Archival Report

Biological Psychiatry

First-Dose Methylphenidate–Induced Changes in Brain Functional Connectivity Are Correlated With 3-Month Attention-Deficit/Hyperactivity Disorder Symptom Response

Richard B. Silberstein, Florence Levy, Andrew Pipingas, and Maree Farrow

ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) symptoms are most commonly treated with stimulant medication such as methylphenidate (MPH); however, approximately 25% of patients show little or no symptomatic response. We examined the extent to which initial changes in brain functional connectivity (FC) associated with the first MPH dose in boys newly diagnosed with ADHD predict MPH-associated changes in ADHD inattentiveness and hyperactivity symptoms at 3 months.

METHODS: Brain FC was estimated using steady-state visual evoked potential partial coherence before and 90 minutes after the administration of the first MPH dose to 40 stimulant drug–naïve boys newly diagnosed with ADHD while they performed the AX version of the continuous performance task. The change in parent-rated inattention and hyperactivity scores over the first 3 months of MPH medication was correlated with the initial 90-minute MPH-mediated FC changes.

RESULTS: Hyperactivity improvements at 3 months were associated with first-dose MPH–mediated FC reductions restricted to frontal-prefrontal sites following the appearance of the "A" and at frontal and right temporal sites during the appearance of the "X." Corresponding 3-month inattention score improvement was associated with initial MPH–mediated FC reductions restricted to occipitoparietal sites following the appearance of the "A."

CONCLUSIONS: These findings are discussed in the context of MPH effects on the default mode network and the possible role of the default mode network in MPH-mediated improvements in inattention and hyperactivity symptom scores.

Keywords: ADHD symptoms, Brain functional connectivity, Methylphenidate, Occipital cortex, Prefrontal cortex, Steady-state visually evoked potential

http://dx.doi.org/10.1016/j.biopsych.2017.03.022

Attention-deficit/hyperactivity disorder (ADHD), a disorder that is characterized by symptoms of inattention and/or impulsivity and hyperactivity, is one of the most commonly diagnosed pediatric neuropsychiatric disorders, affecting an estimated 3% to 6% of children (1). An important component of various theories concerning ADHD has been the role of the catecholamines norepinephrine (NE) and especially dopamine (DA). It has been suggested that ADHD is a consequence of reduced DA activity as a result of either increased DA synaptic reuptake or reduced postsynaptic sensitivity at frontostriatocerebellar networks (2,3). Methylphenidate (MPH) is one of the most commonly prescribed stimulants for the management of ADHD symptoms; it acts to increase DA and NE availability by inhibiting reuptake of these catecholamines (4). While MPH and other stimulants are broadly effective in the management of ADHD symptoms, it is estimated that approximately 25% of patients with ADHD receiving stimulant medication show little or no symptomatic improvement (5). The ability to identify patients with ADHD likely to respond favorably to stimulant medication prospectively is thus important on two grounds. First, if stimulant medication nonresponders can be identified, ineffective medication and related side effects can be avoided. Second, an understanding of the factors contributing to stimulant medication response would shed additional light on the neurobiological basis of ADHD.

While the cognitive enhancing effect of MPH has generally been considered a consequence of DA-related increases in prefrontal activity (6,7), more recently, another perspective on the brain function abnormalities underlying ADHD and the role of stimulants in symptom management has emerged. This perspective views ADHD as a disorder of functional connectivity (FC) rather than an abnormality restricted to specific cortical regions (8). The main development making this reappraisal possible was the recognition of a specific cortical network known as the default mode network (DMN) (9). The DMN is most active when awake subjects are engaged in

ISSN: 0006-3223

stimulus-independent cognition, such as daydreaming, and exhibits reduced activity when task-positive networks become active during a cognitive task (9,10).

A reduced negative correlation between the DMN and task active networks has been reported in ADHD suggesting that the inattentiveness observed in this condition is a consequence of inadequate suppression of the DMN and increased intrusion of thoughts unrelated to the task (11,12). A number of authors suggest that ADHD could be considered a default network disorder (13–17). The suggested role of the DMN in ADHD symptomatology is also consistent with findings concerning the effects of stimulant medication on DMN activity. While undertaking a cognitive task, subjects with ADHD showed greater suppression of the DMN while on stimulant medication compared with the off-medication state (18–20).

Given the centrality of the role of DA in theories of ADHD, a number of studies have examined the relationship between the acute effects of DA on brain function in ADHD and the long-term clinical response to stimulant medication. Bush (21) examined the effect of MPH in a group of adults diagnosed with ADHD and reported that 6-week clinical improvements were associated with increased activity in task-positive networks and greater inhibition of the DMN. Analogous findings were reported by Schulz *et al.* (22), noting that the major MPH-related changes in brain activity associated with ADHD symptom improvements over a 6- to 8-week period were reductions at bilateral primary motor cortex, left supplementary motor cortex, and bilateral posterior cingulate cortex. While the authors attributed the reductions in motor cortex activity to the improvements in impulse control, the posterior cingulate reductions were interpreted as reflecting improved suppression of the DMN. However, while the relationship between MPH and the resultant changes in brain activity in ADHD appears robust, the relationship between changes in brain activity and improvements in ADHD symptoms is not always apparent (23).

We have previously used a steady-state visually evoked potential (SSVEP)–based methodology to examine cognitive task-related changes in brain electrical activity in ADHD (24) as well as task-related changes in brain FC in ADHD (25). In an earlier study (26), we examined FC changes in response to an MPH dose in a stimulant drug–naïve group of boys newly diagnosed with ADHD while they performed the AX version of the continuous performance task (CPT-AX). We found that MPH robustly reduced the task-related transient FC increase observed in the ADHD group. Furthermore, we observed a significant positive correlation between MPH-induced changes in reaction time (RT) during the CPT-AX and the MPH-induced changes in FC so that larger RT reductions were associated with larger FC reductions. Given that RT deficits are one of the most common observations in ADHD (27), we hypothesized a relationship between the initial changes in FC observed as a result of a single MPH dose and the change in clinical symptom score observed over a longer and more clinically relevant interval. In the present study, we specifically hypothesized that the 3-month improvement in ADHD symptom scores would be associated with the initial FC reduction observed following the first administration of MPH to a group of boys newly diagnosed with ADHD.

METHODS AND MATERIALS

Participants

The participants comprised 40 right-handed, stimulant drug–naïve boys (mean age 121 months [SD 21 months], mean IQ 101.3 [SD 14.4]) newly clinically diagnosed with ADHD according to DSM-IV criteria (28). All participants were prescribed MPH as the sole pharmaceutical treatment for ADHD. Parents gave their written consent after receiving a complete detailed description of the study. The study was approved by the Human Research Ethics Committees of Swinburne University and the Royal Children's Hospital.

ADHD Symptom Score Assessment

Before the electroencephalogram (EEG) recording session and 3 months after the recording session and the start of MPH treatment, parents completed a questionnaire based on DSM-IV criteria for ADHD (28) to rate the severity of inattention and hyperactivity symptoms. The maximum symptom score for either inattention or hyperactivity symptoms is 27 based on a 4-point scale (0, 1, 2, 3) for nine questions in each category. A symptom improvement score (SIS) was calculated separately for inattention (I-SIS) and hyperactivity (H-SIS) symptoms based on the following proportional difference formula: SIS = (initial symptom score − final symptom score)/(initial symptom score).

Procedures

Participants first performed a low-demand reference task followed by the CPT-AX. Both the reference task and the CPT-AX were undertaken twice: immediately before and then 90 minutes after the participants were administered their first MPH dose (0.3 mg/kg participant weight).

In the reference task, participants viewed a repeated presentation of the numbers 1, 2, 3, 4, and 5 and were required to press a microswitch on the appearance of the number 5. In the CPT-AX, participants were required to respond on the unpredictable appearance of an "X" that had been preceded by an "A." In all tasks, the numbers and letters remained on the screen for 2.0 seconds and were followed by a blank screen for 1.5 seconds. The ratio of targets to nontargets was 1:4, and the task duration was 280 seconds. For all tasks, a correct response to a target was defined as one that occurred no less than 100 ms and no more than 1.5 seconds after the appearance of the target. Any responses outside the correct time intervals were defined as errors of commission, or false alarms, while failure to respond in the correct interval was defined as an error of omission.

The cognitive tasks were presented on a computer monitor. Each letter subtended a horizontal and vertical angle of approximately 1.0° when viewed by subjects from a fixed distance of 1.3 m. The stimulus used to evoke the SSVEP was a spatially diffuse 13-Hz sinusoidal flicker subtending a horizontal angle of 160° and a vertical angle of 90°, which was superimposed on the visual fields. This flicker was present throughout the task, and special goggles enabled subjects to simultaneously view the cognitive task and the sinusoidal flicker.