Lisdexamfetamine Targets Amygdala Mechanisms that Bias Cognitive Control in Attention Deficit Hyperactivity Disorder

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Abstract

Background
Prefrontal-limbic circuits that form the neural architecture for emotion to influence behavior have been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD), and represent a potentially important target of medication treatment that has not been substantively evaluated. This study tested the effect of the psychostimulant prodrug lisdexamfetamine dimesylate on amygdala activation and connectivity during the emotional bias of response execution and inhibition.

Methods
Twenty-five adults with ADHD were scanned twice with event-related functional magnetic resonance imaging while performing an emotional go/no-go task following three to four weeks of lisdexamfetamine treatment and three weeks off medication in a randomized, counterbalanced, hybrid crossover design. Drug, trial type, and face emotion (happy, sad, neutral) were included as within-subjects factors in repeated measures analyses of activation and connectivity.

Results
Lisdexamfetamine was associated with increased right amygdala activation and reduced psychophysiological interactions with the orbital aspect of left inferior frontal gyrus specifically for responses to sad faces compared to placebo, but there was no effect on the accuracy of response execution or inhibition. The relative gain in right amygdala activation in response to sad faces for lisdexamfetamine was correlated with a reduction in symptoms of ADHD.

Conclusions
Treatment with lisdexamfetamine potentiates affective encoding in amygdala, purportedly via catecholaminergic mechanisms, but functionally disconnects amygdala from inferior frontal regions that encode behavioral significance—resulting in reduced emotional bias of cognitive control. Pinpointing the neurophysiologic underpinnings of therapeutic improvement with lisdexamfetamine represents a first step in developing targeted approaches to treatment of ADHD.