NeuroImage: Clinical 10 (2016) 274–282

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Original Research Article

Dissociation of working memory impairments and attention-deficit/hyperactivity disorder in the brain

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ARTICLE INFO

Article history:
Received 16 September 2015
Received in revised form 20 November 2015
Accepted 7 December 2015
Available online 10 December 2015

Keywords:
ADHD
n-Back
fMRI
Longitudinal
Working memory

ABSTRACT

Prevailing neuropsychological models of attention-deficit/hyperactivity disorder (ADHD) propose that ADHD arises from deficits in executive functions such as working memory, but accumulating clinical evidence suggests a dissociation between ADHD and executive dysfunctions. This study examined whether ADHD and working memory capacity are behaviorally and neurobiologically separable using functional magnetic resonance imaging (fMRI). Participants diagnosed with ADHD in childhood who subsequently remitted or persisted in their diagnosis as adults were characterized at follow-up in adulthood as either impaired or unimpaired in spatial working memory relative to controls who never had ADHD. ADHD participants with impaired spatial working memory performed worse than controls and ADHD participants with unimpaired working memory during an n-back working memory task while being scanned. Both controls and ADHD participants with unimpaired working memory exhibited significant linearly increasing activation in the inferior frontal junction, precuneus, lingual gyrus, and cerebellum as a function of working-memory load, and these activations did not differ significantly between these groups. ADHD participants with impaired working memory exhibited significant hypoactivation in the same regions, which was significantly different than both control participants and ADHD participants with unimpaired working memory. These findings support both a behavioral and neurobiological dissociation between ADHD and working memory capacity.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, affecting an estimated 11% of children (Visser et al., 2014) and 5% of adults (Kessler et al., 2006). Patients with ADHD exhibit significant impairments on executive function (EF) tasks, with the strongest impairments observed on tasks measuring working memory, response inhibition, vigilance, and planning (Willcutt et al., 2005). Subsequent studies, however, reported that up to half of individuals with ADHD have intact EF (Biederman et al., 2004, 2006; Nigg et al., 2005). Furthermore, when executive dysfunctions are identified in ADHD patients they remain stable over long periods of time (Biederman et al., 2007, 2008; Miller et al., 2012). The well-documented heterogeneity among ADHD patients in performance on measures of EF (Biederman et al., 2004, 2006; Doyle et al., 2005; Fair et al., 2012; Sonuga-Barke et al., 2010) suggests that ADHD and EF deficits, such as working memory impairments, are behaviorally separable and thus support the hypothesis that they may also be neurobiologically dissociable.

Behavioral and neuroimaging studies of ADHD have examined differences in a range of EF abilities, including working memory or the ability to maintain and manipulate information over a short period of time. Studies of verbal and visuo-spatial working memory have consistently observed behavioral deficits in individuals diagnosed with ADHD (Burgess et al., 2010; Gau and Shang, 2010; Kofler et al., 2010; Rapport et al., 2008; Rommelse et al., 2008; Toplak et al., 2005). Neuroimaging studies of both visuo-spatial and verbal working memory have observed brain activation differences (both increased and decreased activation) in frontal–parietal circuits in people diagnosed with ADHD relative to typically developed controls (Bayerl et al., 2010; Chantiluke et al., 2015; Cubillo et al., 2014; Fassbender et al., 2011; Ko et al., 2013; Kobel et al., 2009; Li et al., 2014; Silk et al., 2005; Valera et al., 2005, 2010; Vance et al., 2007).

Working memory is conceptualized as being multi-componential, with domain-specific mechanisms for the short-term maintenance of verbal and visuospatial information, and a central executive mechanism

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http://dx.doi.org/10.1016/j.nicl.2015.12.003

(Baddeley and Hitch, 1974). The verbal and visuospatial maintenance mechanisms can be assessed, respectively, by digit or block span measures. In contrast, working memory capacity measures have been developed to assess the executive mechanism by requiring both maintenance and manipulation of information (Conway et al., 2003; Daneman and Carpenter, 1980; Engle and Kane, 2004). Indeed, variation in working memory capacity has been strongly associated with variation in many forms of higher-level cognition, including reading comprehension, problem solving, and inhibitory control (Conway et al., 2003; Daneman and Carpenter, 1980; Engle and Kane, 2004).

Patients with ADHD are especially at risk for deficits in the executive mechanism of working memory, and this has been demonstrated in the n-back task. In this task, participants view a series of stimuli, such as letters, and respond to a designated target. In the 0-Back condition, participants respond to a constant target (such as "X"), but in 1-back, 2-back, and 3-back conditions they respond to any letter that matches the letter seen 1, 2, or 3 letters ago. Thus, the 0-back and 1-back conditions require maintenance of a single target in mind, whereas the 2-back and 3-back conditions require constant updating and manipulation of multiple items. Correspondingly, some studies have reported that ADHD patients are unimpaired in the lower-load (0-back and 1-back) conditions, but impaired at the higher-load conditions that stress working memory capacity and demand executive functions (Cubillo et al., 2014; Kobel et al., 2009). Thus, the observed impairments in working memory capacity in ADHD in prior studies are likely reflective of central executive impairments rather than deficits in the maintenance of domain specific information (Baddley, 1992, 2003).

A paradox, however, is that multiple neuroimaging studies reporting activation differences in ADHD on working memory tasks also reported an absence of significant behavioral differences on the same tasks during the neuroimaging (Chantiluke et al., 2015; Fassbender et al., 2011; Ko et al., 2013; Li et al., 2014; Valera et al., 2005, 2010; Vance et al., 2007). One possible explanation for the apparently paradoxical results concerning working memory performance and brain activation across studies is that there is a fundamental heterogeneity among ADHD patients that yields different findings depending upon the proportion of patients with impaired or intact working memory represented in any given sample. The observations that fully half of ADHD patients are unimpaired on any particular measure of executive function (Biederman et al., 2004, 2006; Nigg et al., 2005) raises the concern that such diversity among ADHD patients can lead to misleading findings when the diversity is not accounted for.

In the current study, we evaluated working memory capacity and its related neurobiological substrates in well-characterized, longitudinally followed adults diagnosed with and without ADHD at initial baseline assessment in childhood. Participants who were originally diagnosed with ADHD either persisted in their diagnosis or remitted from their diagnosis as adults. Thus, this cohort afforded the possibility to evaluate the relevance of the active diagnostic ADHD status in relationship with impairments in working memory capacity and related neurobiological mechanisms.

We recorded blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) data while participants performed a verbal n-back working memory task that parametrically varied working memory demands, which results in monotonic increases of activation in prefrontal and parietal neocortical regions (Braver et al., 1997). We characterized participants who had ADHD in childhood as either impaired or unimpaired relative to controls on an independent measure of spatial working memory. If ADHD and a core executive function – working memory capacity – are dissociable, we expected that behavioral and brain differences would only be observed in the subset of patients who had reduced working memory capacity.

2. Materials and methods

2.1. Participants

Participants (N = 54) from longitudinal family studies of boys (N = 29) and girls (N = 25) diagnosed with and without ADHD in childhood (6–17 years of age at baseline) (Biederman et al., 1992, 1996, 2012) volunteered for this study. Participants who were adopted, diagnosed with psychosis or autism, had an inadequate command of the English language, a full scale IQ < 80, or any major sensorimotor disability were excluded from the original ascertainment. All participants diagnosed with ADHD at the initial baseline assessment met DSM-III-R criteria for ADHD in childhood. Functional and structural neuroimaging was conducted approximately 16 years after the original baseline assessment. Data from two ADHD participants were not included in the analyses due to complications with the experimental paradigm at the scanner. Two additional participants were excluded from analyses because 1 control participant met diagnostic criteria for ADHD at follow-up and 1 ADHD participant had a poorly documented baseline diagnosis. The final participants included 17 controls never diagnosed with ADHD, 12 ADHD participants who persisted in their ADHD diagnosis into adulthood, and 21 ADHD participants who no longer met a subthreshold diagnosis of ADHD in adulthood. Eight participants were currently being treated with stimulant medications. All participants refrained from taking ADHD medications 24 hours prior to scanning. We obtained written informed consent from all participants following complete description of the study according to the protocols approved by the human research committees at Massachusetts General Hospital and the Massachusetts Institute of Technology.

2.2. Assessment procedures

Diagnostic assessment at the time of the scan relied on the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). To assess childhood diagnoses, such as ADHD, we used modules from the DSM-IV modified K-Kiddie Schedule for Affective Disorders and Schizophrenia-Epidemiological Version (K-SADS-E) (Orvaschel, 1987). We determined the current diagnostic status (e.g., persistent versus remitted) by the number of symptoms of ADHD derived form the SCID. Patients with persistent ADHD met full or subthreshold criteria for DSM-IV ADHD. We defined subthreshold ADHD as endorsing at least four ADHD symptoms in either the inattentive or the impulsive/hyperactive criteria lists and meeting all other diagnostic criteria such as age at onset. Both controls and remitted ADHD did not meet subthreshold criteria in adulthood.

At the time of scanning, participants were administered the Spatial Working Memory subtest of the Cambridge Neuropsychological Test Assessment Battery (CANTAB) (Sahakian and Owen, 1992) and the Color-Word Interference and Trail Making subtests from the Delis Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) to measure executive function performance and the Wechsler Abbreviated Intelligence Scale (WASI) (Wechsler, 1999) (scaled scores were analyzed) as a measure of IQ. At the initial (childhood) baseline assessment, participants were administered the Wechsler Intelligence Scale for Children — Revised (WISC-R) (Wechsler, 1974) subtests of digit span, coding, and arithmetic which yield a Freedom from Distractibility Index. This Index is similar to the Working Memory Index in later versions of the WISC, and thus constitutes the measure most like the working memory measures of interest employed in the current adult study.

2.3. Participant groups

ADHD participants were separated into subgroups based on working memory performance on the independently obtained measure of spatial working memory collected outside of the scanner. An ADHD patient was categorized as unimpaired or impaired if the individual scored above or below, respectively, 1.5 standard deviations of the mean

control performance CANTAB Spatial Working Memory subtest. Similar cut-offs for designating an individual impairment have been used in prior studies of ADHD in children and adults (Biederman et al., 2004, 2006; Nigg et al., 2005). On this basis there were three groups: Control group (N = 17), Unimpaired ADHD group (N = 16), and Impaired ADHD group (N = 17).

2.4. N-back behavioral task during neuroimaging

Participants performed a 4-level parametric block design n-back working memory task with 0-back, 1-back, 2-back, and 3-back blocks during a single scanning run while in the scanner. Blocks lasted 32 s and each memory load was repeated 4 times in pseudorandom order, resulting in approximately 8.5 min of scanning. Each block began with the presentation of an instruction screen for 2 s indicating the current memory load. The instruction screen was followed by the presentation of 15 2 s trials. Each trial consisted of the presentation of an upper case letter in the middle of the screen for 1.5 s followed by a fixation cross for 0.5 s. Participants responded to each stimulus by pressing one of two buttons with a scanner-compatible response box using the index finger to respond to target stimuli and the middle finger to non-target stimuli. The target in the 0-back condition was the letter "X". In the 1-back, 2-back, and 3-back conditions, targets were any stimulus identical to the stimulus presented one, two, or three trials before.

2.5. Statistical analyses

Neuropsychological variables and behavioral performance on the n-back task were compared across groups using analysis of variance (ANOVA) followed by *post hoc* Tukey–Kramer pairwise comparisons to correct for multiple comparisons. To identify significant clusters in all functional neuroimaging comparisons we used an uncorrected height threshold of $z > 2.57$ ($p < 0.005$) combined with Familywise Error (FWE) correction at the cluster level using FSL's *cluster* algorithm, resulting in an overall corrected $p < 0.05$. We analyzed the linear effects of load (0-back < 1-back < 2-back < 3-back) within each group and then compared those effects directly between groups.

2.6. Scanning

Neuroimaging data were collected on a 3 Tesla Siemens Trio scanner using a 32-channel head coil. Single-shot echo planar imaging (EPI) data were collected using a pulse sequence with a field of view of 64 × 64 mm, echo time (TE) of 30 ms, flip angle of 90°, repetition time (TR) of 2000 ms resulting in a resolution of 3.0 mm isotropic voxels. The first four volumes were discarded to allow for T1 equilibration. Thirty-two AC–PC aligned slices were acquired during a single run that lasted approximately 8.5 min. Whole brain T1-weighted magnetization-prepared rapid gradient-echo (MP RAGE) structural scans were acquired with a FOV of 256 × 256 mm, TE of 3.48 ms, flip angle of 90°, and TR of 2530 ms, resulting in 1 mm isotropic voxels.

2.7. fMRI preprocessing and analyses

Preprocessing and data analyses were performed using the following software packages: Nipype (Gorgolewski et al., 2011) and standard preprocessing pipelines from BIPs, Nipy (Millman and Brett, 2007), FSL v5.0 (Smith et al., 2004), Analysis of Functional NeuroImages (AFNI) (Cox, 1996), FreeSurfer (Dale et al., 1999), Advanced Normalization Tools (ANTS) (Avants et al., 2008), and artifact detection toolbox (ART — as implemented in Nipype). We created cortical surfaces and subcortical segmentations using FreeSurfer and verified their quality via visual inspection. Simultaneous slice timing and motion correction were performed using default parameters of the Nipy algorithm, aligning all volumes to the first volume of the run using a rigid body affine transformation (Roche, 2011). Intensity outliers in the functional time series were interpolated using the *3dDespike* algorithm from AFNI. We applied a high pass temporal filter (1/128 Hz) and spatially filtered functional data using the FSL *SUSAN* algorithm with a 5 mm FWHM kernel. Functional volumes that either had a global intensity that exceeded 3 standard deviations of the mean intensity of the time series or greater than 1 mm of composite frame-to-frame displacement were flagged as outliers by ART to be regressed out of the first level design matrices as separate regressors of no interest for each outlier time point consisting of zeros and a one at the flagged time point. A mean functional image was coregistered to the structural scans using FreeSurfer's *bbregister* algorithm.

First-level analyses were performed in FMRIB's Software Library (www.fmriib.ox.ac.uk/fsl) according to a general linear model approach. Participant specific models included event and nuisance regressors. Event regressors consisted of separate regressors for each memory load block (0-back to 3-back) convolved with FSL's double gamma hemodynamic response function with duration of 32 s. Nuisance regressors included motion parameters (x, y, z translations; pitch, roll, yaw rotations) and outlier regressors identified by ART. Additional covariates at the group level were included to control for potential confound variables including age, sex, and smoking status. Each participant's contrast effect size (copes) and variance files (varcopes) were normalized to the study-specific template. Group-level analyses were performed using a mixed effects general linear model in the study specific template space using FSL's *flameo*.

2.8. Study-specific template

To optimize normalization for subsequent group comparisons we created a study-specific template using ANTS. We skull stripped the structural scans from 20 participants (10 control and 10 ADHD). The skull-stripped brains were then rigid-body (six degrees of freedom) transformed to Montreal Neurological Institute (MNI) space. We used this first pass to establish our template generation close to a commonly used reference frame (MNI space) and to provide an initial common registration during template construction to mitigate large spatial shifts between participants. After the study-specific template had been created each participant's original skull stripped brain was normalized to the template using the non-linear symmetric diffeomorphic mapping implemented by ANTS. The use of custom-made study specific templates has been shown to improve registration over direct pairwise registration (Klein et al., 2010).

3. Results

3.1. Working memory abilities

By design, performance on the CANTAB spatial working memory subtest differed among the groups ($F(2,46) = 31.7$, $p < 0.0001$). *Post hoc* pairwise comparisons using the Tukey–Kramer method demonstrated that both the Control and the Unimpaired ADHD groups had scores that were significantly better than the Impaired ADHD group (Control vs. Impaired ADHD groups: $q = 8.60$, $p < 0.0001$; Unimpaired ADHD vs. Impaired ADHD groups: $q = 8.09$, $p < 0.0001$). The Control and Unimpaired ADHD groups did not exhibit significantly different scores ($q = 1.61$, $p = 0.79$) (Fig. 1A).

Similar group differences in the WISC-R Freedom from Distractibility Index were observed during original baseline assessment in childhood, the measure most related to working memory at the time ($F(2,47) = 3.9$, $p = 0.02$). Tukey–Kramer *post hoc* pairwise comparisons showed that both the Control and Unimpaired ADHD groups had better performance than the Impaired ADHD group at baseline, but that the Control and Unimpaired ADHD groups did not differ significantly (Control vs. Impaired ADHD groups: $q = 3.29$; $p = 0.04$; Unimpaired ADHD vs. Impaired ADHD groups: $q = 3.31$, $p = 0.05$; Control vs. Unimpaired ADHD groups: $q = 0.18$, $p = 0.99$) (Fig. 1B).

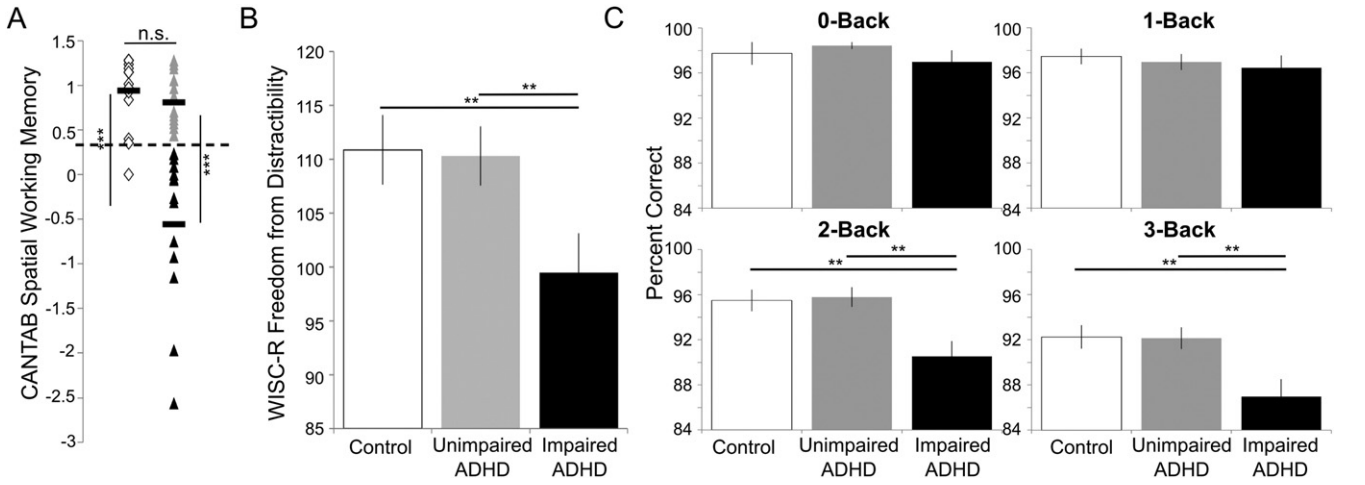

Fig. 1. (A) Participants diagnosed with ADHD in childhood (triangles) were characterized as similar or dissimilar to controls (open diamonds) by their scores on the CANTAB spatial working memory task scoring either above (unimpaired working memory; grey triangles) or below (impaired working memory; black triangles) 1.5 standard deviations of the mean of the control performance (horizontal dashed line). (B) The Impaired ADHD group (black bar) performed worse relative to the Control (white bar) and Unimpaired ADHD (grey bar) groups, who were not statistically different from each other on the WISC-R Freedom from Distractibility factor obtained at baseline assessment approximately 16 years ago. (C) All three groups had similar behavioral performance in the 0- and 1-back conditions. The Impaired ADHD group (black bars) performed worse relative to Control (white bars) and Unimpaired ADHD (grey bars) groups, who were not statistically different from each other, in the 2- and 3-back conditions. *** $P < 0.0001$; ** $P < 0.01$. Error bars represent ± standard error of the mean.

The Unimpaired ADHD group consisted of 9 remitted and 7 persistent ADHD participants, while the Impaired ADHD group consisted of 12 remitted and 5 persistent ADHD participants. The current diagnostic status was unrelated to the grouping based on the CANTAB spatial working memory task scores following a chi-squared test for independence ($\chi^2_{(1)} = 0.24$, $P = 0.62$).

The Unimpaired and Impaired ADHD groups both differed significantly from the Control group but did not differ from each other on numbers of current ADHD symptoms or ADHD symptoms at baseline (Table S1). The groups differed in their full-scale IQ scores ($F(2,47) = 12.6$, $p < 0.001$). Tukey–Kramer *post hoc* pairwise comparisons showed that the Control group had higher full-scale IQ scores compared to the Impaired ADHD group ($q = 6.93$, $p < 0.0001$), but not the Unimpaired ADHD group ($q = 3.07$, $p = 0.13$). The Unimpaired ADHD group had significantly higher full-scale IQ scores compared to the Impaired ADHD group ($q = 3.89$, $p = 0.01$). The two ADHD groups were not significantly different from each other or from the control group on executive tests of inhibition (D-KEFS color-word interference: $F(2,47) = 1.6$, $p > 0.05$) or switching (D-KEFS trail making: $F(2,47) = 0.75$, $p > 0.05$) (Table S1). Because of the IQ differences, we performed all following neuroimaging analyses both with and without including IQ as a regressor in the general linear model at the group level.

3.2. N-back working memory performance during neuroimaging

Accuracy of performance on the n-back declined as a function of working memory load (main effect of load: $F(3,141) = 47.3$, $p < 0.0001$) and differed among groups (main effect of group: $F(2,47) = 6.2$, $p = 0.003$). The group differences occurred in the more demanding 2-back and 3-back conditions relative to the less demanding 0-back and 1-back conditions (group × load interaction: $F(6,141) = 2.9$, $p = 0.008$). Tukey–Kramer *post hoc* pairwise comparisons showed the Impaired ADHD group performed worse than the Control group (2-back: $q = 4.36$, $p = 0.005$; 3-back: $q = 3.96$, $p = 0.01$) and the Unimpaired ADHD group (2-back: $q = 4.69$, $p = 0.006$; 3-back: $q = 4.08$, $p = 0.02$) in the 2-back and 3-back conditions, but did not differ in the 0-back and 1-back conditions (all $q < 1.9$, all $p > 0.42$). The Control and Unimpaired ADHD groups did not differ significantly in performance from one another at any memory load (all $q < 0.81$, all $p > 0.85$) (Fig. 1C). Performance in the more demanding verbal 2-back and 3-back conditions from the scanning session was highly correlated with performance on the spatial working memory measure ($r > 0.50$, $p < 0.0003$).

3.3. N-back working memory neuroimaging activations

3.3.1. Within group — linear comparisons

A linear contrast across increasing memory load (0-back < 1-back < 2-back < 3-back) showed significantly increasing activation in bilateral dorsolateral prefrontal cortex, intraparietal sulci, anterior insula, pre-supplementary motor area, and cerebellum in all three groups (Fig. 2) (Table S2).

3.3.2. Between group — linear comparisons

The Control group exhibited significantly greater linear increases in activation across memory loads than the Impaired ADHD group in the left inferior frontal junction, precuneus, supracalcarine cortex, lingual gyrus, and cerebellum (Fig. 3A). The Unimpaired ADHD group also exhibited significantly greater linear increases in activation across memory loads than the Impaired ADHD group in the right dorsal lateral prefrontal cortex extending medially into the right pre-supplementary motor area, cingulate gyrus, left inferior frontal junction, left caudate, thalamus, left lingual gyrus, and cerebellum (Fig. 3B) (Table S2). There was no significant difference between the Control group and Unimpaired ADHD group when they were compared directly (Fig. 3C). No group differences in decreasing activation with increasing memory load survived corrections for multiple comparisons. Similar differences among the groups were observed when IQ was added as a covariate to the general linear model (Fig. S1) and when participants who were currently taking stimulant medications were removed (Fig. S2).

In order to better characterize the significant linear differences between groups, we extracted the contrast parameter estimates for each working memory load from the left inferior frontal junction identified clusters that differed significantly between the Control and Impaired ADHD groups and between the Unimpaired and Impaired ADHD groups (there were no significant differences between the Control and Unimpaired ADHD groups) (Fig. 4). Both the Control and Unimpaired ADHD groups exhibited progressively increasing activation with increasing working memory load (0-back to 3-back). The Impaired

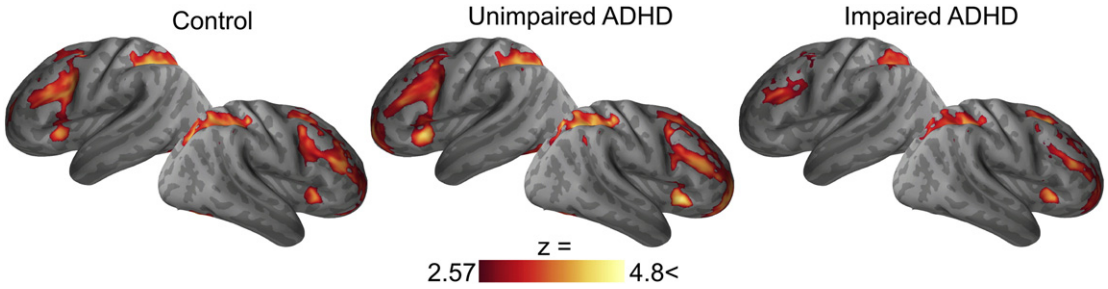

Fig. 2. Increases in BOLD fMRI activation with linear changes in working memory load (3-back > 2-back > 1-back > 0-back). All three groups exhibited linear increases in activation with increasing working memory loads in bilateral dorsolateral prefrontal, intraparietal, insula, precuneus, and pre-supplementary cortices. Uncorrected height threshold of $P < 0.005$ ($z > 2.57$), whole-brain cluster corrected for multiple comparisons, corrected $P < 0.05$.

ADHD group showed little growth of activation across loads in the same region, although activation for the 0-back condition was almost identical across groups.

4. Discussion

Deficits in working memory capacity, a core executive function, were dissociated from ADHD both behaviorally and neurobiologically. Behaviorally, CANTAB spatial working memory capacity and n-back verbal working memory capacity were unrelated to current ADHD diagnostic status. Neurobiologically, ADHD patients with unimpaired working memory exhibited the same increases of activation, as a function of verbal working-memory load, as did control participants in prefrontal, precuneus, lingual, and cerebellar regions (there were no significant differences between these groups). In contrast, ADHD patients with impaired working memory exhibited significantly reduced activations in most of these regions relative to both the control and unimpaired ADHD groups. The sparing or compromise of working memory in adulthood was strongly foreshadowed by sparing or compromise of related abilities measured about 16 years beforehand in childhood. These findings further support the dissociation between dysfunction in a core executive function, working memory capacity, and ADHD.

4.1. Behavioral dissociations between working memory and ADHD

Spatial and verbal working memory tasks were used to group and evaluate the neurobiology of working memory capacity impairments, respectively. Working memory for spatial and verbal information are thought to be independent systems utilizing distinct neural substrates (Smith and Jonides, 1998; Thomason et al., 2009), but both spatial and verbal working memory are often impaired in ADHD (Alderson et al., 2013; Martinussen and Tannock, 2006; Rapport et al., 2008). Perhaps more relevant for ADHD is not the spatial or verbal nature of the stimuli, but rather the *amount* of goal-relevant information to be both maintained and manipulated. Simple short-term maintenance of a small amount of information (e.g., digit span) is thought to depend on modality-specific neural networks reflecting both dorsal/ventral and hemispheric specialization (Smith and Jonides, 1998; Wager and Smith, 2003; however see Nystrom et al., 2000). In contrast, maintenance and manipulation of a larger amount of information is thought to reflect central executive capability (Baddley, 1992), an operation with a potentially common neural substrate (D'Esposito et al., 1995; Nystrom et al., 2000).

In the present study, the critical factor in whether an ADHD patient was impaired or unimpaired was not the verbal or spatial nature of the material, but rather the executive processes invoked by working memory conditions that required maintenance and manipulation of

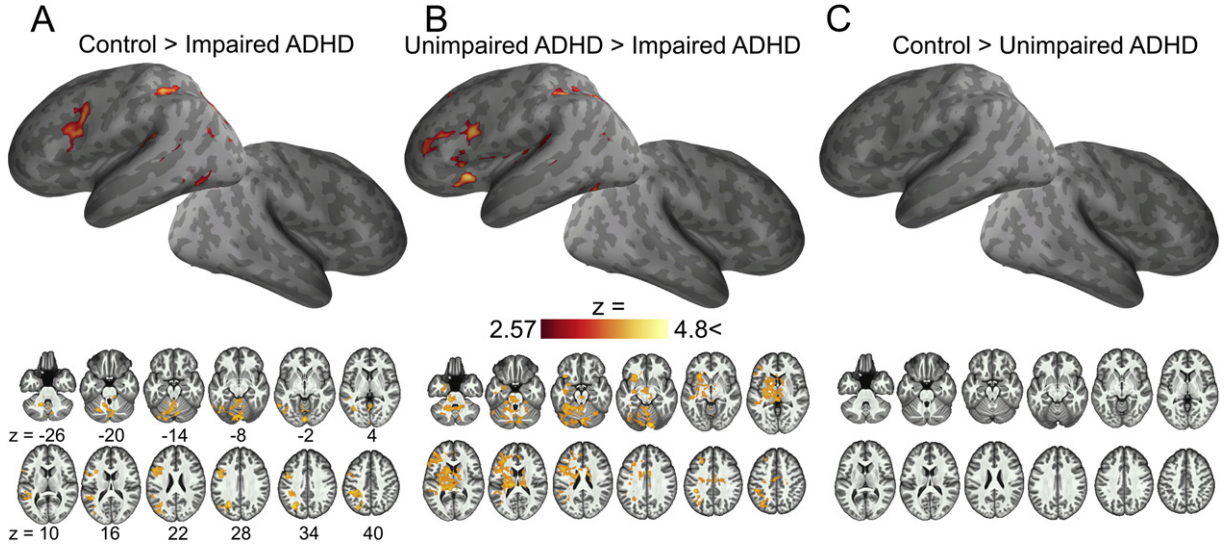

Fig. 3. (A) The Control group exhibited significantly greater linear increases in activation across working memory loads than the Impaired ADHD group in left inferior frontal junction, precuneus, supracalcarine cortex, lingual gyrus, and cerebellum. (B) The Unimpaired ADHD group exhibited significantly greater linear increases in activation across working memory loads than the Impaired ADHD group in the cingulate gyrus, left inferior frontal junction, left caudate, thalamus, left lingual gyrus, and cerebellum. (C) There were no significant differences in activation between the Control and Unimpaired ADHD groups. Uncorrected height threshold of $p < 0.005$ ($z > 2.57$), whole-brain cluster corrected for multiple comparisons, corrected $p < 0.05$.

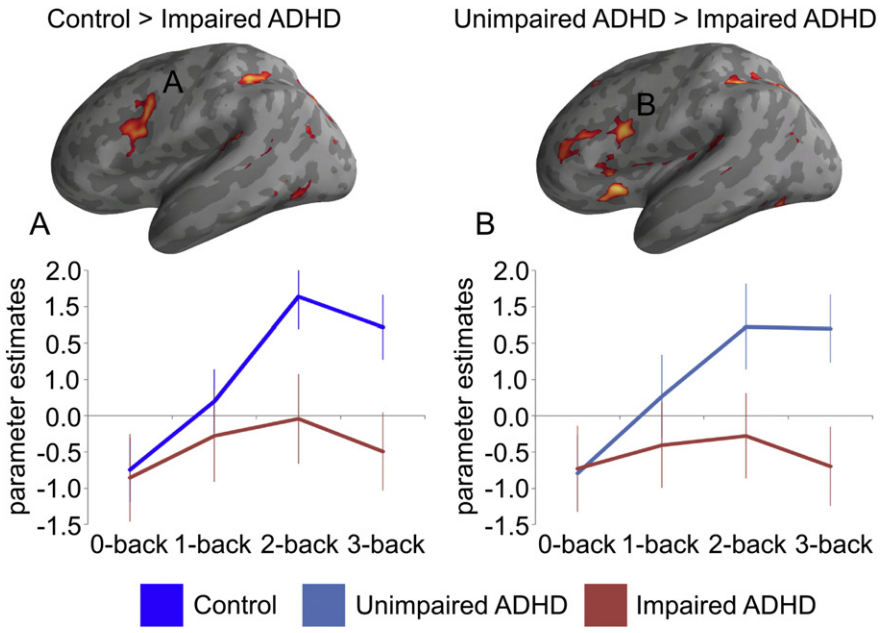

Fig. 4. To characterize the significant group differences in linear activations, contrast parameter estimates for each working memory load were extracted from the left inferior frontal junction identified from both the Control > Impaired ADHD group difference (A) and the Unimpaired ADHD > Impaired ADHD group difference (B). Both the Control (dark blue) and Unimpaired ADHD (light blue) groups exhibited increasing activation across working memory loads, which was absent in the Impaired ADHD group (red). Error bars represent ± standard error of the mean.

larger amounts of information. In the 0-back and 1-back n-back conditions in which a small amount of information had to be maintained in working memory, there were no accuracy differences among any of the groups. In the 2-back and 3-back conditions of the n-back task and in the CANTAB spatial task, in which large amounts of information had to be maintained in working memory, the Impaired ADHD group performed less well than the Unimpaired ADHD and Control groups, who did not differ from one another.

The significant correlation between performance on the CANTAB spatial working memory task and the high loads (2- and 3-back) but not low loads (0- and 1-back) on the n-back verbal working memory paradigms suggests that domain general (i.e., central executive) rather than domain specific (i.e., spatial or verbal storage) working memory processes were affected in the Impaired ADHD group. Further, upon reanalysis of data obtained during the original childhood ascertainment, the unimpaired and impaired ADHD adults showed the same pattern of intact or impaired scores on the most comparable measure in childhood, the WISC-R Freedom from Distractibility Index. These findings are consistent with studies of considerably larger groups of ADHD patients whose executive deficits tended to persist longitudinally (Biederman et al., 2007, 2008; Miller et al., 2012).

The dissociation between working memory and ADHD was also apparent in the relation between adult diagnostic status (e.g., remitted vs. persistent) and working memory ability. Spared or compromised working memory ability occurred regardless of current ADHD diagnostic status, with deficits appearing equally often in persistent or remitted ADHD groups. In this context, it is noteworthy that the adult diagnostic status of ADHD patients was considerably more variable, relative to childhood diagnosis, than was the working memory capacity of these patients, which tended to remain longitudinally fixed.

4.2. Neural dissociations between working memory and ADHD

In control participants and unimpaired ADHD patients, greater working memory demands invoked greater activations in brain regions previously associated with working memory, including dorsolateral prefrontal cortex, inferior frontal junction, parietal cortex, basal ganglia, and cerebellum (Braver et al., 1997). The fact that control and unimpaired ADHD patients exhibited similar patterns of activation (i.e., did not differ from one another significantly) at every load indicates that both groups invoked the same neural systems to support working memory. In contrast, working-memory impaired ADHD patients exhibited significantly less of a relation between working-memory load and activation in the prototypical working memory circuitry.

There was a strong load-dependent coupling between behavioral deficits and activation deficits in the impaired ADHD patients. The Impaired ADHD group performed as well as the Control and Unimpaired ADHD groups at the lesser loads (0- and 1-back), and exhibited lesser activation differences compared to the Control and Unimpaired ADHD groups at those lesser loads. The Impaired ADHD group performed significantly worse than the other groups at the greater loads (2- and 3-back), and exhibited significantly reduced left DLPFC activation than the other two groups at those greater loads. Thus, both behavioral and brain deficits were specific to the greater loads that invoked more executive demands than the lesser loads. Similar patterns of lesser activation and performance on the n-back task have been reported in schizophrenia (Jansma et al., 2004) and in older relative to younger healthy adults (Mattay et al., 2006). What is distinctive about the present findings is the clear-cut distinction within ADHD between a half of patients whose activation and performance is fully intact and another half of patients whose activation and performance is impaired.

The present findings align with prior fMRI studies of n-back working memory that have observed altered (both increased and decreased) frontal–parietal activations in ADHD patients relative to controls (Chantiluke et al., 2015; Cubillo et al., 2014; Fassbender et al., 2011; Ko et al., 2013; Kobel et al., 2009; Li et al., 2014; Silk et al., 2005; Valera et al., 2005, 2010; Vance et al., 2007). Many of the prior studies observed activation differences in the absence of significantly impaired working memory performance in the ADHD patients (Chantiluke et al., 2015; Fassbender et al., 2011; Ko et al., 2013; Li et al., 2014; Silk et al., 2005; Valera et al., 2005, 2010; Vance et al., 2007). The absence of a working memory deficit in the ADHD patients in these imaging studies is in direct contradiction with many studies reporting impaired working memory in ADHD (Burgess et al., 2010; Gau and Shang, 2010; Kofler et al., 2010; Rapport et al., 2008; Rommelse et al., 2008; Toplak et al.,

2005). Further, it is difficult to interpret the importance of a difference in brain function if there is no consequence in behavior.

Although some of the apparent contradictions among these neuroimaging studies of working memory in ADHD may relate to how working memory was operationalized and measured, the present study suggests that a critical factor is fundamental heterogeneity in executive function among ADHD patients (Biederman et al., 2004, 2006; Doyle et al., 2005; Fair et al., 2012; Nigg et al., 2005; Sonuga-Barke et al., 2010). Prior neuroimaging studies have considered ADHD patients as a single group and did not differentiate between ADHD patients with versus without working memory deficits. Thus, one possibility for the discrepancy between intact behavioral task performance and impaired functional brain activations may be that prior imaging studies of ADHD have mixed together, in various proportions, patients with impaired and patients with unimpaired working memory. Such heterogeneity in performance may have obscured behavioral deficits occurring in some, but not other, ADHD patients. The present findings therefore may reconcile the apparent contradiction between the many studies reporting impaired working memory ability in ADHD with the neuroimaging studies reporting intact working memory ability in ADHD.

The relation between variation in working memory (measured by maintenance spans) and variation in brain function in adult ADHD has been examined previously (Burgess et al., 2010). Activation differences in left DLPFC between control and ADHD groups performing an inhibitory control task were partially accounted for by the span scores treated as continuous values across the patients. Broadly, these findings are consistent with the present study in relating variation in working memory ability to variation in DLPFC activation among ADHD patients. In the present study, variation in working memory capacity completely accounted for variation in DLPFC and other activations. Future studies considering both executive (working memory capacity) and maintenance (span) measures of working memory in a single ADHD group can examine whether group differences in behavior or brain function are better understood in relation to categorical versus continuous analyses of working memory ability in ADHD.

The present findings are also consistent with the emerging consensus that executive deficits, such as impairments in working memory, do not constitute a core syndromic feature of ADHD (Biederman et al., 2004, 2006; Castellanos et al., 2006; Nigg et al., 2005). Rather, heterogeneity across individuals with ADHD on performance of executive tasks may reflect nesting within the normal variability of the population (Fair et al., 2012). Further, patients with an ADHD diagnosis may vary in specific associated deficits, with independent sparing or compromise of not only EF, but also reward processing and sustained attention (Castellanos et al., 2006; Doyle et al., 2005; Sonuga-Barke et al., 2010). By this view, patients with ADHD have considerable heterogeneity in regard to specific deficits in working memory, sustained attention, or reward processing.

4.3. Limitations

The complexity of treatment is a notable limitation that is common in psychiatric research. However, there are several facts all favoring the idea that medication history had little or no influence on the main finding of the distinction between impaired and intact ADHD groups. First, all ADHD participants, whether unimpaired or impaired in working memory, had a history of taking stimulant medications. Second, all participants who were currently taking medications did not take their medications 24 hours prior to scanning. Third, the impaired and unimpaired groups of ADHD patients had similar proportions of patients currently taking stimulant medications. Fourth, and most importantly, when participants who were taking ADHD medication were removed from the analyses, similar group differences remained despite the loss of power, suggesting that any differences derived from current medication status had minimal contributions to the group differences.

The Impaired ADHD group had lower IQ scores than both the Unimpaired ADHD group and the Control group, who were not significantly different from each other. These are expected findings because, on average, IQ scores are lower in ADHD (Kuntsi et al., 2004; Rapport et al., 1999) and also IQ generally correlates strongly with working memory capacity (Ackerman et al., 2005; Colom et al., 2004; Kane et al., 2005). It is typically not recommended to match groups on IQ when IQ differences are inherent to a clinical group because such matching results in non-representative groups (Dennis et al., 2009). Prior studies have also found that group differences in EF performance, including working memory, were not related to group differences in IQ (Rommelse et al., 2008; Toplak et al., 2005). Most importantly, the same major differences in activation between groups were found when individual IQ scores were added as a regressor at the group level.

5. Conclusions

The present study provides a mechanistic dissociation between ADHD and a major kind of executive dysfunction, such that the status of working memory capacity was dissociable from current clinical ADHD status. Nevertheless, the frequent co-occurrence of ADHD and executive dysfunction does have important implications. For example, ADHD patients with executive dysfunctions suffer from greater occupational and academic underachievement than those with unimpaired executive functions (Biederman et al., 2004, 2006). The observed heterogeneity and higher prevalence of executive deficits in ADHD may be the result of partially overlapping etiological genetic pathways. Polymorphisms in both D4 receptor (DRD4) and D2 receptor (DRD2) genes have been linked to ADHD (Kirley et al., 2002; LaHoste et al., 1996) and variation in response inhibition (Congdon et al., 2008) and working memory (Zhang et al., 2007) in typically developing individuals.

The present finding demonstrates that ADHD and working memory, a core executive function, are dissociable at both behavioral and neural levels of analysis. The two groups of ADHD patients were well matched clinically: they did not differ on the number of ADHD symptoms at the time of the imaging study, the number of ADHD symptoms at uniform childhood characterization, or in the persistence of their diagnosis at the time of imaging. Working memory capacity and its underlying neural circuitry, however, was fully intact in one ADHD group and clearly impaired in the other ADHD group. Prior studies with larger cohorts have shown that ADHD and executive functions are dissociable (Biederman et al., 2004, 2006; Nigg et al., 2005), and the present study shows for the first time a brain basis for this dissociation in working memory.

Acknowledgments

We thank Steve Shannon, Sheeba Arnold, and Christina Triantafyllou for technical assistance. Imaging was performed at the Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research, MIT. We thank Elana Kagan for assistance in recruitment and data collection. The Poitras Center for Affective Disorders Research at the McGovern Institute for Brain Research at MIT, the Pediatric Psychopharmacology Council Fund at MGH, and the NIMH (J.B., grant numbers R01 HD036317 and R01 MH050657) supported this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2015.12.003.

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