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The attenuation of dysfunctional emotional processing with stimulant medication: An fMRI study of adolescents with ADHD

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ABSTRACT

Functional neuroimaging studies of attention-deficit/hyperactivity disorder (ADHD) have focused on the neural correlates of cognitive control. However, for many youths with ADHD, emotional lability is an important clinical feature of the disorder. We aimed to identify the neural substrates associated with emotional lability that were distinct from impairments in cognitive control and to assess the effects that stimulants have on those substrates. We used functional magnetic resonance imaging (fMRI) to assess neural activity in adolescents with ($N=15$) and without ($N=15$) ADHD while they performed cognitive and emotional versions of the Stroop task that engage cognitive control and emotional processing, respectively. The participants with ADHD were scanned both on and off stimulant medication in a counterbalanced fashion. Controlling for differences in cognitive control, we found that during the emotional Stroop task, adolescents with ADHD as compared with controls demonstrated atypical activity in the medial prefrontal cortex (mPFC). Stimulants attenuated activity in the mPFC to levels comparable with controls.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is among the most common diagnoses in pediatric psychiatry with 3–10% of school age children affected by the disorder (Barkley, 2005). Although ADHD is characterized by inattention, hyperactivity, and impulsivity, one of the most challenging aspects of the disorder is the heightened emotional lability (EL) that is highly prevalent in children with ADHD (Barkley, 1997a). Emotional lability indicates a tendency for intense, or strong, emotional reactions (Maedgen and Carlson, 2000; Conners, 2008; Sobanski et al., 2010) and has been described in youths with ADHD in both the clinical and research literature (Barkley and Fischer, 2010) for several decades, beginning as early as 1798 with Alexander Crichton's description of hyperactive children demonstrating a "morbid exaggeration of emotional excitability" (Crichton, 1798). In addition, epidemiological studies demonstrate that youths with ADHD have rates of depression and anxiety disorders far beyond those expected by chance alone (Biederman et al., 1991).

Despite the clinical significance of EL in ADHD, its neurobiological substrates are unknown. There are two main, competing hypotheses. The first maintains that EL in ADHD patients stems primarily from impairments in cognitive control and this manifests itself as an impaired capacity to suppress responses elicited by emotional stimuli (Barkley, 1997b). The competing hypothesis maintains that it is emotional processing itself that is dysfunctional with emotional stimuli generating unusually, strong emotional responses in youth with ADHD (Sonuga-Barke et al., 1992). Neuroimaging studies that have examined emotional processing in ADHD subjects have not fully tested these two hypotheses because they did not attempt to disentangle emotional processing from more general deficits in cognitive control (Peterson, 2003). To overcome this, we used functional magnetic resonance imaging (fMRI) to examine whether adolescents with ADHD have altered task-related activation during an emotional processing task and whether these atypical task-related activations could be dissociated from activations associated with cognitive control.

To examine emotional processing, we used an emotional Stroop task (Whalen et al., 2006; Passarotti et al., 2009). In this task, we presented participants with neutral and emotionally salient words (i.e., words such as 'month' and 'death,' respectively). The emotionally salient words had either positive or negative valence (e.g., 'happy' or 'hate,' respectively). On each trial, the same word was written several times (Fig. 1A). The task was to indicate on a keypad the number of

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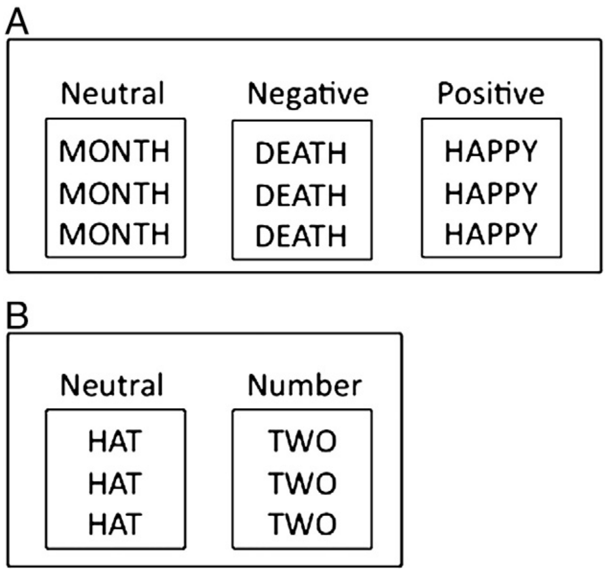

Fig. 1. Examples of the trial types for the emotional and cognitive Stroop tasks. (A) In the emotional Stroop, there were 3 conditions: neutral words, negatively valenced words, and positively valenced words. During the neutral word trials, subjects were presented with words lacking emotional content; during the negatively and positively valenced word trials, subjects were presented with words associated with high emotional valence. The subject's task was to indicate on a keypad the number of times that the word was written. For each of the examples provided, the correct response is "3." (B) In the cognitive Stroop, there were 2 conditions: neutral words and number words. During the neutral word trials, subjects were presented with words describing an article of clothing; during the number word trials, subjects were presented with number words that were incongruent with the number of times the word was presented (e.g., "two" written 3 times, in which the correct response would be "3"). As with the emotional Stroop, the subject's task was to indicate on a keypad the number of times that the word was written.

times the word was written. Participants are often slower and less accurate in counting the number of times that a word is presented during trials with emotion-denoting words than during the neutral trials (i.e. trials with words without emotional salience) (Williams et al., 1996). This effect of emotion-denoting words on task performance is referred to as an attentional bias, or distraction, and it is thought to reflect participants' difficulty in diverting attention away from the emotion evoked by the emotional words.

To dissociate emotional processing from cognitive control, we also used a cognitive Stroop task (Bush et al., 2006) that was analogous to the emotional Stroop. As in the emotional Stroop, the subject's task was to indicate the number of times that a word was written. The difference, however, was that with the cognitive Stroop, the distracter trials consisted of number words that conflicted with the number of presentations (e.g., the word "two" presented three times, in which case the correct answer is three; Fig. 1B). Conversely, during neutral trials, participants were shown words denoting an article of clothing. Like other cognitive versions of the Stroop, this task requires cognitive control, because during the distracter trials participants automatically read the number word and then have to inhibit the tendency to answer with the number indicated by the word (MacLeod, 1991; Bush et al., 2006).

By using both cognitive and emotional versions of the Stroop, we aimed to test the following hypotheses: During the cognitive Stroop, we hypothesized that activation would be detected in the neural substrates associated with cognitive control. These substrates include the dorsal striatum, dorsal anterior cingulate, lateral prefrontal cortex (PFC), and thalamus (Casey et al., 2007). (Prior research has addressed group level differences between ADHD subjects and controls during the cognitive Stroop; this was not a focus of this study.) Having identified brain region associated with cognitive control, we then aimed to covary for the effects of cognitive control and identify brain regions that differed between ADHD participants and controls in their responses during the emotional Stroop. In doing so, we intended to tease apart the effects of cognitive control (as determined by the cognitive Stroop) from the effects of emotional processing (as determined by the emotional Stroop). We hypothesized that the ADHD participants would differ from controls in emotional processing even after covarying for their impaired cognitive control. More specifically, we predicted different patterns of activation, depending on the mechanism by which ADHD subjects differed from controls in emotional processing. If ADHD participants differed from controls in the processing of positive emotions, we expected to find increased activation in the ADHD participants in regions that are most typically associated with positive affect (e.g. ventral striatum) (Posner et al., 2005) during the presentation of positively valenced words. Likewise, if ADHD participants differed from controls in the processing of negative emotions, we expected increased activation in regions associated with negative affect (e.g. insular cortex) (Phan et al., 2002) during the presentation of negatively valenced words. Alternatively, if the ADHD participants differed from controls in emotion regulation, we should find altered activation during the presentation of either positively or negatively valenced words because emotion regulation should be engaged to modulate emotional processing regardless of the valence (i.e., positive or negative) of the words presented. Moreover, the task-related activations should be detected in brain regions associated with the regulation of emotion (e.g. medial PFC and hippocampus) (Davidson et al., 2000; Posner et al., 2009). Lastly, we scanned the ADHD participants while they were on and off stimulant medication. We hypothesized that stimulants would attenuate the atypical emotional processing that we expected to find in the unmedicated ADHD youth.

2. Methods

The Institutional Review Board of the Oregon Health & Science University (OHSU) approved the study procedures. All child participants provided informed assent and a legal guardian provided informed consent.

2.1. Subjects

Participants were 15 adolescents with ADHD and 15 healthy control adolescents. Controls were age- and gender-matched to the ADHD subjects (Table 1). Controls were screened for psychiatric disorders using the Diagnostic Interview Schedule for Children (DISC) — Predictive Scales (Lucas et al., 2001) and were excluded if they had any probable, active Axis I disorder. ADHD subjects, and at least one

Table 1
Demographic and clinical characteristics of the study sample. CDI, Children's Depression Inventory; STAI, Spielberger State Anxiety Inventory; FSIQ, Full Scale Intelligence Quotient estimated from the Wechsler Abbreviated Scale of Intelligence. Socioeconomic status was assessed with the Hollingshead Index of Social Position. Pubertal status was assessed with the Puberty Development Scale (PDS). *Indicates a statistically significant difference between the ADHD and control participants. The ± indicate standard deviations.

	ADHD	Healthy controls	Test statistic	*P* value
Age in years	13.5 ± 1.2	13.4 ± 1.2	$t = 0.3$	0.8
Gender	13 males; 2 females	13 males; 2 females	$\chi^2 = 0$	1.0
Hollingshead Index of Social Position	32.4 ± 13.9	31 ± 11.8	$t = 0.3$	0.8
FSIQ	111.4 ± 16	114.1 ± 10	$t = 0.5$	0.6
Pubertal status	2.5 ± 0.8	2.7 ± 0.7	Mann–Whitney $U = 98$	0.5
STAI	45.2 ± 7.3	39.5 ± 7.4	$t = 2.1$	0.04*
CDI	46.4 ± 7.0	39.5 ± 0.9	$t = 3.4$	0.003*