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Original Research Article

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

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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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(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