◆ Human Brain Mapping 34:566–574 (2013) ◆

Broadband Neurophysiological Abnormalities in the Medial Prefrontal Region of the Default-Mode Network in Adults with ADHD

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Abstract: Previous investigations of the default-mode network (DMN) in persons with attention-deficit/hyperactivity disorder (ADHD) have shown reduced functional connectivity between the anterior and posterior aspects. This finding was originally demonstrated in adults with ADHD, then in youth with ADHD, and has been tentatively linked to ultra low frequency oscillations within the DMN. The current study evaluates the specificity of DMN abnormalities to neuronal oscillations in the ultra low frequency range, and examines the regional specificity of these DMN aberrations in medicated and unmedicated adults with, and those without ADHD. An individually matched sample of adults with and without ADHD completed 6-minute sessions of resting-state magnetoencephalography (MEG). Participants with ADHD were known responders to stimulant medications and completed two sessions (predrug/postdrug). MEG data were coregistered to the participant's MRI, corrected for head motion, fitted to a regional-level source model, and subjected to spectral analyses to extract neuronal population activity in regions of the DMN. The unmedicated adults with ADHD exhibited broadband deficits in medial prefrontal cortices (MPFC), but not other DMN regions compared to adults without ADHD. Unmedicated patients also showed abnormal cross-frequency coupling in the gamma range between the MPFC and posterior cingulate areas, and disturbed balance within the DMN as activity in posterior regions was stronger than frontal regions at beta and lower frequencies, which dissipated at higher γ-frequencies. Administration of pharmacotherapy significantly increased prefrontal alpha activity (8–14 Hz) in adults with ADHD, and decreased the cross-frequency gamma coupling. These results indicate that neurophysiological aberrations in the DMN of patients with ADHD are not limited to ultra slow oscillations, and that they may be primarily attributable to abnormal broadband activity in the MPFC. *Hum Brain Mapp 34:566–574, 2013.* © 2011 Wiley Periodicals, Inc.

Key words: attention; stimulant; gamma; theta; magnetoencephalography; MEG; delta; ADD

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Received for publication 17 March 2011; Revised 29 July 2011; Accepted 9 August 2011
DOI: 10.1002/hbm.21459
Published online 18 November 2011 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder seen in children and adolescents, with core symptomatology that includes inattention and hyperactivity/impulsivity [CDC, 2005]. Some clinically impairing symptoms (e.g., inattention) will persist into adulthood for about 65% of these children, while another 15% will exhibit the full-blown disorder as adults [Faraone et al., 2006]. In most cases the hyperactivity component decreases as the child approaches adulthood, but the inattention and impulsivity symptoms are maintained and generally become the dominant features of the disorder in adult life [Seidman et al., 2004; Wilens et al., 2009]. Overall, ADHD prevalence estimates for adults living in the United States are at 4–5% of all persons between 18- and 44-years-old [Kessler et al., 2006], which positions it as one of the three most common psychiatric disorders in adults [NIMH, 2010].

Although ADHD is one of the better success stories of psychopharmacology, the neuronal bases of the disorder remain poorly understood. Several recent functional imaging studies of ADHD have focused on the brain's so-called default-mode network (DMN), which refers to a group of brain areas that are active when a person engages in processes such as self-reflection or mind wandering [Raichle et al., 2001]. A large corpus of normative studies have identified and characterized this network, which includes medial prefrontal cortex (MPFC), the posterior cingulate/precuneus cortices (PCC), and the mediolateral inferior parietal cortices bilaterally (RIPL and LIPL) [Konrad and Eickhoff, 2010; Laird et al., 2009; Schilbach et al., 2008]. These brain regions are generally more active in healthy persons during awake rest than during cognitively active states, and appear to maintain strong inter-regional coupling [Fox and Raichle, 2007; Greicius and Menon, 2004; Raichle et al., 2001]. These brain areas also seem to maintain a fairly robust inverse correlation with task-oriented cortices, as they exhibit deactivations when attentional and other networks are strongly engaged and become reactivated when such task-oriented processing subsides [Fox et al., 2005; Singh and Fawcett, 2008].

Studies of resting-state DMN activity in ADHD have reached somewhat heterogeneous results, but the most consistent finding has been reduced functional connectivity between MPFC regions and the PCC cortices [Castellanos et al., 2008; Fair et al., 2010; Uddin et al., 2008]. Castellanos et al. also found less functional connectivity between superior precuneus and medial posterior cingulate regions, which may suggest aberrations within the PCC node of the DMN [Castellanos et al., 2008]. Evidence for increased resting-state activation in the primary sensory and sensory-related cortices of adolescents with ADHD is also available, which although indirect does point to abnormalities in DMN function [Tian et al., 2008]. A recent pharmacological-fMRI study reported reduced deactivation of medial frontal cortices during the task period in unmedicated adolescents with ADHD compared with matched controls, as well as enhanced suppression of activity in medial frontal and posterior cingulate cortices following stimulant administration in the ADHD group [Peterson et al., 2009]. Thus, at a minimum, stimulant medications act to normalize fMRI measures of DMN activity in adolescents with ADHD. Finally, two electrophysiological studies have shown reduced ultra low frequency activity in children and adults with ADHD using scalp electrodes that are roughly aligned with DMN structures [Helps et al., 2008, 2010]. Such ultra low frequency oscillations are thought to reflect the same physiological phenomena that are captured by BOLD-based functional connectivity metrics. However, the connection between functional anatomy and electrophysiology remains very tenuous given that these studies are based on scalp measurements [Helps et al., 2008, 2010], which are spatially nonspecific in regard to DMN structures and associated with several other limiting factors.

fMRI studies of the DMN have generally identified the component structures by utilizing a task period and a resting period to isolate the task-negative components (i.e., DMN regions), or have selected a seed region (e.g., PCC) from which temporal correlations of the BOLD signal can be computed. Another common method of isolating the DMN is to use independent components analysis, which normally yields similar results to the seed-region correlation method. Although these methods have provided tremendous insight, they cannot evaluate the absolute (not relative) function of individual DMN regions. Here we evaluate neurophysiological function within cortices of the DMN during a period of awake rest, without a comparison task, using magnetoencephalography (MEG) in unmedicated and medicated adults with ADHD (predrug/postdrug), as well as group of adults without ADHD. Although previous EEG and fMRI studies have illuminated ultra low frequency aberrations, we chose to take a more exploratory approach and examine oscillations across a broader range of the spectrum. We also probed for any cross-frequency coupling (i.e., amplitude correlations between frequency bands in the single-trial data) amongst areas of the DMN. Our primary hypotheses were that unmedicated adults with ADHD would show reduced MPFC and PCC oscillatory activity in the alpha and lower bands (< 12 Hz), and that this would be normalized by the administration of stimulant medications.

MATERIALS AND METHODS

Subject Selection

We studied 12 adults (four females) with ADHD, inattentive type and 12 adults (four females) without ADHD. Mean ages were 40.58 years (ADHD) and 40.08 years (controls) at enrollment. All participants were right-handed, except one participant with ADHD. All participants with ADHD had shown a satisfactory clinical response to a

mixture of dextroamphetamine salts, extended release formula (MAS-XR; Adderall XR), and been prescribed the same regularly monitored dosage for at least 6 months prior to enrollment in this study. ADHD diagnoses were based on a semistructured comprehensive psychiatric assessment by a board-certified psychiatrist (MWW) utilizing DSM-IV diagnostic criteria, the Adult ADHD Symptom Rating Scale [Kessler et al., 2005], and collateral history. Exclusionary criteria included any medical illness affecting CNS function, neurological disorder, history of head trauma, and current substance abuse. After complete description of the study to participants, written informed consent was obtained in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards of the University of Nebraska Medical Center's Institutional Review Board.

Experimental Paradigm

All participants were scheduled for MEG early in the morning (e.g., 07:30–08:00) and for the group with ADHD, a minimum of 18 h since their last stimulant dosage. Upon arrival, each participant was positioned inside the MEG room and completed one 6-min block of awake eyes-closed-rest (ECR). Participants were instructed to relax and remain awake with their eyes closed. After the recording, participants with ADHD were orally administered their standard dosage of MAS-XR and moved to the patient waiting area. Approximately 75 min later, these participants returned to the MEG room and completed a second (identical) block of ECR.

MAS-XR is an extended release amphetamine product FDA approved for the treatment of ADHD in adults. It combines neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate. Upon administration, blood plasma concentration levels rise sharply then begin to asymptote toward a peak of 20–30 ng/mL at 6–8 h postadministration. This is followed by a gradual decline in plasma concentration level over the next 16–18 h. However, the degree to which the brain's response curve follows the plasma concentration curve is entirely unknown.

Structural Magnetic Resonance Imaging (MRI)

High-resolution anatomic images were acquired using a Philips Achieva 3T X-series scanner. The T1-weighted sagittal images were obtained with an eight channel head coil using a 3D fast field echo sequence with the following parameters: field of view, 24 cm; slice thickness, 1 mm with no gap; in-plane resolution, 1.0 × 1.0 mm; sense factor, 1.5. The structural volumes were aligned parallel to the anterior and posterior commissures and used for MEG coregistration.

MEG Data Acquisition

With an acquisition bandwidth of 0.1–330 Hz, neuromagnetic responses were sampled continuously at 1 kHz using an Elekta Neuromag system with 306 magnetic sensors (Elekta, Helsinki, Finland). Using MaxFilter (v2.1.15; Elekta), MEG data from each session and subject were transformed into a standard device-centered head position, individually corrected for head motion, coregistered to structural MRI, and subjected to noise reduction using the signal space separation method with a temporal extension [Taulu and Simola, 2006; Taulu et al., 2005].

MEG Source Analyses

Following tSSS and head-motion correction, the entire magnetic time series was transformed into a 29-node regional source model via inverse spatial filtering (see Fig. 1). Essentially, a 29-point grid with dual orthogonal orientations per point was constructed, and each orientation was used as an inverse spatial filter on the continuous 204-sensor time series data of the entire 6-min recording, per condition and participant [Hoechstetter et al., 2004; Scherg et al., 2002]. After transformation into source space, the current-amplitude (nAm) time series for each of the two orthogonal orientations per source was divided into epochs of 4096-ms duration (4,096 points). Artifact rejection was based on a fixed threshold method supplemented with visual inspection. For each session and participant, artifact-free epochs were transformed into the frequency domain using Fourier analyses (i.e., 4096 data points per window). Average spectra across the 6-min recording were then computed for each orientation per brain region by averaging the ~90 Fourier-transformed epochs. Subsequently, for each of the 29 regional sources, the amplitude per band was summed across the two orthogonal orientations to yield the total current-amplitude per frequency band for the particular brain region. For the cross-frequency correlation analyses, this summing across orthogonal orientations (per band) was performed on each of the ~90 Fourier-transformed epochs, and these individual epochs (per brain region) were maintained for statistical analyses. Based on previous studies of the DMN [Konrad and Eickhoff, 2010; Laird et al., 2009], we focused on regional sources centered in the MPFC, PCC, LIPL, and RIPL regions and examined the local spectral amplitude within nine frequency bands (1–4, 4–7, 8–14, 14–30, 30–56, 64–82, 82–106, 124–168, and 184–228 Hz) using repeated measures ANOVA analyses per frequency band. Initially, we evaluated group differences using mixed-model ANOVAs with brain region as a within-subjects factor and group (with/without ADHD) as a between-subjects factor. Statistical analyses were conducted in SPSS (Release 11.0.1). All MEG preprocessing and source modeling used the Brain Electrical Source Analysis (BESA version 5.3.2) software, and MEG-MRI coregistration and visualization used the BrainVoyager QX (version 2.2) software.

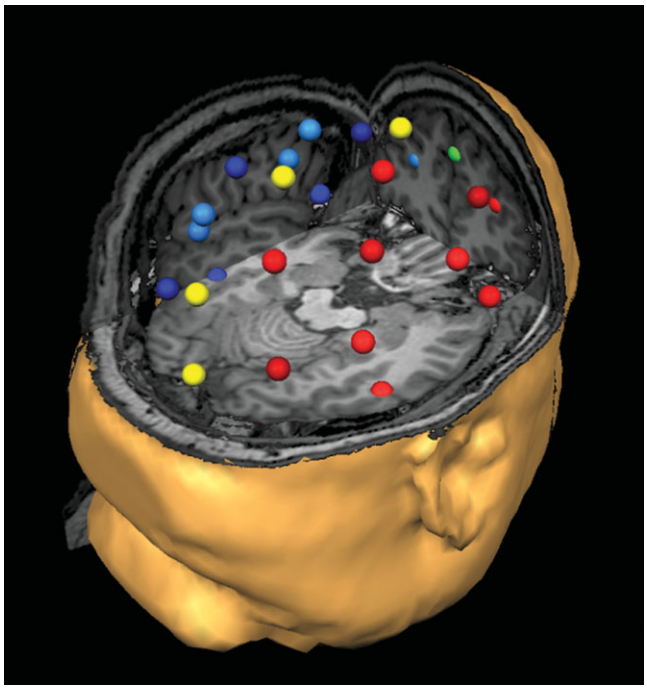

Figure 1.
Representative example of the 29-node regional source model. For each participant, a 29-node (grid-point) model was fitted to their individual MRI following coregistration, and this model was used to estimate regional neuronal activity during the resting-state MEG recording using inverse spatial filtering. In the figure above, the model can be seen overlaid on the MRI of a participant with ADHD. The different colors are only meant to aid in visually distinguishing the regional sources. Note that the regional sources are spaced equidistant apart and that each represents activity over an extended cortical area (i.e., > 1 cm^3). Thus, the time series of each node reflects the average neuronal activity over that brain region, and not the amount of activation at a precise neuroanatomical coordinate (e.g., a voxel in MNI space). The nodes corresponding to the classic DMN regions were the focus of all quantitative and statistical analyses of the current study. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

RESULTS

MEG Data: Between-Group Comparisons

The mixed-model ANOVA analyses for spectral amplitude revealed largely similar effects regardless of frequency band. Essentially, for each band, there was a main effect of region (all P's < 0.0001) and a region-by-group interaction effect (range: $P = 0.03$ to $P < 0.0001$). The main effect of group was not significant for lower frequency bands (i.e., 1–4, 4–7, and 8–14 Hz), but was significant for all higher frequency bins (i.e., 14–30, 30–56, 64–82, 82–106, 124–168, and 184–228 Hz; all P's < 0.03) and always indicated that adults without ADHD had higher amplitudes compared with unmedicated adults with ADHD. Follow-up testing of the region-by-group interaction effects showed that in each frequency bin, MPFC activity was reduced in unmedicated adults with ADHD relative to their peers without ADHD (all P's < 0.01; see Fig. 2). No other DMN area showed significant group effects regardless of frequency. Because of the interaction term, follow-up testing of the regional main effects were conducted on each group individually. In controls, these analyses generally indicated that activity was significantly stronger in the MPFC and LIPL compared to the PCC and RIPL areas. MPFC and LIPL did not statistically differ and RIPL activity was stronger than PCC (see Fig. 3). Regional data from the unmedicated adults with ADHD showed frequency-specific effects. Essentially, at lower frequencies LIPL and RIPL were significantly stronger than the MPFC and PCC areas, but did not statistically differ from each other. At gamma ranges (> 30 Hz), the MPFC was significantly stronger than all other nodes, whereas LIPL and RIPL were greater than the PCC but again did not differ from each other (see Fig. 4).

MEG Data: MAS-XR Treatment Effects

Evaluation of MAS-XR treatment effects was restricted to the MPFC, as this was the only DMN node that showed significant group effects in unmedicated patients. Paired t-tests indicated that MAS-XR increased 8–14 Hz (alpha) activity in the MPFC, $t(11) = -2.861$ ($P = 0.015$) and marginally increased 1–4 Hz delta activity ($P < 0.08$) and 14–30 Hz beta activity ($P < 0.08$) in adults with ADHD (see Fig. 2). No other predrug/postdrug changes were significant. Follow-up testing using the post-treatment ADHD data indicated that all significant group effects for MPFC remained with the exception of 8–14 Hz alpha activity, which did not statistically differ between medicated adults with ADHD and their non-ADHD peers.

MEG Data: Cross-Frequency Coupling

Given our findings of abnormal broadband activity in the MPFC, this node was chosen as the seed region for analyses of cross-frequency coupling. Briefly, the individual Fourier-transformed epochs of each participant ($\sim$90) were subjected to a correlational analysis to derive Pearson-correlation coefficients for the amplitudes of MPFC activity per band and the amplitudes of all other DMN regions per band. This yielded nine cross-frequency correlation matrices per data set, corresponding to the nine frequency bands, each containing 24 correlation coefficients (i.e., the MPFC seed band and the other eight bands per three brain regions). These correlation coefficients were converted to z-values using Fisher's r-to-z transformation to obtain a normally distributed variable [Fisher, 1915, 1921; Hotelling, 1953]. One-sample t-tests were then used to assess significance at the group level for each frequency

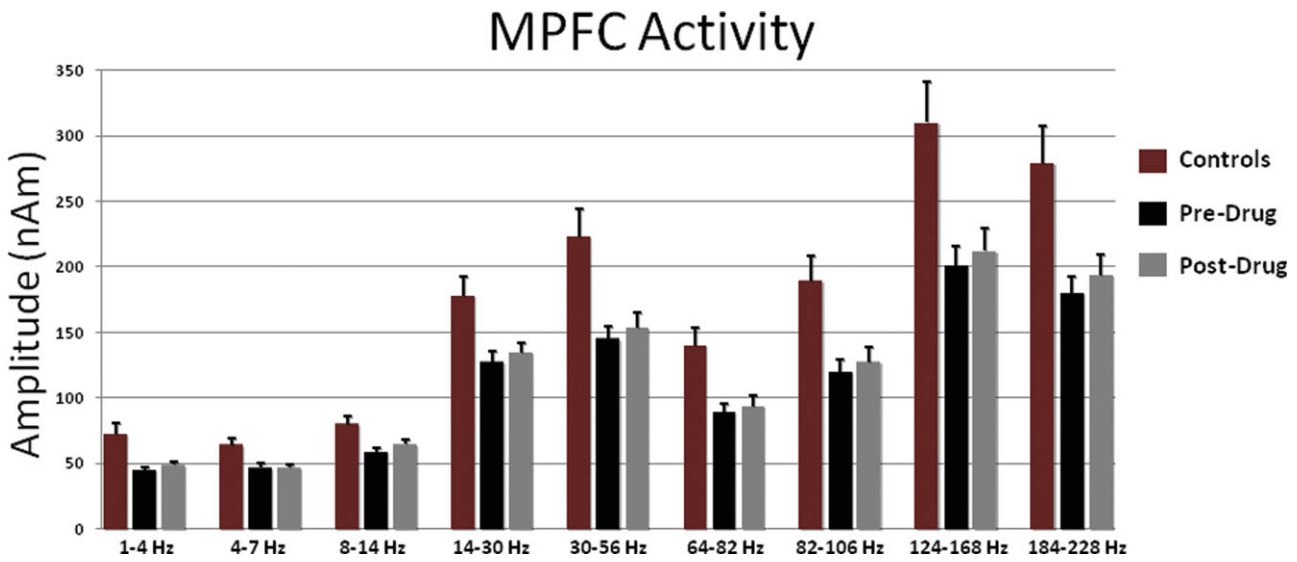

Figure 2.

Medial prefrontal activation per frequency band. Unmedicated adults with ADHD exhibited significantly reduced activity in the MPFC across all frequency bins relative to adults without ADHD. Oral ingestion of amphetamine (MAS-XR) significantly increased MPFC activity in the 8–14 Hz (alpha) range in adults with ADHD, and this increase eliminated the group difference for alpha activity in the MPFC region. However, all other group differences remained after administration of MAS-XR (i.e., medicated adults with ADHD $<$ adults without ADHD). On the *x*-axis, group means of MPFC activity per MEG session and group are shown per frequency band. Color coding is explained in the legend. The *y*-axis reflects total nAm per band. Error bars indicate one standard error of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

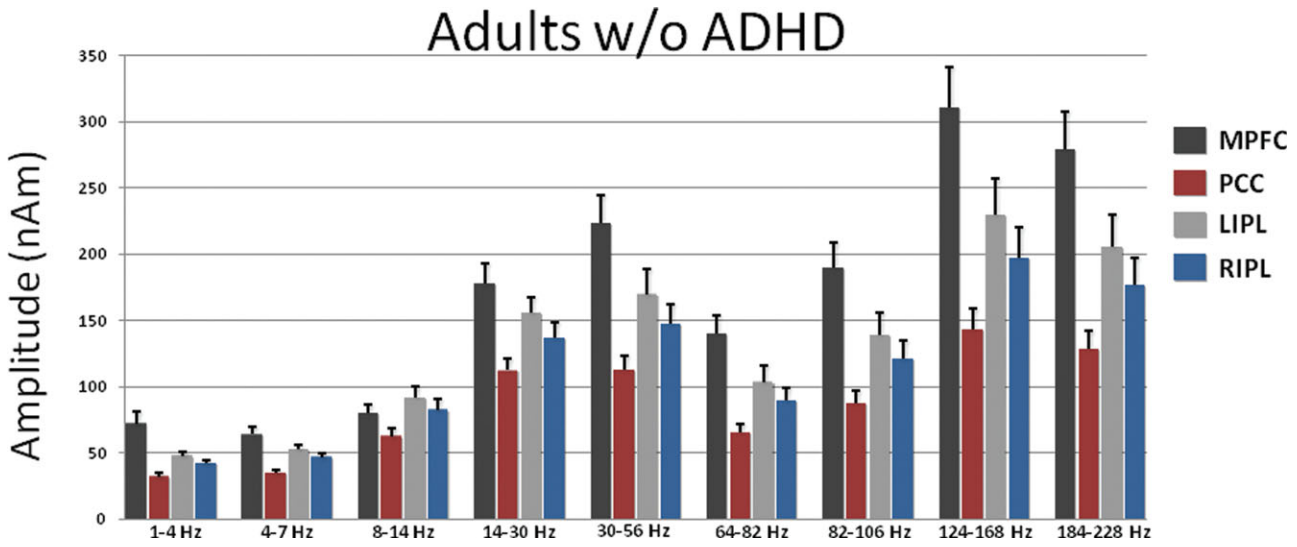

Figure 3.

Data summary for the adults without ADHD. Each of the four DMN regions are shown in a different color (see figure legend) and grouped together per frequency band along the *x*-axis. The *y*-axis reflects total nAm per band. Participants without ADHD showed clear regional amplitude effects that generally favored the MPFC region. Essentially, activity was strongest in the MPFC, then LIPL $>$ RIPL $>$ PCC. However, 8–14 Hz alpha activity was an exception to this overall pattern and showed LIPL $>$ RIPL $=$ MPFC $>$ PCC. Across all bands, PCC activity was the weakest. Error bars indicate one standard error of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

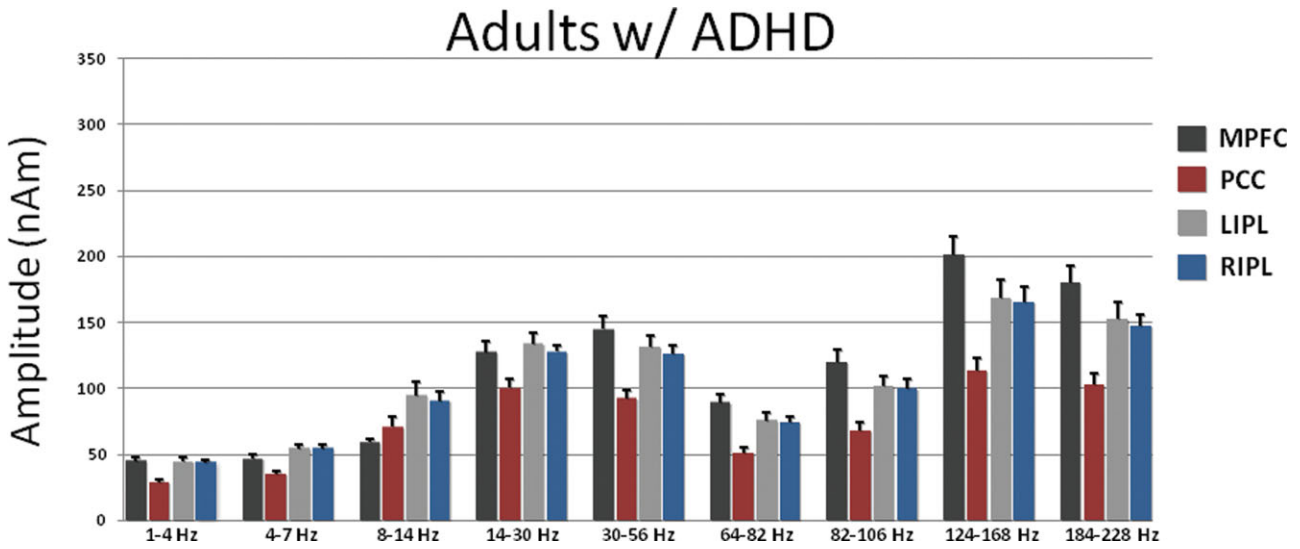

Figure 4.

Data summary for the unmedicated adults with ADHD. As with Figure 3, each of the four DMN regions are shown in a different color (see figure legend) and grouped together by frequency band along the *x*-axis. The *y*-axis reflects total nAm per band. Unlike controls, regional amplitude effects in participants with ADHD showed more frequency-specificity. Within the lower frequency ranges of 4–7 Hz theta and 8–14 Hz alpha, activity was strongest in the LIPL and RIPL areas (i.e., 4–7 Hz: LIPL = RIPL > MPFC > PCC; 8–14 Hz: LIPL = RIPL > MPFC = PCC). However, at higher frequencies (i.e., > 30 Hz) this pattern reversed and the MPFC region showed the strongest resting oscillatory activity, which was consistent with the γ-frequency data from controls. MAS-XR administration was generally associated with nonsignificant increases in neuronal oscillatory activity; although these increases were significant for MPFC activity in the 8–14 Hz range and approached significance for the beta (14–30 Hz) and delta (1–4 Hz) bands (both *P*'s < 0.08; see Fig. 2). Error bars indicate one standard error of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

band of MPFC activity. Bonferroni adjustment was used to correct for multiple comparisons in each set of 24 tests, which yielded a significance level of $P < 0.0021$.

We observed no significant anticorrelations (i.e., negative correlations) in any group. Participants without ADHD exhibited significant cross-frequency coupling involving alpha (8–14 Hz) and beta (14–30 Hz) activity in the MPFC. Essentially, 8–14 Hz activity in the MPFC of controls was positively correlated with 4–7 Hz theta activity in the LIPL [$t(11) = 5.03$, $P < 0.0005$] and PCC regions [$t(11) = 5.08$, $P < 0.0005$], and 14–30 Hz activity in the LIPL and RIPL regions (*P*'s < 0.001). Likewise, the amplitude of 14–30 activity in the MPFC was significantly correlated with alpha activity in the LIPL [$t(11) = 4.38$, $P < 0.001$] and RIPL [$t(11) = 5.28$, $P < 0.0005$]. See Table I for a summary.

In unmedicated ADHD patients, MPFC 8–14 Hz alpha activity was correlated with PCC theta [4–7 Hz; $t(11) = 4.18$, $P < 0.001$], and 14–30 Hz beta activity in LIPL, PCC, and RIPL (all *P*'s < 0.0005). Unmedicated patients also exhibited positive correlations between 14–30Hz MPFC beta activity and LIPL alpha [8–14 Hz; $t(11) = 4.15$, $P < 0.001$] and PCC gamma activity [30–56 Hz; $t(11) = 4.61$, $P < 0.001$]. Additionally, MPFC activity at 64–82 Hz in unmedicated ADHD patients was correlated with 30–56 Hz PCC activity [$t(11) = 4.80$, $P < 0.001$] and 184–228 Hz RIPL activity [$t(11) = 4.21$, $P < 0.001$], while MPFC activity at 124–168 and 184–228 Hz was correlated with 64–82 Hz activity in the PCC [124–184 Hz: $t(11) = 4.74$, $P < 0.001$; 184–228 Hz: $t(11) = 4.12$, $P < 0.001$]. These high-gamma cross-frequency correlations dissipated following stimulant administration. Basically, like healthy controls, medicated patients exhibited significant correlations involving only MPFC alpha (8–14 Hz) and beta (14–30 Hz) activity. Alpha activity in the MPFC was significantly correlated with: LIPL theta [4–7Hz; $t(11) = 4.57$, $P < 0.001$], PCC theta [$t(11) = 4.44$, $P < 0.001$], LIPL beta [14–30 Hz; $t(11) = 4.25$, $P < 0.001$], PCC beta [$t(11) = 6.52$, $P < 0.0005$], RIPL beta [$t(11) = 5.48$, $P < 0.0005$], and 30–56 Hz activity in LIPL [$t(11) = 4.58$, $P < 0.001$] and PCC [$t(11) = 4.31$, $P < 0.001$]. Lastly, MPFC beta activity in medicated ADHD adults was positively correlated with: LIPL theta [$t(11) = 4.48$, $P < 0.001$], PCC theta [$t(11) = 4.52$, $P < 0.001$], and 8–14 Hz alpha activity in LIPL [$t(11) = 6.23$, $P < 0.0005$], RIPL[$t(11) = 6.12$, $P < 0.0005$], and the PCC [$t(11) = 6.99$, $P < 0.0005$]. Table I provides a summary.

DISCUSSION

We evaluated basic neurophysiological functioning within each node of the DMN in medicated and

TABLE I. Cross-frequency coupling

Seed region/band	Significant correlations	Groups
MPFC, 8–14 Hz	4–7 Hz, LIPL	MP, C
	4–7 Hz, PCC	MP, UMP, C
	14–30 Hz, LIPL	MP, UMP, C
	14–30 Hz, PCC	MP, UMP
	14–30 Hz, RIPL	MP, UMP, C
	30–56 Hz, LIPL	MP
	30–56 Hz, PCC	MP
MPFC, 14–30 Hz	4–7 Hz, LIPL	MP
	4–7 Hz, PCC	MP
	8–14 Hz, LIPL	MP, UMP, C
	8–14 Hz, PCC	MP
	8–14 Hz, RIPL	MP, C
	30–56 Hz, PCC	UMP
MPFC, 64–82 Hz	30–56 Hz, PCC	UMP
	184–228 Hz, RIPL	UMP
MPFC, 124–168 Hz	64–82 Hz, PCC	UMP
MPFC, 184–228 Hz	64–82 Hz, PCC	UMP

MPFC: medial prefrontal cortices; PCC: posterior cingulate/precuneus; LIPL: left inferior parietal; RIPL: right inferior parietal; MP: medicated ADHD patient; UMP: unmedicated ADHD patient; C: healthy adult control.
No significant cross-frequency correlations were observed for MPFC activity at 1–4, 4–7, 30–56, or 82–106 Hz.
All correlations were significant at $P < 0.001$.

unmedicated adults with ADHD, and in a group of their non-ADHD peers. Our primary findings included a global reduction of high-frequency activity (14–228 Hz) across the DMN in unmedicated adults with ADHD, and a particularly robust decrease of neuronal activity in the MPFC of adults with ADHD that was frequency-nonspecific. The unmedicated patients also exhibited aberrant regulatory balance within the DMN, as activation in posterior nodes (LIPL and RIPL) was significantly stronger than the anterior MPFC at lower frequencies. Moreover, these unmedicated patients exhibited abnormal cross-frequency coupling in the gamma range between the MPFC and posterior cortices. Finally, the administration of MAS-XR suppressed the cross-frequency gamma coupling and significantly increased, thereby normalizing, 8–14 Hz alpha activity in the MPFC of adults with ADHD; although neuronal activity in all other frequency bins remained abnormal. Below, we discuss the implications of these findings for theories of DMN function and maturation in ADHD.

Recent resting-state fMRI studies have demonstrated that functional connectivity strengthens within the DMN, and decreases between DMN structures and other anatomical areas, as the healthy brain maturates [Fair et al., 2008, 2009; Power et al., 2010]. For example, typically developing children and adolescents exhibit reduced coherence within the DMN relative to their adult peers [Fair et al., 2008]. Interestingly, prior studies have shown reduced coherence within the DMN of adults with ADHD [Castellanos et al., 2008; Uddin et al., 2008] and youth with ADHD [Fair et al., 2010], compared to separate age-matched groups without ADHD. The latter study also evaluated several functional pathways that are known to become stronger or weaker with typical (healthy) maturation [Fair et al., 2008], and demonstrated that youths with ADHD indeed exhibited atypical functional connectivity (i.e., increased and decreased connectivity, depending on the pathway), given their particular stage of development [Fair et al., 2010]. Thus, these studies provide significant credence to the notion of abnormal maturation, especially in regard to functional connectivity, within the DMN of persons with ADHD. The evaluation of basic neuronal function within particular nodes of the DMN has generally been more complicated with fMRI, as it requires an additional task period for comparison and thereby is not an independent assay. Consequently, the degree to which DMN abnormalities are uniquely attributable to deficient interregional interactions, and not one or more pathological nodes disrupting communication across the DMN, is not understood.

Our primary finding of broadband MPFC dysfunction in adults with ADHD may be especially insightful in this regard, as the pathway connecting MPFC and PCC has shown abnormal functional connectivity in all applicable DMN studies [Castellanos et al., 2008; Fair et al., 2010; Uddin et al., 2008]. A recent fMRI study also highlighted that adolescents with ADHD exhibit reduced deactivation relative to age-matched controls within medial frontal cortices during the task period [Peterson et al., 2009]. The suppression of activity in these cortices, and the PCC, was significantly enhanced when a stimulant medication was administered, which effectively normalized DMN activity in these patients [Peterson et al., 2009]. Our current findings suggest that the effect of stimulant medications (i.e., MAS-XR) may be more limited, as only 8–14 Hz activity in the MPFC was significantly altered (but see below). However, the true consistency of these findings is unclear as one cannot isolate particular aspects of the overall fMRI response spectrum (e.g., isolate fMRI signal linked to alpha activity), and current evidence suggests that alpha and higher frequency gamma make independent contributions to the BOLD signal [Scheeringa et al., 2011]. Cortical thickness studies have provided another line of evidence, suggesting that the MPFC node may be critical to DMN abnormalities in ADHD. This work has shown that normal children with many ADHD symptoms have slower cortical thinning than their peers with fewer ADHD symptoms, and that the slowest rate of MPFC thinning is found in youths with the full blown DSM-IV defined ADHD syndrome [Shaw et al., 2011]. Comparable findings of ADHD maturational delays in reaching peak cortical thickness in the MPFC and other regions has been described in groups of substantially younger children [Shaw et al., 2007].

Our secondary finding of aberrant cross-frequency gamma coupling involving the MPFC region of unmedicated patients with ADHD may also be critical to understanding DMN function. In our healthy control participants, there were no cross-frequency correlations involving

gamma activity in the MPFC, which suggests that frontal gamma activity is a more local phenomenon that fluctuates largely independently of oscillatory activity in other brain regions. In contrast, unmedicated ADHD patients showed robust cross-frequency gamma coupling with MPFC activity, across a broad range (i.e., 64–82, 124–168, and 184–228 Hz), being positively correlated with PCC gamma activity at 30–56 and 64–82 Hz, and RIPL activity at 184–228 Hz. This suggests that oscillations in frontal gamma activity are less regionally-specific in unmedicated patients, and may often co-occur with gamma fluctuations in multiple brain areas or even across an extended cortical region. These results may also indicate that, overall, there is less "discreteness" in the γ-frequency activity of unmedicated ADHD patients. In other words, perhaps the average gamma oscillation in unmedicated patients involves a much broader band of activity than is the case in healthy adult controls or medicated patients. Interestingly, all cross-frequency gamma coupling involving MPFC activity dissipated in these patients following the administration of stimulant medication (i.e., MAS-XR). High-frequency gamma activity is believed to be crucial to network-level functional connectivity [Fries et al., 2007; Singer, 1999; Uhlhaas et al., 2009]; thus, although speculative, the presence of cross-frequency coupling in the gamma range may be detrimental to establishing robust inter-regional communication. Finally, it is worth noting that a previous EEG study of cross-frequency coupling showed that typically developing children, but not their peers with ADHD, exhibited significant anticorrelations between posterior alpha and anterior theta activity during visual-cue trials of a cross-modal attention task [Mazaheri et al., 2010]. We did not observe significant correlations (positive or negative) involving frontal (i.e., MPFC) theta activity in any group, but this disagreement likely reflects task differences as one would not expect cross-frequency coupling in the resting-state to be largely similar to that observed during a demanding cognitive task.

CONCLUSION

Several recent studies have described ultra low frequency abnormalities in the DMN of patients with ADHD [Helps et al., 2008, 2010]. These data have been interpreted to reflect electrophysiological correlates of the BOLD-based fMRI findings of abnormal functional connectivity. The current data suggest that such interpretations may be oversimplified. We observed reduced MPFC activity in adults with ADHD across a wide swath of the frequency spectrum (i.e., 1–228 Hz), and group differences tended to be more robust within higher (gamma) frequency bins. Helps et al. [2008 2010] have only examined very low-frequency oscillations at the scalp in their studies; thus, comparability of these data to the current findings is not at all clear. Regardless, at least for neuronal activity within the DMN, ADHD-related abnormalities are not restricted to very slow electrophysiological oscillations. Before closing, it is important to acknowledge the limitations of this work including the modest sample sizes, distinct medication histories of participants with ADHD (e.g., duration of stimulant treatment), and the lack of a placebo-control group. To date, only one imaging study [Rubia et al., 2009] has utilized both a healthy control group and placebo-treatment ADHD group, and this study utilized the same 13 children (at two different time points) to form the placebo and treatment groups. Thus, future work will need to examine larger and more homogeneous patients groups, utilize placebo-treatment and healthy control comparison groups, as well as extend the current observations to younger persons with ADHD.

ACKNOWLEDGMENTS

The Center for Magnetoencephalography at the University of Nebraska Medical Center was founded through an endowment fund from an anonymous donor.

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