

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

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## 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

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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

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:  $SIS = (\text{initial symptom score} - \text{final symptom score}) / (\text{initial symptom score})$ .

### 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  $1.0^\circ$  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  $160^\circ$  and a vertical angle of  $90^\circ$ , 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.

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**SSVEP Recording and Processing**

The EEG was recorded from 64 scalp sites that included all international 10-20 positions, with additional sites located midway between 10-20 locations previously described (25,29). The SSVEP is the event-related potential elicited by the 13-Hz visual flicker and is determined from the EEG Fourier coefficients evaluated over 10 stimulus cycles at the stimulus frequency of 13 Hz, thus yielding a temporal resolution of 0.77 second (25).

**FC and SSVEP Event-Related Partial Coherence**

Brain FC was measured using an event-related potential methodology termed SSVEP event-related partial coherence (SSVEP-ERPC). We have previously used SSVEP-ERPC to examine changes in brain FC associated with cognitive tasks (30) and more recently comparing ADHD and typically developing groups while performing the continuous performance task (25). For more details on the SSVEP-ERPC methodology and statistical considerations, the reader is referred to reference (25).

For each subject, the SSVEP-ERPC was calculated for all 2016 distinct pairs of electrodes averaged across all correct responses in the reference task and CPT-AX before and after MPH administration. Electrode pairs with high partial coherence reflect a stable synchronization or phase difference of the SSVEP between electrode pairs across trials and are thought to reflect FC between the relevant regions, and thus we will use SSVEP-ERPC and FC interchangeably. Details of the SSVEP-ERPC methodology have been previously described (25,29,30).

For both tasks, SSVEP-ERPC was determined for the 7.0-second interval centered on the appearance of the number 5 in the reference task and the "X" in the CPT-AX. To examine the relationship between the initial changes in FC associated with the MPH dose and the 3-month improvement in hyperactivity and inattention symptoms, we calculated the correlation coefficient between the changes in FC (defined as  $\Delta FC = \text{post MPH FC} - \text{pre MPH FC}$ ) and the 3 month SIS for each point in time, separately for inattention (I-SIS) and hyperactivity (H-SIS).

To explore temporal variation in the strength of the correlation between the MPH-induced  $\Delta FC$  and the corresponding H-SIS and I-SIS, we determined the number of electrode pairs where the magnitude of the correlation coefficient  $r$  exceeds .403, ( $|r| \geq .403$ ), a threshold value corresponding to  $p = .01$  at each point in time. Plots illustrating the temporal variation in the number of  $\Delta FC$  measures correlated with H-SIS and I-SIS exceeding the threshold are termed correlation frequency curves. A permutation test was then used to determine the statistical significance of the number of correlations between

SIS and  $\Delta FC$  that exceeded the correlation coefficient threshold at a given point in time (26).

**RESULTS****Behavioral Results**

Premedication and postmedication mean RT (premedication 570 ms [SD 140], postmedication 571 ms [SD 142 ms]) did not differ significantly. However, pooling the MPH-mediated RT changes obscures individual MPH-mediated RT changes. We have previously reported that MPH-mediated changes in RT were correlated with the MPH-mediated changes in FC such that larger RT reductions are associated with larger FC reductions. Readers are referred to our previous article for a more detailed discussion on MPH-mediated RT changes in the CPT-AX (24). While premedication and postmedication mean number of errors of omission did not differ significantly (premedication errors of omission 1.30 [SD 1.9], postmedication errors of omission 1.33 [SD 1.7]), there was a nonsignificant tendency for a postmedication reduction in errors of commission (premedication errors of commission 2.10 [SD 2.6], postmedication errors of commission 1.73 [SD 1.9]).

**Symptom Scores**

The initial and 3-month parent symptom scores are listed in Table 1. While both I-SIS and H-SIS improved over the 3-month period, these changes were not significantly correlated at the individual level ( $r_{38} = .287, p = .07$ ).

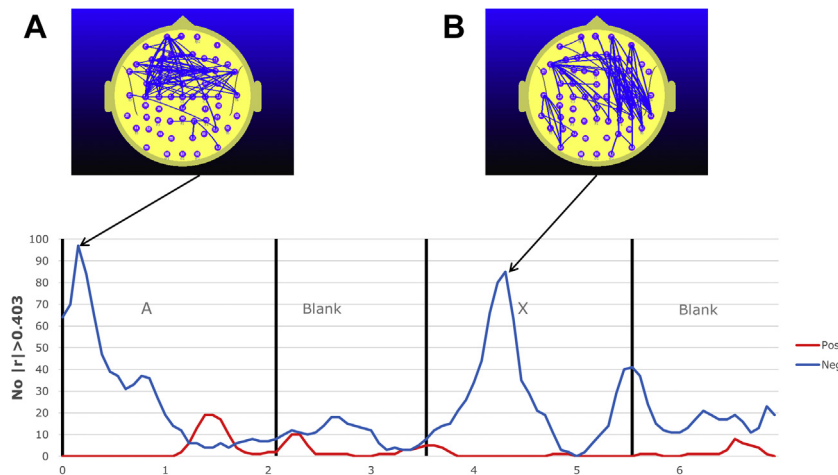
**Relationship Between First-Dose MPH-Induced Changes in FC and 3-Month Symptom Improvements**

The correlation frequency curve for the number of electrode pairs where the acute change in FC induced by the MPH dose,  $\Delta FC$ , is correlated with H-SIS is illustrated in Figure 1. H-SIS is significantly correlated with  $\Delta FC$  at two points in time during the CPT-AX, and in both cases, reductions in FC are associated with increases (improvements) in H-SIS. The first point in time occurs approximately 150 ms after the appearance of the "A" where reductions in frontal-prefrontal FC were correlated with increased H-SIS at a threshold level of  $|r| \geq .403$  corresponding to  $p \leq .01$  (Figure 1A) in 97 electrode pairs. The second point in time occurs approximately 750 ms after the appearance of the "X," shortly after the mean reaction time, where FC reductions at right temporofrontal-prefrontal and frontal-prefrontal regions are correlated with hyperactivity symptom improvements. In both cases, the permutation test indicated that the null hypothesis (no correlation between the number of electrode pairs identified and H-SIS) can be rejected at the  $p = .03$  level. Finally, at an  $r \geq .403$ , we are observing a

**Table 1. Parent-Rated Mean Inattention and Hyperactivity Symptom Scores Before and 3 Months After Starting MPH Medication**

	Initial Symptom Score, Mean (SD)	3-Month Symptom Score, Mean (SD)	Paired <i>t</i> Test for Symptom Score Difference	Mean Improvement Score, Mean (SD)
Inattention	20.2 (4.4)	11.3 (4.5)	$t_{39} = 12.4, p < 10^{-5}$	0.43 (0.17)
Hyperactivity	16.2 (6.3)	9.3 (5.5)	$t_{39} = 8.0, p < 10^{-5}$	0.39 (0.30)

MPH, methylphenidate.



**Figure 1.** Correlation frequency curve for the number of electrode pairs where methylphenidate-induced changes in functional connectivity ( $\Delta FC$ ) are correlated with hyperactivity symptom improvement score (H-SIS), with  $|r| \geq .403$  corresponding to  $p \leq .01$ . The red trace indicates the number of electrode pairs where  $\Delta FC$  is positively correlated with H-SIS, while the blue trace illustrates the corresponding value where  $\Delta FC$  is negatively correlated with H-SIS. Overwhelmingly, we see a negative correlation between  $\Delta FC$  at frontal and prefrontal sites and H-SIS indicating that long-term hyperactivity symptom reductions were associated with a methylphenidate-mediated reduction in FC. Permutation tests indicate that the probability of observing the illustrated number of correlations by chance (the null hypothesis) is  $p < .01$  for the first peak (A) and  $p < .01$  for the second peak (B). Neg, negative; Pos, positive.

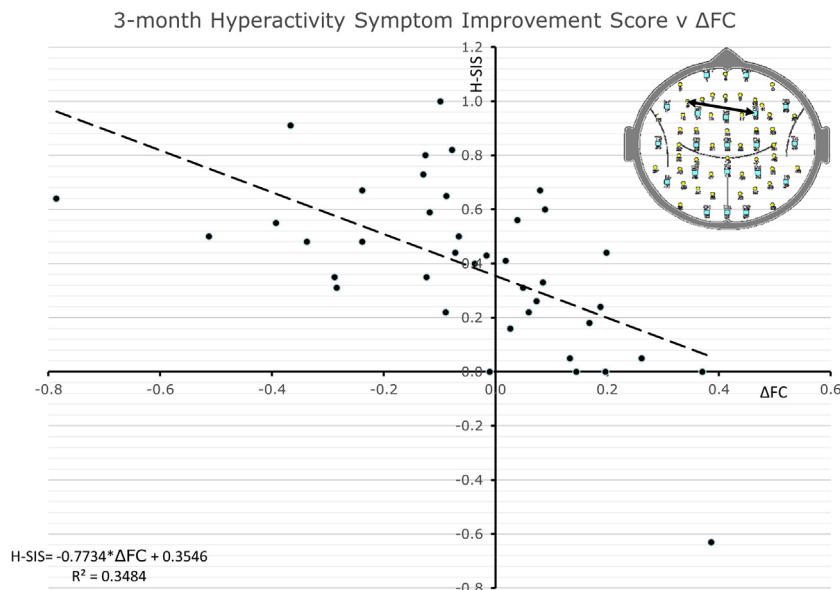
moderate to large effect size in the electrode pairs identified in Figure 1. The extent to which 3-month H-SIS is predicted by a frontal-prefrontal MPH-induced  $\Delta FC$  at a point in time 150 ms after the appearance of the “A” is illustrated in Figure 2.

I-SIS, similar to H-SIS, is also negatively correlated with  $\Delta FC$  in that reductions in inattention (or increases in I-SIS) are associated with an MPH-induced reduction in FC (Figure 3). While the correlations of  $\Delta FC$  with H-SIS and I-SIS are both negative, the time in the task trial where this relationship becomes significant and the topography of the FC correlated with I-SIS are different. I-SIS is maximally correlated with occipitoparietal  $\Delta FC$  approximately 1000 ms after the appearance of the “A.” A permutation test indicated that the null hypothesis (no correlation between the number of electrode pairs identified and I-SIS) can be rejected at the  $p = .01$  level. Finally, the extent to which 3-month I-SIS is predicted by an occipitoparietal MPH-induced  $\Delta FC$  at a point in time 1000 ms after

the appearance of the “A” is illustrated in Figure 4. The Supplement provides an analysis of the findings based on the difference in symptom score rather than the proportional difference used here.

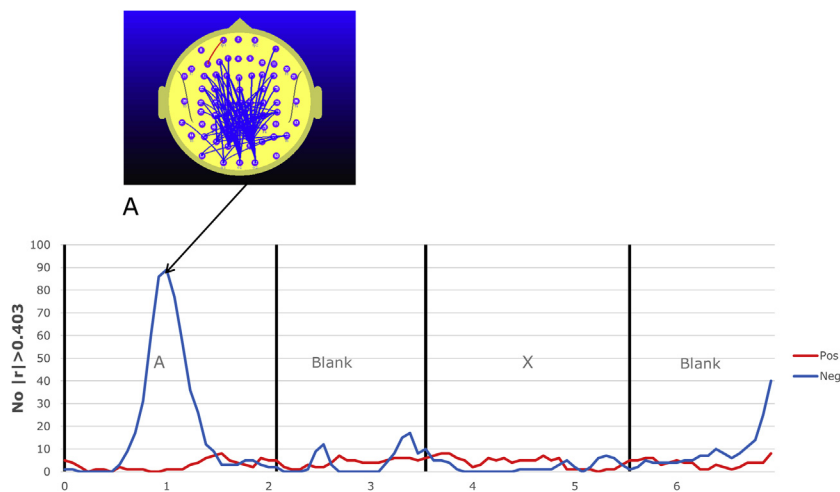
## DISCUSSION

To the best of our knowledge, this is the first study reporting a relationship between first-dose MPH-induced changes in brain FC and long-term response of ADHD symptoms to stimulant medication. It is notable that both inattention and hyperactivity symptoms exhibited improvements after 3 months on MPH and that both of these improvements were associated with initial MPH-induced FC reductions. In broad terms, these findings are consistent with the notion that MPH may achieve its therapeutic effect by increasing DA and NE levels, which suppress brain FC networks interfering with task performance,



**Figure 2.** Scatterplot illustrating the initial methylphenidate-induced change in functional connectivity ( $\Delta FC$ ) between frontal-prefrontal electrodes  $AF_3-F_4$  (arrow) at the point in time illustrated in Figure 1A vs. 3-month hyperactivity symptom improvement score (H-SIS). The best-fit linear relationship between H-SIS and  $\Delta FC$  gives an indication of the likely improvement in hyperactivity symptoms based on the initial changes in  $AF_3-F_4$  FC at the point in time 150 ms after the appearance of the “A” in correct AX continuous performance task trials. v, versus.

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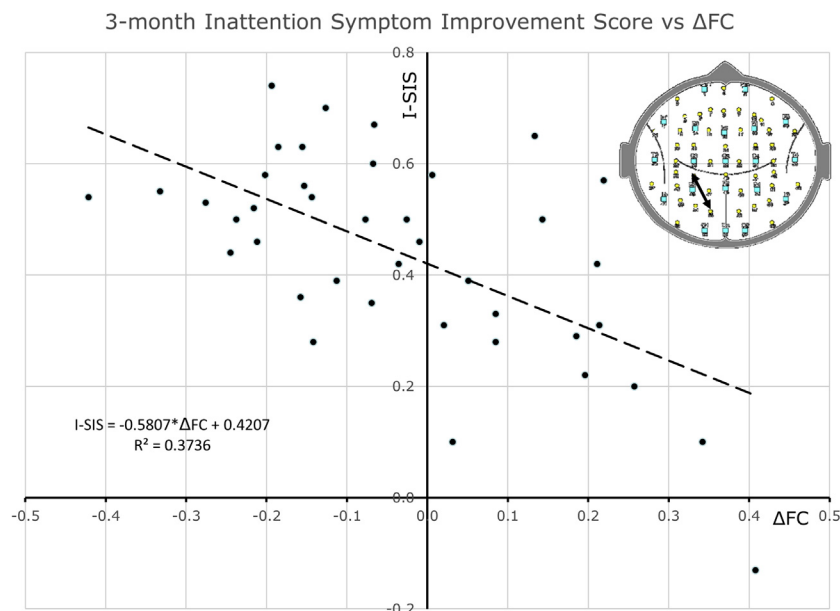
**Figure 3.** Correlation frequency curve for the number of electrode pairs where methylphenidate-induced changes in functional connectivity ( $\Delta FC$ ) are correlated with inattention symptom improvement score, with  $|r| > .403$  corresponding to  $p < .01$ . The red trace indicates the number of electrode pairs where  $\Delta FC$  is positively correlated with inattention symptom improvement score, while the blue trace illustrates the corresponding value where  $\Delta FC$  is negatively correlated with inattention symptom improvement score. As in **Figure 1**, methylphenidate-mediated reductions in parieto-occipital FC were associated with long-term improvements in inattention symptoms. A permutation test indicated that the probability of observing the illustrated number of correlations illustrated in **(A)** by chance (the null hypothesis) is  $p = .01$ . Neg, negative; Pos, positive.

such as, but not limited to, the DMN (31). In the following sections, we consider the relationship between the initial MPH-induced changes in FC and each of the symptoms, hyperactivity and inattention, separately. We base this relationship on the fact that the 3-month MPH-induced changes in hyperactivity and inattention symptom scores are not significantly correlated as well as the fact that the timing and topography of  $\Delta FC$  correlated with long-term improvements in hyperactivity symptoms differ from the timing and topography of  $\Delta FC$  correlated with the inattention symptom improvements.

### Brain FC Correlates of Hyperactivity Symptom Improvements

Of the two points in time during the CPT-AX trials where  $\Delta FC$  was correlated with increased H-SIS, the first of the correlated

FC changes was located at frontal-prefrontal sites and occurred immediately after the appearance of the warning “A” (**Figure 1A**). We suggest this  $\Delta FC$  could represent reduced motor and supplementary motor activity during the appearance of the “A” and could be associated with reduced impulsivity and a reduced tendency to commit an error of commission by responding to the appearance of the “A.” This is consistent with our observation of a nonsignificant decrease in the number of errors of commission in the post-MPH condition. The other point in time where  $\Delta FC$  is correlated with increased H-SIS occurs approximately 750 ms after the appearance of the “X” and approximately 200 ms after the mean response time. At this point in time, the topography of  $\Delta FC$  is predominantly bilateral frontal and right temporofrontal (**Figure 1B**). The timing of this second peak of correlation



**Figure 4.** Scatterplot illustrating the initial methylphenidate-induced change in functional connectivity ( $\Delta FC$ ) between occipital-parietal electrodes  $CP_3-PO_3$  (arrow) at the point in time illustrated in **Figure 3** vs. 3-month inattention symptom improvement score (I-SIS). The best-fit linear relationship between I-SIS and  $\Delta FC$  gives an indication of the likely improvement in hyperactivity symptoms based on the initial changes in  $CP_3-PO_3$  FC at the point in time 1000 ms after the appearance of the “A” in correct AX continuous performance task trials.

suggests that it may represent FC changes associated with the termination of the motor response.

To the extent that our FC measures may give some indication of regional brain activity, our findings are consistent with a number of studies reporting increased regional brain activity at motor execution and planning areas in ADHD (13). The findings are also consistent with transcranial magnetic stimulation studies of ADHD that indicate reduced gamma-aminobutyric acid-mediated synaptic inhibition in the motor cortex (31). However, to interpret our hyperactivity findings in the context of ADHD as a disorder of FC, we draw on functional magnetic resonance imaging (fMRI) findings concerning the relationship between impulsivity and brain FC. Some of these fMRI studies indicated that the normal negative correlation between the DMN and regions associated with motor planning and execution are altered in individuals with high impulsivity. The normal negative correlation is either reduced or replaced with a positive correlation between the DMN and the motor planning and execution regions, such as the left and right dorsolateral premotor cortex (32,33). In other words, high impulsivity was associated with a positive right dorsolateral premotor cortex-DMN correlation, suggesting that impulsivity could arise from the DMN, driving motor planning and execution areas. We consider this finding useful, as it offers an interpretive framework for understanding ADHD hyperactivity symptomatology in the context of DMN connectivity abnormalities. The role of the DMN in ADHD symptomatology is most frequently discussed in the context of attentional deficits, where DMN intrusions are thought to contribute to the attentional deficits in ADHD. The above-mentioned studies offer a parsimonious interpretation of why DMN functional abnormalities may contribute to both attention deficits and hyperactivity and why the frontal-prefrontal FC changes correlated with hyperactivity symptom improvement that we have observed may be driven (directly or indirectly) by abnormal DMN activity. In other words, our observations of MPH-induced reduction in frontal-prefrontal FC being correlated with improved H-SIS is consistent with the possibility that frontal-prefrontal FC reduction is in part mediated by MPH reduction of DMN activity and hence a reduction of DMN activation of the motor planning and motor execution regions previously described (32,33).

### Brain FC Correlates of Inattention Symptom Improvements

While improvements in both hyperactivity and inattention symptoms are associated with reductions in FC during specific intervals in the CPT-AX, the similarity ends there. Not only did the correlation between  $\Delta$ FC and I-SIS occur at one point in time, but more importantly, it exhibited a different topography in that the  $\Delta$ FC associated with inattention symptom improvements was restricted to occipitoparietal sites. The fact that the peak correlation between  $\Delta$ FC and I-SIS occurs only once 1.0 second after the appearance of the alerting stimulus “A” suggests that the improvements are associated with enhanced cue processing. Our findings point to occipitoparietal involvement in ADHD inattention symptomatology and indicate that MPH reductions in parieto-occipital FC during the cue “A” are associated with long-term improvements in

inattention symptom score. The fact that improvement in inattention symptoms is marked by reduced occipitoparietal FC is also consistent with the notion that inattention is associated with an inability to suppress attention to irrelevant stimuli (34).

While the occipital cortex is not normally considered relevant to ADHD (13), a number of EEG and fMRI studies have reported occipital abnormalities in ADHD. For example, Vance *et al.* (35) reported reduced occipitoparietal activity in a cohort of boys diagnosed with ADHD combined subtype while they performed a mental rotation task. Similarly, occipital FC differences between ADHD inattentive subtype and ADHD combined subtype were reported in an fMRI study (36). Our observation that occipitoparietal  $\Delta$ FC correlated with I-SIS during the “A” cue is also consistent with the findings of an ADHD CPT-AX event-related potential study that reported that differences between ADHD and typically developing groups during the alerting “A” were restricted to posterior electrodes (37), findings that were subsequently confirmed (38).

Studies using fMRI that reported increased occipital activity in ADHD have been interpreted as an indication of ADHD-related compensatory activity in a cognitive task (39). While our observation of the relationship between MPH-mediated occipitoparietal FC reduction predicting 3-month inattention symptom improvements is consistent with the compensatory activity hypothesis, we suggest our findings also allow an alternative hypothesis. Specifically, our findings are consistent with the hypothesis that the ADHD inattention symptoms may be in part a consequence of DMN positively activating or driving the visual cortex. In this case, the increased occipital activity observed in ADHD may be due to abnormal DMN activation of the visual cortex rather than compensatory activation of the visual cortex. While task positive networks such as the visual network are normally negatively correlated with DMN activity, this negative correlation is reduced in ADHD, and a positive correlation is frequently observed (40). Such a positive correlation between DMN and occipital activity would be consistent with the possibility of DMN driving the visual network, thereby giving rise to symptoms of inattention and increased distractibility. Our observations of MPH-induced reduction in occipitoparietal FC being correlated with improved I-SIS is consistent with the possibility that the occipitoparietal FC reduction is in part mediated by MPH reduction of DMN activity and hence a reduction of DMN activation of the visual networks.

On a more general note, our findings suggest that improvements in inattention and hyperactivity symptoms may be in part mediated by distinct cortical networks, and this is consistent with some reports suggesting that the ADHD inattentive and ADHD combined subtypes may possibly constitute distinct disorders (41). Hyperactivity symptom improvements may be mediated predominantly by reductions in FC in frontal and motor supplementary cortex networks, whereas inattention symptom improvements may be associated with posterior attentional network system FC reductions. While MPH appears to improve both hyperactivity and inattention symptoms, the distinct anteroposterior distinction in the topography of  $\Delta$ FC suggests that both DA and NE may play distinct roles in symptomatic improvement. Given the predominantly frontal bias of DA projections originating in the ventral tegmental area

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and the corresponding posterior bias of NE projections originating in the locus coeruleus, our findings are consistent with the possibility that MPH-mediated improvements in hyperactivity symptoms are mediated by DA changes, whereas the improvements in inattention symptoms occur as a result of MPH-induced increases in NE (4). Notwithstanding the differing roles of these catecholamines in mediating improvements in inattention and hyperactivity symptoms, our findings are consistent with the possibility that the DMN is likely to play a role in both sets of symptoms.

### Conclusions

While we believe these findings may be of interest, a number of caveats apply. First, no aspect of the diagnosis or treatment of participants was at the discretion of the investigators. As such, we have limited information on the extent to which patients adhered to the prescribed MPH intake level or the changes in MPH dosage recommended by individual clinicians. Second, all participants were MPH naïve, and it is possible that participants who had been previously prescribed MPH may respond differently. In addition, there is a need to determine the replicability of our findings in a larger patient group. Furthermore, any larger replication study should make use of both teacher and parent ratings. Finally, in considering a replication study, it is important to note that the findings depend very much on the methodology used to determine FC. Our method using the 13-Hz SSVEP to determine FC would be biased to cortical communication components mediated by oscillations around 13 Hz. This is important, as top-down or feedback cortical communication is thought to be mediated by synchronous oscillations in the 10- to 20-Hz range (26,42), and thus our findings are preferentially sensitive to top-down processes.

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### ARTICLE INFORMATION

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