

How do stimulant treatments for ADHD work? Evidence for mediation by improved cognition.

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J Child Psychol Psychiatry. 2018 May 7.
doi: 10.1111/jcpp.12917.

Abstract

BACKGROUND:

Stimulant medications such as methylphenidate (MPH) are the frontline treatment for Attention-Deficit/Hyperactivity Disorder (ADHD). Despite their well-documented efficacy, the mechanisms by which stimulants improve clinical outcomes are not clear. The current study evaluated whether MPH effects on classroom behavior were mediated by improved cognitive functioning.

METHODS:

Children with ADHD ($n = 82$; 9-12 years old) participated in a week-long summer research camp, consisting of cognitive testing, classroom periods, and recreational activities. After a baseline day, participants completed a 3-day randomized, double-blind, placebo-controlled trial of MPH (at doses approximating 0.3 and 0.6 mg/kg of immediate-release MPH dosed TID). Cognitive domains included inhibitory control (Stop Signal Task and prepulse inhibition of startle), attention (Continuous Performance Task and reaction time variability), and working memory (forward and backward spatial span). Clinical outcomes included math seatwork productivity and teacher-rated classroom behavior. A within-subjects path-analytic approach was used to test mediation. MPH-placebo and dose-response contrasts were used to evaluate drug effects.

RESULTS:

Methylphenidate improved seatwork productivity and teacher ratings ($d_s = 1.4$ and 1.1) and all domains of cognition ($d_s = 0.3$ - 1.1). Inhibitory control (Stop Signal Task, SST) and working memory backward uniquely mediated the effect of MPH (vs. placebo) on productivity. Only working memory backward mediated the impact of MPH on teacher-rated behavior. The dose-response (0.6 vs. 0.3 mg/kg) effects were more modest for clinical outcomes ($d_s = 0.4$ and 0.2) and cognition ($d_s = 0$ - 0.3); there was no evidence of cognitive mediation of the clinical dose-response effects.

CONCLUSIONS:

These findings are novel in demonstrating that specific cognitive processes mediate clinical improvement with stimulant treatment for ADHD. They converge with work on ADHD theory, neurobiology, and treatment development in suggesting that inhibitory control and working memory may be mechanisms of stimulant treatment response in ADHD. More work is necessary to evaluate the degree to which these findings generalize to chronic treatment, a broader array of clinical outcomes, and nonstimulant treatments.