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Neural activation during response inhibition in adult attention-deficit/hyperactivity disorder: Preliminary findings on the effects of medication and symptom severity

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ABSTRACT

Studies of adults with attention-deficit/hyperactivity disorder (ADHD) have suggested that they have deficient response inhibition, but findings concerning the neural correlates of inhibition in this patient population are inconsistent. We used the Stop-Signal task and functional magnetic resonance imaging (fMRI) to compare neural activation associated with response inhibition between adults with ADHD ($N=35$) and healthy comparison subjects ($N=62$), and in follow-up tests to examine the effect of current medication use and symptom severity. There were no differences in Stop-Signal task performance or neural activation between ADHD and control participants. Among the ADHD participants, however, significant differences were associated with current medication, with individuals taking psychostimulants ($N=25$) showing less stopping-related activation than those not currently receiving psychostimulant medication ($N=10$). Follow-up analyses suggested that this difference in activation was independent of symptom severity. These results provide evidence that deficits in inhibition-related neural activation persist in a subset of adult ADHD individuals, namely those individuals currently taking psychostimulants. These findings help to explain some of the disparities in the literature, and advance our understanding of why deficits in response inhibition are more variable in adult, as compared with child and adolescent, ADHD patients.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD), which is characterized by age-inappropriate symptoms of inattention, impulsivity and hyperactivity, is the most prevalent psychiatric disorder of childhood. ADHD may continue into adulthood, with reports of symptom persistence in as many as 65% of cases (Mannuzza et al., 2003). Compared with controls, children with ADHD exhibit hypoactivation in frontoparietal and attention networks involved in executive function, but hyperactivation across large-scale networks, including the default-mode network, and somatomotor and visual networks (Cortese et al., 2012). Investigations in adults with ADHD are needed to clarify the basis of deficits that persist through the course of the disorder.

Deficient response inhibition, or the ability to suppress a prepotent or habitual response, has been proposed as a central feature of ADHD (Barkley, 2005). Findings obtained with functional magnetic resonance imaging (fMRI) suggest that deficient inhibition in ADHD samples reflects corresponding abnormality in fronto-striatal activation. During response inhibition, healthy individuals show recruitment of a network of brain regions that includes the bilateral ventrolateral prefrontal cortex (VLPFC)

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(encompassing the inferior frontal cortex (IFC) and insula), the pre-supplementary motor area (SMA)/SMA, medial superior frontal gyrus (SFG) and cingulate cortex, as well as subcortical regions including the striatum and thalamus (Aron and Poldrack, 2006; Aron et al., 2007; Swick et al., 2011). Subjects with ADHD show less activation in these regions compared with controls (Dickstein et al., 2006; Epstein et al., 2007). In fact, fMRI studies have consistently shown fronto-striatal hypoactivation in ADHD children and adolescents relative to controls during tasks requiring not only response inhibition but also those requiring interference inhibition, attention, and temporal processing, which together have provided considerable support for a fronto-striatal deficit hypothesis of ADHD (for review, see Cubillo et al. (2012)).

Only a few fMRI investigations of response inhibition, however, have involved adults with ADHD, and these studies have provided mixed results. In some cases, adult ADHD patients showed less activation than controls during response inhibition, including effects in VLPFC, cingulate, and striatal stopping-related regions (as reviewed by Cubillo et al. (2012) and as demonstrated in a meta-analysis by Hart et al. (2013)). For example, Mulligan et al. (2011) reported that a sample of 12 controls recruited a more extensive network of brain regions during inhibition on a Go/No-Go task as compared with 12 adult ADHD patients, and that ADHD subjects showed less activation in regions key for response inhibition, including the right PFC and preSMA. Similarly, Sebastian et al. (2012) reported less activation in an adult ADHD sample as compared with healthy controls during performance of the Stop-Signal, Go/No-Go, and Simon interference tasks, with significant effects in the right pallidum and left IFC in 20 ADHD adults as compared with 24 controls during inhibition of an already-initiated response (Stop-Signal task). Other reports, however, indicated that adults with ADHD showed no differences in (Carmona et al., 2012) or greater (Dillo et al., 2010; Karch et al., 2010) fronto-striatal activation during response inhibition as compared to controls. For example, Dibbets et al. (2009) reported no statistically significant differences in activation in fronto-striatal regions between 16 adult ADHD males and 13 healthy controls performing a modified Go/No-Go task. Similarly, while Dillo et al. (2010) found no difference in fronto-cingulo-striatal activity between 15 adult ADHD and 15 healthy control individuals performing a Go/No-Go task, they did find increased activation in parietal regions. The greater activation in parietal (Dillo et al., 2010) and cerebellar (Cubillo et al., 2012) regions during response inhibition by ADHD patients has been interpreted as reflecting the engagement of compensatory attentional processes. A number of factors may account for these discrepancies, including differences in task parameters (specifically differences between Go/NoGo and Stop-Signal tasks), medication status, and symptom severity, as well as small sample size.

In an attempt to address these limitations in the literature, we examined differences in task performance and associated patterns of neural activation, as measured using fMRI, in a relatively large sample of adult participants with ADHD, as compared to controls, using a tracking version of the Stop-Signal task. We hypothesized that adults with ADHD would exhibit less activation in stopping-related regions than would controls, and we conducted exploratory follow-up analyses to examine potential effects of medication status and symptom severity.

2. Methods

2.1. Participants

All participants were recruited from the Los Angeles area as part of the Consortium for Neuropsychiatric Phenomics at UCLA (www.phenomics.ucla.edu), in which they completed extensive neuropsychological testing (additional details provided in Supplementary Materials). All candidates were screened by telephone and then in person. Participants were men or women ages 21–50 years; NIH ethnic category either White, not Hispanic or Latino, or Hispanic or Latino, of any racial group; primary language (as determined by a verbal fluency test) either English or Spanish; completed at least 8 years of formal education; had no significant medical illness; adequately cooperative to complete assessments; and had visual acuity 20/60 or better. Urinalysis was used to screen for drugs of abuse (cannabis, amphetamine, opioids, cocaine, and benzodiazepines), and participants were excluded if results were positive. Additional exclusion criteria for participants in the imaging portion of the study were left-handedness, pregnancy, history of head injury with loss of consciousness or cognitive sequelae, or other contraindications to scanning (e.g., claustrophobia, metal in body).

After receiving a verbal explanation of the study, participants gave written informed consent following procedures approved by the Institutional Review Boards at UCLA and the LACDMH. All subjects underwent a semi-structured assessment with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (SCID-I; First et al., 2004), supplemented for ADHD diagnoses with the Adult ADHD Interview (a structured interview form derived from the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (KSADS-PL) (Kaufman et al., 1997)), in order to enable a more detailed characterization of lifetime history of ADHD in adults. For the purpose of this investigation, participants were excluded for lifetime diagnoses of schizophrenia or other psychotic disorders, bipolar I or II disorder; or current major depressive disorder, suicidality, anxiety disorder (obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, post-traumatic stress disorder), or substance abuse/dependence other than nicotine dependence (which was allowed). Stable medications were permitted in ADHD participants (discussed below); any self-reported psychoactive medication use by controls was an exclusion factor. Symptom severity in patients was assessed with the Adult ADHD Clinical Diagnostic Scale (ACDS), which provides a quantitative assessment of how current Inattention and Hyperactivity symptoms impact patient functioning (Goodman, 2009; Kessler et al., 2010).

2.2. Procedure

Participants completed a tracking version of the Stop-Signal task, which enabled isolation of activation associated with the inhibition of an already-initiated motor response, and calculation of an individualized measure of inhibitory control (Stop-Signal Reaction Time, SSRT). On the testing day, participants first received training on the Stop-Signal task in the form of one initial demonstration, before completing two experimental runs (one run outside of the scanner and one while inside of the scanner). A complete description of the fMRI acquisition and preprocessing steps is presented in Supplementary Materials.

2.2.1. Stop-Signal task

Participants were instructed to respond quickly when a “go” stimulus was presented on the computer screen, except on the subset of trials where the “go” stimulus was paired with a “stop” signal (Fig. 1). Specifically, participants were shown a series of go stimuli (left- and right-wards pointing arrows), to which participants were told to respond with left and right button presses, respectively (Go trials). On a subset of trials (25%), a stop signal (a 500-Hz tone presented through headphones) was presented a short delay after the go stimulus appeared and lasted for 250 ms (Stop trials). Participants were instructed to respond as quickly and accurately as possible on all trials, but to withhold their response on Stop trials (on trials with the tone). They also were instructed that stopping and going were equally important.

On Stop trials, the delay of the onset of the stop signal, or Stop-Signal Delay (SSD), was varied, such that it was increased after the participant successfully inhibited in response to a Stop-Signal (making the next Stop trial more difficult), and decreased after the participant failed to inhibit in response to a Stop-Signal (making the next Stop trial less difficult). Each SSD increase or decrease was in 50-ms intervals. The SSD values were drawn from two interleaved staircases per block, resulting in 16 trials from each staircase for a total of 32 Stop trials per block. In the first task run completed outside of the scanner, SSD values started at 250 and 350 ms for staircases 1 and 2, respectively. At the end of the behavioral run, the last SSD time from each staircase was then carried over to be the initial SSD for the scan run. This one-up/one-down tracking procedure ensured that subjects successfully inhibited on approximately 50% of inhibition trials. Also as a result, difficulty level is individualized across subjects and both behavioral performance and numbers of successful Stop trials are equated across subjects.

Each experiment run contained 128 trials, 96 of which were Go trials and 32 of which were Stop trials, each presented randomly. All trials were preceded by a 500 ms fixation cross in the center of the screen, and then each trial began with the appearance of an arrow and ended after 1000 ms, followed by the null period. Jittered null events separated every trial (with a blank screen), with the duration of null events sampled from an exponential distribution (null events ranged from 0.5 to 4 s, with a mean of 1 s). Stimulus presentation and timing of all stimuli and response events were achieved using Matlab (Mathworks) and the Psychtoolbox