Confirmatory factor analyses of EWM task accuracy found acceptable model fit for both a 1-factor model where all EWM accuracy scores contributed to a single latent EWM construct (i.e., GFI=.947, RMSEA=0.072), and a 4-factor model showing each type of EWM ability had unique variance (GFI=.971, RMSEA=.049, and a non-significant CMIN test *p*=.155). This combination of shared and unique variance supports that they all fit underneath an umbrella EWM construct, but also that none of the EWM operations could be considered redundant. As such, all seem to be viable candidates for EWM training exercises.

Neurobiological Basis of EWM EWM operations have been extensively studied with fMRI [151-174]. Meta-analysis of EWM-specific fMRI studies [140] (Fig. 1) find EWM operations overlap with a core frontoparietal WM representation network for information encoding, storage and retrieval (Fig. 2) found by meta-analysis of literally hundreds of fMRI studies, but engage a more extensive set of brain regions throughout lateral/medial PFC and parietal cortices. Current 'state representation' WM neural models describe how the core WM network is integrated with these EWM-linked regions via selective attention mechanisms that activate and integrate information processed in distal regions. This engages information in an active form that can be manipulated and used to guide behavior (sometimes termed 'primary memory' [112, 175-177]). Within this state representation theoretical context, the so-called 'working' parts of WM are simply these various specific attention-based EWM processes – *Shifting*, *Updating*, *Filtering*, and *Suppression*. D'Esposito and Postle [178] recently gave a cogent summary of the considerable neurobiological evidence for how WM arises from such attention-related network connectivity changes during EWM task performance. That is, functionally heterogeneous [179-182], hierarchically-

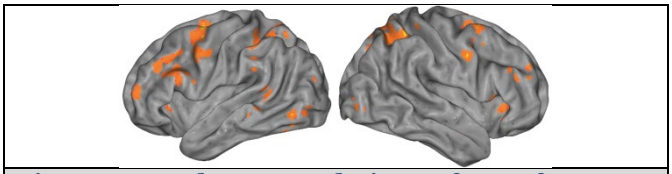

Fig. 1: Nee et al. meta-analysis [140] of *n*=36 fMRI WM studies showing activation during 4 different types of EWM tasks.

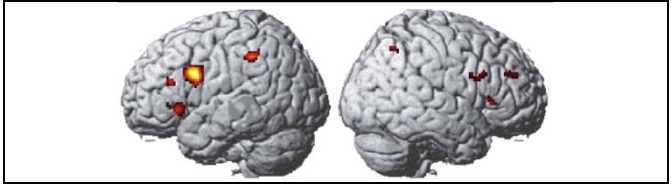

Fig. 2: Frontoparietal domain-general 'core' WM system localized in an ALE meta-analysis of 189 fMRI studies [150].

organized [183-185] prefrontal cortex (PFC) regions engage sustained activation [186-188] during WM that biases activity in other PFC brain regions or other parts of the brain in a 'top-down' way [189-191] via synchronized activation [192, 193] to support WM state representations for information manipulation. Two brain regions seem to be particularly important for these EWM operations – caudal superior frontal sulcus (SFS) linked to feature prioritization within WM [140], and a mid-lateral PFC region of the inferior frontal junction (mid-latPFC), immediately below and posterior to BA 9/46 linked to selecting among competing contexts or rules. Meta-analysis shows that SFS and mid-latPFC are engaged for all EWM operations, possibly because they are key nodes in 'where' and 'what' WM information selection systems [140]. We demonstrated the importance of these regions in pilot Dynamic Causal Modeling (DCM) [194, 195] analyses of EWM fMRI task data that characterized causal relationships among EWM task-engaged brain regions (Fig. 3). While extensive details are not necessary to illustrate the key point, SFS and mid-latPFC exert direct excitatory causal influences on other prefrontal and posterior brain regions engaged for EWM. Those influences also are strongly correlated with behavioral accuracy. The position of SFS and mid-latPFC near the top of EWM network hierarchy and their role as ubiquitously-engaged information processing nodes for many types of EWM operations make them promising EWM training target candidates.

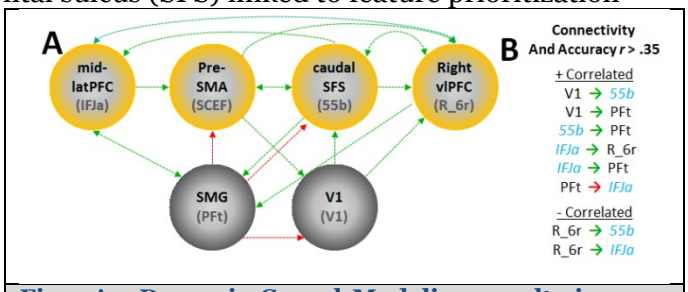

Fig. 3A: Dynamic Causal Modeling results in *n*=15 adults during EWM Updating. GREEN dashed lines show excitatory intrinsic causal influences; RED inhibitory influences (Cohen's *d* > .50).
Fig. 3B: Specific DCM matrix B modulatory connections that are + or – correlated *r* > .35 ('medium' effect size) with Updating task % accuracy. 88% of connections involved mid-latPFC (IFJa) or SFS (55b) parcels.

Support for EWM as a Training Focus in ADHD Here, we review neuropsychological and neuroimaging evidence that supports EWM is meaningful in ADHD and that SFS and mid-latPFC EWM-related brain regions have a plausible relationship to symptom expression. First, *meta-analysis shows EWM deficits are by far the strongest WM deficits in ADHD*. Meta-analytic statistical comparison finds they EWM deficits are significantly stronger than WM storage [72] in ADHD (p<.037 for verbal; p<.022 nonverbal). Moreover, if one re-arranges the 64 ADHD deficits Hedge's g effect sizes from this meta-analysis [72], the simplest short-term storage tasks' have an average g=0.54 ("medium" deficit), while low executive demands like reversing information before recall g=0.72 ("large"). The greatest ADHD effect size impairments (average g=1.13; very "large") were seen for very high executive WM demands, such as switching attention among concurrently held information sets, etc. This EWM effect size also is notably larger than any other cognitive impairment linked to ADHD (e.g., response inhibition, set shifting, timing, etc. [74, 196-198]). So perhaps one reason prior ADHD WM storage training trials have failed to benefit clinical symptoms is they have not targeted the most-impaired WM abilities that have the greatest likelihood of being related to the brain dysfunction central to ADHD.

Second, *fMRI EWM studies offer clear treatment targets because they reliably converge on specific ADHD brain abnormalities*. Functional MRI study reviews and meta-analyses fail to precisely localize abnormalities in ADHD brain regions activated by simple WM information storage tasks [76, 199, 200]. Close examination shows no two ADHD fMRI WM storage studies [103-106] have localized ADHD abnormality to exactly the same brain region. In contrast, fMRI studies consistently find evidence for ADHD dysfunction in brain regions specialized for EWM operations [201-210]. For instance in McCarthy et al.'s meta-analysis [211] of 4 fMRI studies that used an N-Back WM task (which engages EWM operations on each trial – *Shifting*, *Updating*, and *Suppression* [212]), ADHD hypofunction was reliably found in the same bilateral SFS and medial PFC regions. To date, only 1 ADHD fMRI study has attempted to localize neural dysfunction to a specific, isolated EWM operation (i.e., distractor filtering [106]). It also found findings consistent with our conceptual model – lower ADHD intra-PFC functional connectivity, and blunted WM load-dependent activity increases in left ventrolateral PFC, right insula and right medial PFC. Again, these are mostly regions implicated in EWM instead of the 'core' WM representation network. Fig. 4 shows pilot study results that bolster confidence that impaired ADHD

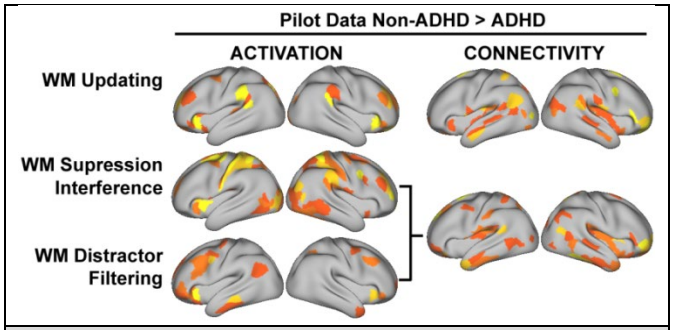

Fig. 4. Comparison of non-ADHD (*n*=5) > ADHD (*n*=5) executive WM fMRI Cohen's *d* effect size maps for activation and connectivity. Maps thresholded at *d* > 0.50 ("medium" effects).

activation in SFS, mid-latPFC and other EWM-linked brain regions is found during all EWM operations we propose for the new intervention. (Note, this pilot study used fMRI analysis methods and a cortical atlas developed by the Human Connectome Project (HCP) that refers to discrete brain regions as HCP atlas 'parcels'.) During WM *Updating*, ADHD had less activity in bilateral dlPFC parcel p9-46v and parcel PF (in the supramarginal gyrus; SMG). ADHD had lower activation to parcel AAIC (insula) to recall probes on the WM *Suppression* condition – an effect made more prominent in the presence of proactive interference. For *Distractor Filtering*, ADHD had less activation of parcel 7PL (superior parietal lobule) and parcels in both dorsal and ventral regions of bilateral PFC. Several bilateral dACC parcels were hypofunctional during *Distractor Filtering* and *Updating*. ADHD functional connectivity estimated by graph theory-based methods [213-216] was weaker connectivity in parcel 55b (caudal SFS) in the *Suppression* task, parcel PGi (SMG) for *Updating*, and tasks in SPL parcels 7PC and 7AL for *Filtering*.

Third, if the ultimate goal of ADHD WM training research is to reduce ADHD symptoms, we suggest *the most suitable brain treatment targets are those with a convincing association with ADHD symptom expression*. Very often, only a subset of brain abnormalities found to be abnormal within a given psychiatric diagnostic phenotype has a direct association with the severity that disorder's symptom expression. In the largest study of ADHD brain structure abnormalities ever undertaken (*N*=2,246 ADHD patients), the ENIGMA consortium found throughout all cortex that only a superior frontal gyrus region (*r*=-0.19, *p*=0.01) (i.e., encompassing our proposed SFS target) and rostral cingulate (*r*=-0.18, *p*=0.03) surface area measurements were associated with ADHD Hyperactive/Impulsive symptom severity. Surprisingly few published ADHD fMRI studies examined brain activity correlations with symptom severity in *post hoc* analyses (only 6 of >6 dozen reports we reviewed). Nevertheless, there is piecemeal evidence that links ADHD symptom severity to lateral PFC. One study found a correlation between symptom severity and right lateral PFC activation during WM for emotional stimuli [207]. Another found a link between lower ADHD symptoms and methylphenidate-induced normalization of Stroop task-elicited left dlPFC activity [217]. Another type of evidence for a link between WM change and ADHD symptom change recently was found in a prospective study that showed normative improvements in ADHD patients' WM ability from childhood to early adolescence directly predicted lower ADHD symptoms in patients [218]. This was a specific relationship, as similar developmental gains in response inhibition and sustained attention ability did not predict symptom levels. All these indications are suggestive, but admittedly limited. However, even stronger evidence exists linking ADHD symptom reductions to activity changes in our specific proposed EWM-related brain targets. In our recent R21HD061915 study, we examined the effect of 5 weeks of Cogmed™ WM storage training on ADHD adolescent brain activation elicited by a WM fMRI probe [103]. After training, ADHD PFC activity elicited during WM storage improved to non-impaired levels (Fig. 5). However, those WM storage-related neural gains did not predict clinical improvement. Instead, when meaningful clinical improvement was seen (in 61% of the ADHD sample), symptom reductions correlated with increased activity in brain regions known to be functionally specialized for EWM [139] (e.g., bilateral SFS, ventrolateral PFC, pre-SMA, and IPL/SMG and SPL parietal lobe regions). These findings not only provide clues as to why WM storage training fails to reduce ADHD symptoms (i.e., it targets the wrong brain regions), it offers a strong indication that EWM brain region change underlies ADHD symptom remission. Because Cogmed™ exercises have minor executive demands, our observations likely resulted from an unintended, coincidental strengthening of EWM-related neural circuits despite Cogmed™ targeting of WM

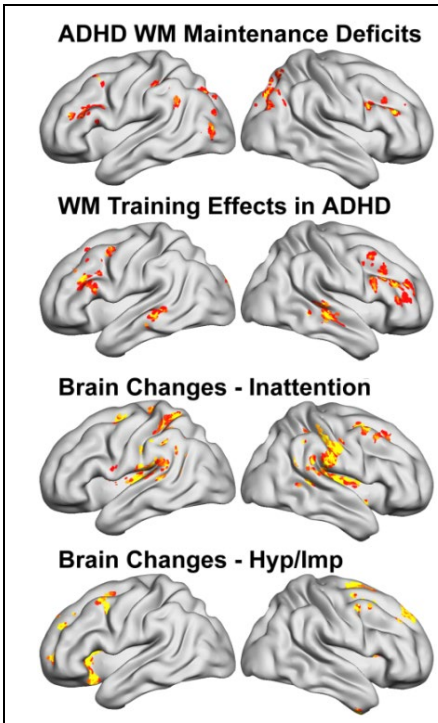

Fig. 5. WM Training effects on WM Maintenance (whole brain *p*<.05 corrected). Data from [103].

storage. Interestingly, our findings showed only the caudal SFS gains correlated with improvements in *both* Hyperactive/Impulsive and Inattentive symptoms, suggesting it might have relatively greater therapeutic potential than other regions.

Finally, we conducted a proof-of-concept pilot study to show *EWM training alters ADHD activity and functional connectivity in the proposed brain treatment targets*. *N*=7 ADHD-diagnosed adolescents drilled on all EWM operations in exercises over a brief, 2-week course of practice (6 sessions). Fig. 6 depicts widespread increased brain functional connectivity to the right SFS parcel in different EWM task contexts after EWM practice. Both 'large' and 'very large' effect size connectivity increases were seen, within 'core' WM and EWM-specialized regions, as well as with other brain regions. Interestingly, different connectivity changes were seen when brain function was elicited by different EWM tasks, consistent with WM state representation theories that the key SFS and mid-latPFC regions will dynamically reconfigure their connectivity strength for different EWM demands. Therefore, we are likely to have the most widespread effect on EWM neural network function if we include all 4 different EWM operations as training exercises. Although this is strong evidence of these regions' malleability and responsiveness to EWM practice, the next step of this research is to give patients a typical course of WM training (e.g., 20-25 sessions over 5 weeks) to assess the extent of brain target engagement with fMRI analyses of activation and network connectivity. In this pilot, behavioral gains were not expected because participants only performed rote practice. Actual EWM training will adaptively increase task difficulty and include intervention design elements that ensure engagement and motivation. These are essential ingredients generally believed necessary to alter behavioral performance [43].

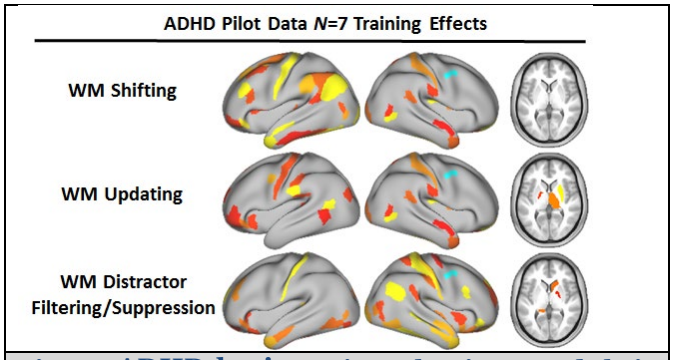

Fig. 6. ADHD brain regions that increased their functional connectivity with right Superior Frontal Sulcus (SFS) HCP 'seed' parcel [55b] (outlined in turquoise) after 6 EWM training sessions. Maps are thresholded at *d* > 1.0 ('large' effect sizes).

Synthesis and Potential Impact There generally is increasing enthusiasm and optimism for using cognitive training to treat psychiatric disorders as more and more studies discover its principles of application, and document its ability to re-sculpt brain networks through experience-dependent neuroplasticity [219]. Although the basic premise underlying some sort of WM training in ADHD still seems sound, a WM storage training behavioral target has been proven ineffective. Broadly speaking, it makes sense that any link between WM and ADHD-related behavioral impairment is likely to be more greatly related to patients' ability to effectively *use* the information represented in WM in the service of cognition and behavioral control instead of merely how much information can be temporarily held in WM. Guided by a careful synthesis of neuroscience evidence from the past decade, this proposal argues for new EWM-focused exercises as a vehicle for modifying specific new brain-based targets. To recap, we conceptualize EWM impairments as the behavioral manifestation of a dimensional, RDoC-like [220-224] neurobiological abnormality in patients diagnosed with ADHD. Although not all ADHD patients show every cognitive impairment that has been linked to the diagnostic phenotype [64, 77, 225-228], EWM tests have the strongest effect size of any cognitive impairment in ADHD. This suggests EWM impairments are more important, or perhaps expressed in a greater proportion of ADHD patients than WM storage or other executive deficits. Cognitive neuroscience neuroimaging studies point to SFS and mid-latPFC as ubiquitously important for all EWM operations; they direct the dynamic reconfiguration of EWM neural network function when accessing or protecting information held in mind to direct behavior that predict EWM task accuracy. Clinical neuroscience studies also show these regions have abnormal activation in ADHD during EWM task performance and are linked to ADHD symptom expression. As such, these two regions represent potential intervention targets whose engagement likely have a stronger potential to produce ADHD symptom severity or functional level improvements that have been so elusive in prior WM storage training research (e.g., Cogmed™). We contend brain-based training targets ultimately will prove better than behavioral performance-based targets because they are more proximal to putative disease mechanism. In this context, EWM behavioral change remains an important focus of cognitive training interventions, but primarily for interpretive reasons (i.e., to ensure training exercises have the intended effect). Furthermore, our consideration of EWM brain region inter-connectivity to evaluate target engagement is consistent with the most recent ADHD neurobiological models of the disorder stemming from neural network connectivity abnormalities [229-237]. It also is noteworthy that success here is potentially relevant for other disorders whose putative etiology is linked to WM (e.g., schizophrenia and bipolar illness [238-

[240], TBI [241], MS [242], stroke [243]). A successful target engagement demonstration here might open new therapeutic avenues for any disorder that shares diagnostically cross-cutting abnormalities in EWM abilities.

The R61/R33 phased grant mechanism for efficient experimental therapeutics development is ideal for the current stage of this research. The obvious next step is to repackage the EWM probes used in prior neuroscience research into a multi-week, intensive drilling format commonly used to maximize participant engagement and to continually challenge EWM ability. Two carefully designed clinical trials will let us determine if the SFS and mid-latPFC targets are indeed engaged by EWM training, to replicate findings, and assess if target engagement has clinical relevance – all necessary to support future clinical efficacy testing. There should be optimism for success because a small handful of EWM training trials already have shown some success in both ADHD [244, 245] and non-ADHD samples [92, 136, 246-249], at least at the behavioral performance level. Those studies trained comparable EWM operations to what we propose to study here. But they typically did not ensure training on all possible EWM operations linked to the proposed SFS/mid-latPFC brain targets. Moreover, we focus here on both brain and behavioral levels. The R33 will examine a larger replication sample. It will test 'near-transfer' generalization, and consider training delivery and patient characteristics as potential outcome moderators (e.g., pre-existing WM impairments vs. strengths, sex, age, ADHD subtype, etc.). These analyses will ensure target engagement evidence meets all theoretical expectations and is robust to the likeliest potential confounds. By the end of this R61/R33 project, we either will know to abandon this proposed new line of inquiry, or we will be positioned to conduct one of several possible 'next step' studies. Ideally, we expect to be ready to propose a well-informed preliminary clinical efficacy trial. Alternatively, we may learn we need to optimize the intervention delivery based upon the results of some proposed R61/R33 supplemental analyses that will determine if target engagement is moderated by the pace of EWM gains, exposure to training (i.e., 'dose'), or patient characteristics.

Innovation The primary study proposal innovations are the new EWM treatment target and its primary focus on neurobiological targets presumably closer to ADHD etiology. Despite strongly converging evidence, none of these EWM operations have been explored in depth in ADHD at the brain level, either in ADHD itself or within a cognitive training context. Another important novel feature is our successfully-piloted remotely-supervised 'at home' EWM training that effectively substitutes for in-person appointments. Not only should this delivery approach greatly enhance protocol adherence and retention, it provides a potentially paradigm-shifting option for a way to deliver personalized cognitive training that should prove to be more practical for typical families in future efficacy trials. There also are many advantageous clinical trial design elements and analyses we describe in the Approach that were not used in most prior ADHD WM training trials. These should overcome common clinical trial pitfalls to help ensure the most definitive possible answers to our target engagement hypotheses.

APPROACH - Methodology in the R33 Project Phase

Participants ADHD participants in the R33 (n=90) trial will be representative of adolescents with a primary diagnosis of DSM 5 ADHD who have common minor secondary psychopathology (see the **Eligibility Criteria** section). The R33 also will recruit n=40 demographically-equivalent non-ADHD participants for a useful comparison of ADHD EWM performance and brain function against a typical normative sample. We focus on adolescent ADHD rather than children in part to avoid pre-pubertal neural differences and to continue our prior ADHD fMRI research (all of which focuses on teens). But also, adolescence represents an ideal developmental period for neuroplasticity-based interventions. It has been well-established that post-pubertal neural system changes mostly involve experience-dependent refinements to a largely-established 'adult-like' brain organization (see our recent adolescent network connectivity review [250]). We are experienced from nearly a dozen current and recent R01s with large N recruitment for fMRI studies of adolescents. As in our recent R21HD061915 and R01MH080956 ADHD fMRI studies, ADHD participants will be recruited from both clinical and community resources. ADHD is ~4 times more common in boys [251], but we will over-sample ADHD females to assess sex effects on outcome, as per NOT-OD-15-102 ($\geq$ ⅓ will be female). *A Note on ADHD Medications*: All 'in person' visits for ADHD fMRI/neurocognitive evaluations will require a 24-hour medication washout if patient symptoms are managed with typical, short half-life psychostimulants. This is a common, widely-accepted research practice to ensure test results cannot be attributed to the temporary, palliative effects of those drugs on the brain on assessment days (see **Eligibility Criteria** section for detailed discussion of the issues involved and list of permitted medications).

Clinical Assessment This evaluation will fully assess all the study exclusion criteria and quantify ADHD symptom severity and functional ability. Table 1 lists evaluation instruments, noting when multiple respondents will provide subjective ratings. All measures are validated for adolescents. As per K-SADS-5 guidelines, collateral parent interview will inform diagnosis decisions. Diagnostic interviews will be performed by clinically-trained postdoctoral staff supervised in a weekly diagnosis consensus meeting by PI Stevens (a licensed clinical psychologist with >16 years' experience supervising K-SADS interviews for NIH-funded studies). Staff interviewing training will include 10 "modeled" interviews, direct observation of the first 10 interviews, and quarterly review of all interview videotapes by other clinically-trained research staff to control for assessment 'drift'. We also will assess participants' age, race/ethnicity, education level, handedness [262], and socioeconomic status [263]. Parents will detail family psychiatric history [264] and confirm child's medical history. These clinical evaluations usually last between 2 - 3 hours.

Table 1. Clinical Assessment (R61/R33)

Task Name	Domain	Min
K-SADS-5 [252]	DSM Axis I diagnosis	30-120
Child Behavior Checklist (CBCL) [253]	Psychiatric/problem behavior	10
Conners 3 (P/S) [254]	ADHD symptom severity	20
* Weiss Func Impair Rating Scale (P/S) [255]	Psychosocial function	5
* Inven. of Parent and Peer Attach. (P/S) [256]	Social relationship quality	10
* Wide Range Achievement Test-5	Academic Achievement	45
Beck Depression Inventory II [257]	Depression severity	5
Multidimen. Anxiety Disorder Scale 2 [258]	Anxiety	5
Olin Health Care Questionnaire	Health and substance use	10
Adol Alcohol/Drug Involv. Scale (AADIS) [259]	Alcohol/Drug involvement	5
Fagerstrom (FTND) [260]	Smoking status/nicotine use	1
Petersen Physical Develop. Scale [261]	Pubertal status	5

* Clinical severity measures to assess functional impairment; P – Parent, S – Self

Neurocognitive Assessment Cognitive testing will exclude WASI FS IQ [271] <80. It also will detail common WM processes, assess EWM tests of 'near transfer' to test the generalizability of EWM training outside of trained tasks, and test 'far transfer' of training effects to other abilities often impaired in ADHD. Table 2 lists tests along with their test-retest reliability. Cognitive testing will require ~2 hours. Co-I Dr. Hawkins will supervise staff training and cognitive testing procedures throughout the project.

Table 2. Cognitive Tests (R61/R33)

Domain/Task Name	Ref	Reliability	Min
Working Memory Capacity			
WISC-IV Letter-Number Sequencing	[265]	.90	15
WISC-IV (Integrated) Spatial Span	[265]	.79 - .81	5
WISC-IV Digit Span	[265]	.80 - .83	5
EWM 'Near Transfer' Tests			
Shifting – Refresh/Repeat Task	[156]	n/a	12
Updating – Spatial Updating Task	[266]	n/a	14
Filtering – Attend-Ignore Task	[172]	n/a	4
Suppression – Intr. Resistance Task	[160]	n/a	12
Executive/Other Abilities			
CPT-II Omissions (Sustain. Attention)	[267]	.84	15
CPT-II Commissions (Resp. Inhib.)	[267]	.65	-
CogState Detection (Process Speed)	[268]	.92	2
CogState Set Shifting Task (Shifting)	[268]	n/a	5
Temporal Estimation Task (Timing)	[269]	n/a	6
Stroop Color/Word (Cog Control)	[270]	0.97	6

MRI Assessment Overview MRI data will be collected using a Siemens 3T Skyra. Subjects will wear hospital 'scrubs' to minimize the chance of introducing metal into the MRI. They will provide a urine sample before MRI to test for drug metabolites, and pregnancy in females. Positive drug results could defer MR data collection and will be noted for *post hoc* analyses. Caffeine/nicotine intake and cigarette smoking will be as normal to prevent acute withdrawal effects on brain activity, but restricted to ≥1 hour prior to MRI to avoid well-documented neural effects of recent use.

fMRI Paradigms There are two important differences between the fMRI tasks that will assess EWM ability before and after training and the EWM training exercises. First, 4 separate tasks will be used during training to isolate each EWM operation, whereas fMRI uses 3 because WM *Distractor Filtering* and WM *Suppression* can be efficiently combined into a single paradigm. WM *Updating* and WM *Shifting* cannot be evaluated by fMRI simultaneously because each operates differently on the stimuli set held in WM. In contrast, EWM stability operations can be assessed in using the same trials because the EWM operations take place after WM short-term maintenance [272]. By combining them for fMRI, we lessen the fMRI scanning time burden. Second, to avoid stimulus familiarity confounds the fMRI tasks will use stimuli sets never seen during EWM training (different counter-balanced sets between pre-/post-training MRI scans). Because SFS and mid-latPFC engagement has proven by meta-analysis to be largely domain-general [140], we include both verbal and nonverbal versions of each task with the expectation they will be collapsed for stable measurements. The

visuospatial versions will use fractal images that are not easily encoded verbally. All were constructed with adequate delays for WM maintenance, but not so long to raise concerns over different WM decay times or possible use of undirected rehearsal strategies. Because it is crucial we avoid exceeding typical WM storage span (which could result in our study testing WM storage capacity more than EWM), no exercise uses more than 4 stimuli at a time (i.e., this is the well-replicated limit of the primary memory span [54]). Task visual layout and pacing are similar so any cross-task differences can be confidently attributed to the EWM operations themselves.

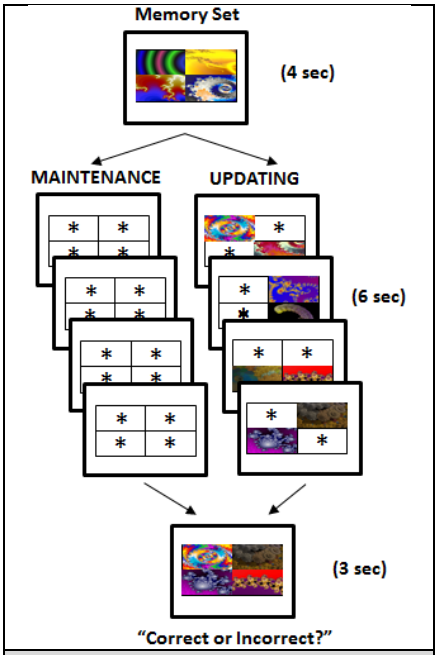

Fig 7. WM Updating Task trial.

WM Updating This task measures replacement of items in WM. It is based upon Murty et al. [273], simplified to 2 conditions. Each trial begins with 4 stimuli presented for 4 sec, followed by 2 to 4 successive presentations (2 sec each) of an asterisk as placeholder or a new stimulus in each position (Fig. 7). For asterisks, participants are instructed to retain the previously viewed stimulus in WM, but to update the contents of WM for any new stimulus. During a final 3 sec response phase, participants indicate if the presented stimuli match the contents of WM (half the probes are correct/half incorrect). For fMRI, the primary contrast of interest is Updating > Maintenance. Each of two fMRI runs (verbal or visuospatial) has 20 Maintenance and 20 Updating trials. Each run=11:39 min (23:18 total).

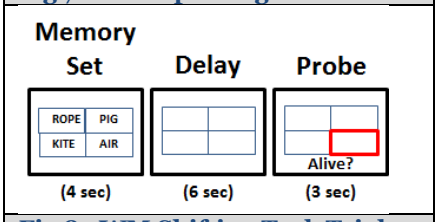

Fig 8. WM Shifting Task Trial.

WM Shifting This task measures the ability to refocus selective attention to different stimuli held concurrently in WM without altering WM contents. Each trial (Fig. 8) begins with 4 stimuli (verbal or visuospatial) for 4 sec, then a 6 sec delay with no stimuli. In a 4 sec probe phase, one location is highlighted and subjects are cued to respond to different Yes/No questions about item content (i.e., randomly chosen to ensure participants do not just encode answers instead of stimuli). For verbal – "Alive?" vs. "3 Letters?" For visuospatial – "Color?" vs. "Fills Screen?"). For Control trials, subjects are prompted to hit a randomly-chosen button. For fMRI, the contrast of most interest is Shift > Control. Each of two fMRI runs (verbal or visuospatial) has 12 Control and 12 Shift trials. Each run=7:10 min (14:20 total).

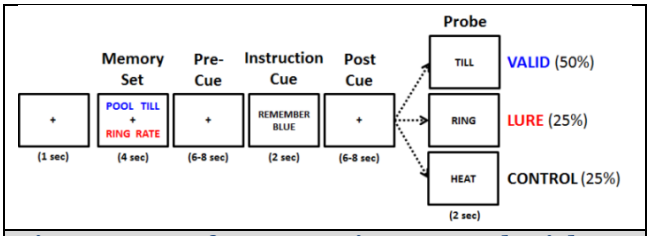

Fig 9. Layout of a Suppression WM Task trial.

WM Distractor Filtering/Interference Suppression This task assesses brain function engaged to a) suppress/inhibit irrelevant, distractor information from WM and b) suppress proactive interference during WM retrieval [272]. Participants are asked to retain a 4-item memory set in WM (Fig. 9). For the verbal task, two stimuli are shown in red, two blue. Our visuospatial version has a comparable format, except instructions are to retain the two top or bottom stimuli. After a PreCue retention-interval, a 2 sec Cue instructs participants to retain in WM only items of that color (i.e., 50% red or 50% blue) throughout a PostCue WM retention-interval. A probe word requires an affirmative dominant-hand response if it matches either of the items retained in WM (e.g., POOL and TILL). On 50% of trials the probe matches one of the items that should be in WM (Valid probes), on 25% the probe matches one of the items that should have been inhibited from WM (Lure probes), and on the remaining 25% of the trials the probe does not match any WM items (Control). For fMRI, the contrasts of interest for this study are PreCue > PostCue (efficacy of suppression) and Lure > Control probe (resolution of proactive interference). Each fMRI run=5:28 min (21:52 total).

Stimulus Delivery/Response Recording E-Prime (Psychology Software Tools, Inc.) will implement fMRI tasks. Stimuli will be projected via a 3200 ANSI lumens system onto a screen behind the patients head in MRI. Participants view this screen using a mirror on the head coil. An MR-compatible 5-button fiber optic response device (Current Designs, Inc.) will acquire behavioral responses. Each fMRI task is programmed to track accuracy and RT for conditions of interest for offline analysis. Participants communicate with staff during MRI using an MR-compatible auditory sound system delivered by 30 dB sound-attenuating headphones.

MRI Sequences *fMRI* gradient EPI (TR/TE 900/35 msec, flip 60°, multi-band AF=7). *Fieldmaps* (TR/TE 8400/62 msec, flip 80°, AF=1, 0:25 min, run twice with reversed A>>P phase encoding) (EPI/fieldmap

sequences have 2.1 mm isotropic voxels, 70 interleaved slices, 228 mm FOV). *T1-weighted* (3D MPRAGE, TR/TE/TI=2400/2.07/1000 msec, flip 8°, FOV=256×256mm, 0.8 mm isotropic vox; 7:02 min). *T2-weighted* (TR/TE=3200/565, FOV=256x256, 0.8 mm isotropic vox; 6:45 min). Images will be Radiologist-assessed to be free of macroscopic pathology. Daily MR stability/QA will ensure equal scan quality throughout the project.

HCP Pipeline MRI Processing We have experience with Human Connectome Project (HCP) [274] pre-processing pipelines [275] from several prior and ongoing large R01 MRI studies. They provide highly-accurate, structural image-guided brain atlas normalization for fMRI data. T1/T2 images will be ACPC-oriented, brain extracted, B_0 inhomogeneity-corrected, mutually co-registered, distortion fieldmap-corrected, and finally MNI152 atlas-registered using FSL FLIRT+nonlinear FNIRT algorithms [276]. FreeSurfer-based [277] registration, skull-stripping, and pial extraction on 1mm downsampled T1/T2 data will create structural volume/cortical ribbon files. After fMRI EPI data is motion-corrected, it will be registered to FreeSurfer output, resampled to atlas space, intensity normalized, smoothed (cortical ribbon surface mapping data @2mm FWHM), and written as timeseries in CIFTI format for analysis. All fMRI analyses will examine brain regions localized to the cortical subdivisions identified by the recently released HCP multimodal-derived map of 180 cortical parcels [278]. We emphasize this point, as this atlas represents the highest-resolution cortical atlas to date, including 97 new regions. It divides conventionally-recognized structures into numerous sub-regions defined by uniquely demarcated boundaries constructed using each brain's functional connectivity and myeloarchitecture. We also will use a recently-developed sub-cortical/cerebellar map that reveals 358 highly-organized parcels that align with these new cortical regions [279]. Together, these atlases represent the cutting-edge in brain localization.

MRI and Head Motion Total MRI session time is 1h 10 min, of which 50 min involves fMRI data collection. Although this scan duration can be challenging for adolescents who are prone to fidget (especially unmedicated ADHD participants), we have ample experience scanning ADHD teens (R01MH080956, R21HD061915, K23MH070036) and non-ADHD teens for these scan lengths. A mock scanner will acclimate subjects. Framewise Integrated Real-Time MRI Monitoring (FIRMM; www.firmm.io [280]) will prompt staff to discontinue obviously unusable scans (i.e., data with movement >1 2.1 mm voxel); these will be replaced with parallel task versions in the same session. This will be more time/cost-efficient than a 2nd scan. If needed, substitute scans at a proximal session will be done to avoid discarding an entire dataset. Minor head motion or sharp spikes will be addressed using ICA-FIX [281, 282], which isolates/de-noises such signal artifacts and regresses linearly-detrended motion parameters from the HCP-processed timeseries. We have learned in 15+ years of pediatric fMRI experience >90% of adolescent non-ADHD and >80% of ADHD fMRI data meets QC criteria, while roughly 10% of ADHD ultimately can be replaced by a second scan session with careful participant re-training.

Conventional fMRI Analyses Single-subject activation will be quantified with FSL FEAT with FMRIB's Improved Linear Model, using geodesic Gaussian algorithms to estimate autocorrelation and smooth surface-based fMRI data. Explanatory Variables (EVs) will use a double-gamma HRF convolution to translate event onsets in conditions-of-interest into regressors to be fit to the BOLD timeseries. EV contrasts (against other conditions) will create activation maps. Task performance will be considered by 1) separately modeling correct vs. incorrect events, then collapsing across them if SFS/mid-latPFC measurements are unaffected by accuracy, and 2) examining the effect of accuracy for *post hoc* analyses at the group-level.

Functional Connectivity Analyses Graph theory (GT) offers a diverse variety of useful and informative network metrics. In GT, networks are mathematical representations of real-world complex systems. GT metrics parameterize these systems to describe relationships among fMRI-measured region activity profiles [283, 284]. GT metrics range from those that simply quantify how integrated a single brain region is with others in a network or sub-network, to others that capture more complex properties of network structure, integration, segregation, or resilience to insult [215]. Although it is possible to examine thousands of connections among SFS, mid-latPC and other relevant brain network regions, GT also can focus hypothesis-testing on individual brain regions to reduce multiple comparisons demands. Our primary functional connectivity metric will be 'weighted-degree,' which quantifies the number of edges (connections) to a any network node of interest, weighted by their association strength. In this way, we will have a single value per participant for SFS and mid-latPFC parcels that represents nodal functional connectivity strength. When preparing data, we will follow detailed published recommendations to mitigate any head motion signal artifacts [285, 286] on fMRI timeseries data. Because ICA-FIX already will have been applied and motion parameters regressed from the data from HCP processing, we additionally will regress white matter, CSF and global signal from the data, then apply a 0.8 Hz low-pass filter. The residualized timeseries will use partial correlation to form adjacency matrices [287]. Un-thresholded, full adjacency matrices will avoid the arbitrariness of threshold selection and loss of information when binarizing connections.

EWM Training Trial Methodology Considerations Although the primary purpose of the R61 and R33 trials is a to assess target engagement, not clinical efficacy, the major criticisms of prior ADHD WM training efficacy trials noted in reviews of the available literature [109, 112, 113, 115, 134-137] provide design considerations that are germane to any cognitive training trial. These issues are summarized in Table 1, along with our innovations to avoid the same limitations to enhance this project's methodological rigor and potential reproducibility.

Table 3. Methodological Criticisms of Previous WM Training Clinical Trial Design or Interpretation

Issue	Solution
Active placebos in RCTs also can produce clinical improvement, possibly undermining clear understanding of WM training efficacy	Use a carefully-chosen placebo arm, and supplement with other methods for ensuring any gains after EWM training are valid
RCTs do not examine how treatment compliance affects outcome	CACE analysis of the effect of compliance on WM outcome metrics
EWM test performance at trial outcome might be contaminated by practice effects	Ensure stimuli used for training are not used for pre- and post-training fMRI assessment; for all WM neuropsych tests used for assessment, choose those with reliable parallel forms
Near- and far-transfer inconsistently evaluated	Include commonly-used tests for comparability across studies
Not all previous studies evaluated psychiatric comorbidity (e.g., CD/ODD), ADHD DSM-IV clinical subtype, or LD	Conduct full diagnostic interview and assess possible academic disparity with IQ; evaluate outcome moderation effects statistically
The medication status of ADHD participants has been inconsistent and often un-evaluated across studies	Limit to unmedicated ADHD and those on stable, short-acting psychostimulants; use 24 hour "washout"; assess moderator effect
Not clear to what extent age influences one's ability to benefit from executive WM training; possible pubertal confounds	Avoid pre-pubertal children to circumvent major developmental confounds; examine age (or time since puberty onset) moderation
Previous studies typically ignored any effects that individual differences in pre-training WM ability might have on outcome	We will randomly assign participants to active/placebo treatment and examine the role of pre-training EWM ability on outcome

Placebo Condition The strongest criticisms of prior ADHD WM training RCTs are the absence of placebo control, as results could be driven by expectancy effects. Although neural and neurocognitive measures of target engagement that are the focus of this project are less vulnerable to expectancy, we chose to add a placebo training group to both R61 and R33 for methodological rigor and to enhance the certainty of causality inferences. Choice of placebo for WM training trials is challenging because some previously-used WM 'active placebos' have changed brain function [288]. We will use Mahjong and Bejeweled tile games for the placebo condition. These deliver an equivalent 'training time' exposure, are compatible with remote monitoring, the game elements can be presented as a feasible treatment to preserve the blind, and we provide the same coaching experience. We only will use these tile ganes for placebo exercises as they have low EWM demands [196, 197].

Executive WM Training Sessions Each ~50 min EWM training session will include sixteen 3 min EWM exercises (counter-balancing the order of EWM task types and verbal vs. nonverbal versions). To avoid stimulus familiarity effects, the stimulus set for all exercises will be unique each training day, drawn randomly from a large pool. Importantly, EWM training task difficulty will be adaptively increased across the 5 weeks of training based on session-to-session performance. Day 1 EWM training will begin with relatively easy 2-item memory sets. These will quickly ramp up to 4-item stimuli sets across the first 2-3 sessions as each participant attains 80% accuracy for each 3 min exercise. After this familiarization/confidence-building period across the 5 Week 1 sessions, EWM task difficulty manipulations will begin using an adaptive staircase design. Each EWM exercise will manipulate difficulty in different ways. For WM *Updating*, the number of updates per trial will increase from 1 to 4. If a participant achieves proficiency when challenged by 4 WM updates, the speed of each update will be shortened by 100 msec until behavioral gains plateau or a minimum of a 1 sec response window. For WM *Shifting*, the number of shifts per trial will be increased from 1-4, then duration of each response window successfully shortened by 100 msec. For WM *Distractor Filtering*, the number of possible colors used for directed forgetting will be increased from 2 to 4, then response window shortened by 100 msec. For WM *Suppression,* more proactive interference probes will be given at once (from 1 to a max of 4), then 100 msec response window will decreases once consistent optimal performance on 4 probes is attained. Patient differences between stimulus manipulation difficulty level and fastest response window size will provide improvement indices to characterize each subject. All adjustments will be based on running weighted averages of trial accuracy and reaction time, continually saved/updated by the E-Prime stimulus presentation software.

Engagement/Motivation Cognitive training gain are believed to be optimized when patients approach trials with consistent high motivation [43]. We have incorporated social and minor financial incentives for engagement (rapid response time consistency) and improvements in each session. It is hoped this also will partially reduce boredom. The coach also will assess participants' subjectively-rated motivation on a 10-point Likert scale.

Remotely-Supervised EWM Training Our EWM training delivery is designed to maximize compliance. For a typical family with late middle- or high-school age children who have many, often-conflicting priorities, visits

to the Olin NRC 4 times a week for 5 weeks will impossibly compromise study feasibility. Consistent with guidelines we have proposed for other forms of remotely-supervised interventions [291, 292], WM training will be done 'at home' on a study-provided Lenovo TP X1 Tablet with a cellular modem and Verizon data plan. Tablets will run GoToAssist's 'RemoteDesktop' software so Olin NRC staff can remotely administer EWM practice sessions. Study staff can remotely start the session (even when the tablet is powered down), initiate Skype videoconferencing for a 'virtual presence' during training, and load pre-configured E-Prime EWM task training exercises. Training behavioral data are transferred daily to Olin NRC servers for archiving via FTP. Each tablet is password-locked and will run Absolute software that provides GPS location and the ability to erase all data in case of loss or theft. We successfully used these procedures for our *n*=7 EWM training ADHD pilot study. This, and our other success with supervised ADHD WM training [103], validates the feasibility of the novel training delivery approach. *Coaching* During each session, a project staff member will interact with each participant through this virtual connection. As in other types of WM training, such a 'coach' works closely with families to help problem-solve unanticipated barriers to regular practice.

R61 and R33 Hypothesis-Testing General Comments Missing data bias tests will use Little's multivariate test, as well as univariate counterparts [293]. Missing data will be dealt with using Full Information Maximum Likelihood algorithms [294] or pattern mixture modeling, as appropriate [295]. Outlier and specification error diagnostics will be examined. All data will be examined to ensure they meet statistical test assumptions. If not, we will use robust estimators based either on Huber-White estimation, bootstrapping, or methods described in Wilcox [296]. Group fMRI analyses will use PALM [297] – a CIFTI data format-compatible analysis tool that applies threshold-free cluster enhancement for surface-based fMRI analysis and multiple comparisons corrections with permutation-based inference. All group analyses will use age as a covariate to account for any maturational differences. We will examine sex differences as per NOT-OD-15-102.

R33 Goals The 3-year R33 study will seek to replicate R61 target engagement evidence in a larger sample, using analyses robust to factors that potentially might mitigate outcomes. It also will determine if EWM training target engagement can be linked to clinically-relevant behavioral change. We do not intend the R33 to be a formal efficacy test; it is intended only to inform a decision about the potential of an EWM training intervention for a subsequent efficacy trial testing. Secondary goals are to inform the design of possible future efficacy studies by a) learning if ADHD EWM gains represent resolution of brain function deficits compared to non-ADHD, assessed by recruiting a demographically-matched *n*=40 non-ADHD comparison adolescent sample who will undergo 2 evaluations, also ~5 weeks apart, b) determining whether EWM gains generalize to non-trained EWM tasks, c) examining the effect of intervention non-adherence on target engagement, and d) identifying ADHD characteristics that might moderate EWM training outcomes which could influence the design of subsequent efficacy research.

Gene Banking We envision a need to have whole-genome data in this richly phenotyped dataset to answer emerging questions. Saliva sampling costs were budgeted and samples will be stored at Olin for future use.

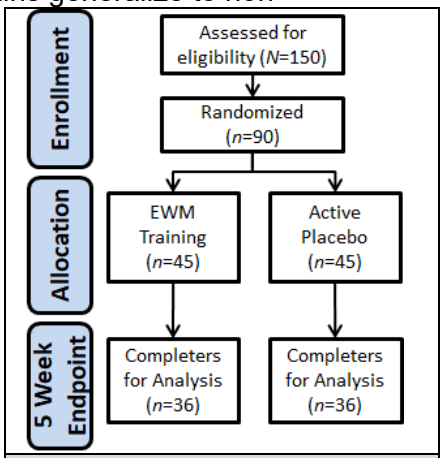

Fig 11. R33 CONSORT diagram

R33 Trial Methodology The R33 will use the same R61 EWM training intervention. As such, it will have the same randomization, coaching, discontinuation rules, allocation concealment, 5-week baseline/endpoint assessment timeframe, target 'dose' of 20-25 EWM training or 'sham training' placebo sessions, and www.clinicaltrials.gov registration. After 20% expected attrition, there should be 36 ADHD 'completers' in each arm (Fig. 11). Unlike the R61, the R33 also will examine a primary clinical endpoint (ADHD symptom severity) and secondary outcomes (3 psychosocial function assessment measurements; see Table 1). The R33 also will formally evaluate *Training Non-Adherence* using CACE analyses of compliance effects [300] on target engagement. We define 'protocol non-adherence' as <80% session completion, with the goal of at least 20 sessions by an endpoint 5 weeks after trial start. Any change to a participant's type/dose of medications or adding another form of treatment (e.g., neurofeedback, etc.) also will be non-compliance. 'Procedural non-adherence' is defined as poor quality engagement, as rated both subjectively and objectively by the training coach via virtual observation of each session (see appended **Intervention Manual**).

R33 Hypothesis-Testing We remind reviewers PHS-CT supplement Section 4 contains the detailed hypothesis-testing plan, including several important supplemental analyses to greatly enhance study impact.

R33 Power Analysis Power for this study's ANCOVA analyses of treatment outcome is primarily impacted by three factors – 1) sample size, 2) effect size *d*, and 3) the strength of association R^2 between the dependent variable and any model covariates. Figure 12 shows ANCOVA power analysis estimates for the expected 81 of 90 R33 completers. We see power will be at or greater than 80% for Cohen's $d \geq 0.57$ effect sizes for any ANCOVA test where the R^2 for the covariate terms alone falls above 0.16. These anticipated R^2 values we tested are realistic. Quantile analysis found a convincing majority (85%) of the R^2 distribution values across all the R61 trial's functional connectivity ANCOVA models were well above 0.16. In sum, the R33 design is adequately powered for a credible replication study. Its power will suffice to confirm R61 findings even if the new R33 ADHD sample shows the same result at a slightly lower effect size magnitude. Alternatively, we could decrease α to .01 for any specific brain connectivity replication test while maintaining sensitivity to a comparable $d = 0.68$ effect size magnitude (i.e., approximately the same as the smallest effects reported in the R61).

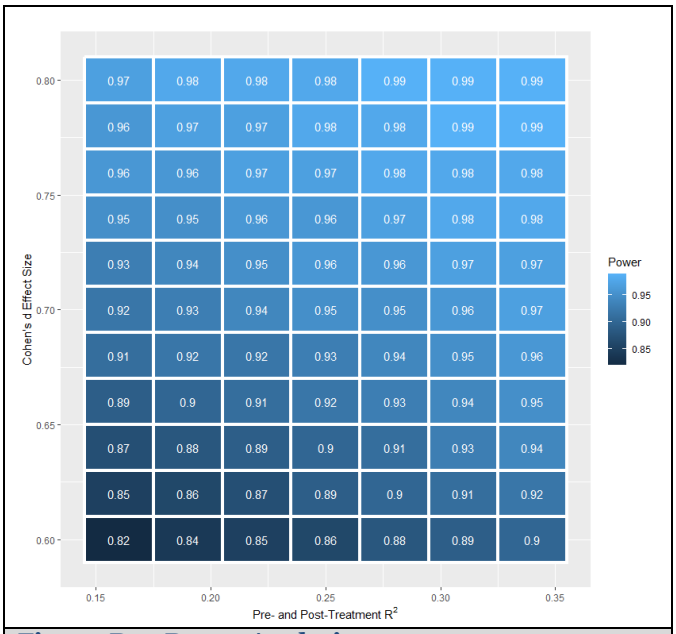

Fig 12. R33 Power Analysis

R33 Impact on Decision to Continue Research The R33 phase results will inform a decision about whether the intervention shows potential for improving clinical outcomes. A large-scale efficacy trial will be recommended only if a) R61 behavioral and biological target engagement evidence is replicated in the new R33 ADHD sample, and b) if there is evidence for a meaningful association between EWM training-induced target engagement and credible ADHD clinical changes over the brief 5-week R33 trial. The magnitude of any clinical changes (great or small) also will be instructive in deciding whether or not this intervention development research should advance in future studies to efficacy testing. Moreover, the specific endpoints that show improvement will be the focus of any subsequent RCT proposal. Secondary R33 analyses will confirm the remotely-supervised EWM training approach has the anticipated acceptability, tolerability, and retention.

Key Study Design Choices to Maximize Robust Results

1) Sample Sizes – Careful statistical power analyses were done to support adequate sampling for confidence that both R61 and R33 phase results would provide a definitive Yes/No answers about target engagement.
2) Use of Placebo Control – Both R61 and R33 include random assignment to placebo for strongest inference possible about whether target engagement is due to the intervention. Moreover, the behavioral and neural targets are objective and likely robust to any expectancy effects seen in prior research.
3) How To Handle ADHD WM Deficits – Pre-existing cognitive ability has an equivocal relationship to training-related cognitive gains [301-303] and there is no published guidance as to what effect ADHD deficits might have on training outcomes. As such, our R33 will ensure any evidence for target engagement is robust to sample variability in pre-training EWM ability levels.
4) Other ADHD Clinical Heterogeneity – There are many ADHD clinical characteristics (co-morbidities, medication histories, etc.) and suspected etiological biomarkers (including variable WM expression) that might influence EWM target engagement. If the R61/R33 is successful, supplemental analyses will begin to assess possible moderation effects to inform future sampling plans and research design.
5) EWM Tasks for Training vs. Brain Target Assessment? – The only way to be confident neural target engagement reflects EWM training effects is to use the exact same tasks for both fMRI and training. However, it remains important to show EWM is training actual 'ability' and not just maximizing specific task performance. As such, we will examine 'near transfer' of training gains to 4 non-trained EWM *Shifting*, *Updating*, *Distractor Filtering* and *Suppression* tests (Table 2). We also will conduct exploratory 'far transfer' analyses of simple WM short-term storage and any training effects on other executive function [304-306] tasks.
6) Interpretation of EWM Training Effects – We will compare ADHD training effects to data from non-ADHD participants to better understand trial outcomes. We are open to the possibility that brain changes either

resolve abnormalities, or alternatively that they build upon intact neural systems to enhance ability, thereby 'compensating' for other deficits. Either underlying mechanism would support future efficacy research.

7) Theoretical Advances – PHS-CT Section 4 describes several supplemental analyses using pooled R61 and R33 trial outcome data that might refine our conceptual model of how the EWM intervention works.

Other Study Design Features For Rigor/Reproducibility This R61/R33 provides a built-in replication by design. We use strong RCT design principles and we avoid many methodological pitfalls of prior ADHD WM training RCTs. We base sampling attrition estimates on direct experience to ensure our final sample size will be adequate; statistical power was carefully confirmed for our planned hypothesis-testing, using conservative estimates. Only a small handful of treatment targets will be tested for engagement, requiring a very specific, narrow path towards study milestone achievement. The R61 and R33 use the same intervention to ensure continuity between the two study phases. Protocol compliance will be closely monitored and its effects on target engagement will be formally evaluated in the R33 analysis plan. Clinical and cognitive tests have high test-retest reliability and are validated for adolescents. We use well-validated, piloted fMRI tasks with rigorous QC procedures to obtain high-quality, movement free MRI data. HCP methods offer the most accurate localization of brain function. We avoid the interpretive confounds of assessing ADHD patients' EWM ability when they are medicated. Data will be made available in NDA repositories so other investigators will be free to re-examine our results, or extend findings with new analyses.

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