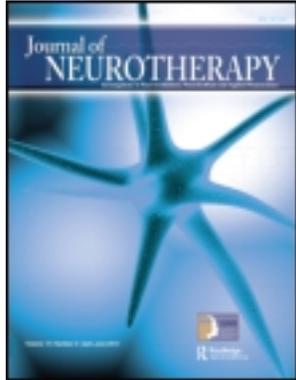


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RESEARCH ARTICLES

sLORETA AND fMRI DETECTION OF MEDIAL PREFRONTAL DEFAULT NETWORK ANOMALIES IN ADULT ADHD

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Attention deficit hyperactivity disorder (ADHD) is a developmental psychiatric disorder thought to affect approximately 5 to 10% of school-age children, of whom 30 to 65% continue to exhibit symptoms into adulthood. The prevalence of ADHD in adults is also an estimated 4%, second only to depression. Across studies there appear to be significant network dysfunctions involved in ADHD. Typically the foci of interest in ADHD included the insular cortices, frontal lobes, basal ganglia, and cerebellum. More recently, attention has been directed to the default network of the brain and its functional integrity in ADHD with focus on the precuneus and parietal lobes and interactions with medial prefrontal cortices. Functional magnetic resonance imaging (fMRI) measures neurovascular coupling as measured by the blood oxygenated level dependent signal (BOLD). Electroencephalogram (EEG) measures brain electrical information. Because fMRI is an indirect measure of neuronal activity and EEG is a direct measure, combining the results from these two imaging modalities under the same task conditions may provide a more complete story as to the what (EEG) and where (fMRI) activity exists. This article discusses the benefits of using standardized low resolution electromagnetic tomography (sLORETA) analysis of the EEG as compared to fMRI. The goal of the study, the data from which we use for our justification, was to discover the functional differences in ADHD and non-ADHD brains with different brain imaging modalities. We hoped to elucidate functional connectivity patterns by interpreting the data acquired with the EEG using sLORETA and the data acquired with the fMRI scans. We further hoped to find correlation with the sLORETA and fMRI interpretations so as to confirm that EEG is an adequate stand-alone methodology to evaluate ADHD. Participants included 6 ADHD and 7 non-ADHD subjects. They were initially interviewed by phone and administered the Connors Rating Scale and the Mini International Neuropsychiatric Interview to determine accuracy of symptom reporting and to rule out psychological comorbidities. Exclusion criteria consisted of previous head trauma, recent drug or alcohol abuse (14 days), or neurological syndromes. We recorded sequential 19-channel EEG and fMRI during the eyes-open and eyes-closed states and while performing the Stroop test. The QEEG results were evaluated with comparison to a normative database and with sLORETA analysis.

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Functional connectivity was assessed using the seed-based approach in sLORETA. The fMRI results were evaluated using Brain VoyagerTM and other neuroimaging software packages. sLORETA and fMRI data identify a region in medial Brodmann Area (BA) 10 of the default network. Furthermore, regional frontal differences extend to medial BA 32 with more emphasis to left prefrontal. sLORETA determines there is less current source density at BA 10 in the ADHD participants than controls. sLORETA is adequate in localizing the sources of the EEG in the default network as contrasted with fMRI. It is important to note that sLORETA can provide important information about the direction of difference relative to the BOLD signal increase, which cannot be done with the fMRI alone.

INTRODUCTION

This study aimed to determine if the standardized low-resolution electromagnetic tomography (sLORETA) current source density (LCS) levels in the default mode network (DMN) would correspond to other neuroimaging techniques, with the implication that differential changes in LCS would occur relative to task condition. Functional magnetic resonance imaging (fMRI) offers increased spatial resolution, whereas an electroencephalogram (EEG) offers unsurpassed temporal resolution and a direct measure of neuronal activity (Hu, Stead, Dai, & Worrell, 2010). Through use of the inverse solution methodology, sLORETA melds both and advises brain activity from a temporal and spatial perspective, providing a much more comprehensive view (Pascual-Marqui, 2002; Pascual-Marqui, Michel, & Lehmann, 1994) and has received considerable validation from studies combining it with more established localization methods, including fMRI (Mulert et al., 2004; Vitacco, Brandeis, Pascual-Marqui, & Martin, 2002). However, localization of EEG current source density levels in the default network has not been contrasted with fMRI validation.

The original version of LORETA has undergone extensive validation by independent laboratories, including mathematical proofs (Sekihara, Sahani, & Nagarajan, 2005; Wagner, Fuchs, & Kastner, 2004). This method finds a particular solution to the nonunique EEG inverse problem by assuming similar activation of neighboring neuronal sources, followed by an appropriate standardization of the current density, producing images of electric neuronal

activity without localization bias (Greenblatt, Gan, Harmatz, & Shader, 2005; Pascual-Marqui, 2002; Sekihara et al., 2005).

Attention deficit hyperactivity disorder (ADHD) is a developmental psychiatric disorder thought to affect approximately 5 to 10% of school-age children (Faraone, Sergeant, Gillberg, & Biederman, 2003), of whom 30 to 65% continue to exhibit symptoms into adulthood (Faraone, Biederman, & Mick, 2006). Individuals with ADHD exhibit tendencies toward reduced educational outcomes and an increased incidence of comorbid psychiatric syndromes, including substance abuse, antisocial behavior, anxiety, and depression (Spencer, Biederman, & Mick, 2007). The etiology of ADHD and exact neurological substrates are currently unknown; in addition, the interactions between genetics and environmental influences are still unclear. However, across studies there appear to be significant network disruptions involved in ADHD.

Recently, the default network of the brain (DMN) has gained growing interest in ADHD (Tian et al., 2008; Zang et al., 2007). The DMN consists of functionally related regions (Table 1) that are consistently shown increased in activity during rest with the eyes closed as compared to functionally specific cognitive tasks or the eyes-opened resting condition (Shulman et al., 1997; Shulman et al., 1999; Shulman, Schwarz, Miezin, & Petersen, 1998). The DMN is synonymous with resting state network; however, the resting state network has been suggested to include numerous networks of functionally connected neuronal assemblies (Damoiseaux et al., 2008; Damoiseaux et al., 2006; Fransson et al., 2007). It is important to

TABLE 1. sLORETA/Montreal Neurological Institute Coordinates for Default Network Regions (Raichle et al., 2001)

Orientation brodmann area	X	Y	Z	Neuroanatomical label
(1) Medial 31/7	-5	-49	40	Dorsal Posterior Cingulate/Precuneus
(2) Left 40	-53	-39	42	Parietal lobe/supramarginal gyrus
(3) Left 39/19	-45	-67	36	Angular gyrus
(4) Right 40	45	-57	34	Parietal Lobe/supramarginal gyrus
(5) Left lateral 8	-27	27	40	Frontal eye fields
(6) Right 8/9	5	49	36	Frontal lobes
(7) Left 9	-15	55	26	Dorsolateral prefrontal cortex
(8) Left 10	-19	57	8	Anterior prefrontal cortex
(9) Medial 10	-1	47	-4	Middle frontal lobe
(10) Left 10/47	-33	45	-6	Inferior frontal lobe
(11) Medial 32	3	31	-10	Anterior cingulate
(12) Left 20	-49	-19	-18	Inferior temporal gyrus

note that the DMN is not to be confused with networks of executive attention or networks associated with monitoring attention and the physical body (Buckner, Andrews-Hanna, & Schacter, 2008). Recent work by Fair and colleagues (2008) have demonstrated that the brain's DMN exhibits less functional connectivity in children than in adults. The DMN is proposed to support such core functions as theory of mind, self-related activities such as autobiographical self, stimulus independent thought, self-projection, self-reference and introspective processes (Fair et al., 2008).

Concerning ADHD the DMN, insular cortices, frontal lobes, basal ganglia, and cerebellum are foci of interest with a more recent interest directed to the precuneus and parietal lobes and their interactions with anterior cingulate and medial prefrontal cortices (Castellanos, 2001; Castellanos & Acosta, 2002; Castellanos, Glaser, & Gerhardt, 2006; Castellanos et al., 2008). Functional neuroimaging investigations of brain activation patterns in ADHD in response to cognitively demanding tasks have frequently been used. These studies have shown that differences in cognitive control between subjects with and without ADHD are associated with differences in brain activation patterns (Bush et al., 1999; Bush et al., 2002; Durston, 2003; Durston et al., 2003; Rubia, 2002; Rubia et al., 2001; Rubia, Smith, Taylor, & Brammer, 2007). In particular, reduced activation in prefrontal areas and linked decreases in the recruitment of the subcortical striatal

regions during actions that require subjects to inhibit (or self-regulate) responses as part of the task, such as in the go/no-go or Stroop tasks (Bush et al., 1999; Rubia, 2002; Zang et al., 2005). This research paradigm has also demonstrated the anterior cingulate gyrus to be less responsive in ADHD populations as compared to controls and has led to the suggestion that these regional deficits are central to ADHD (Bush, Valera, & Seidman, 2005).

Neuroimaging studies have also investigated behavioral control, attention, mental rotation, and employed tasks thought to be associated with motivated behavior, such as reward anticipation tasks (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Scheres, Milham, Knutson, & Castellanos, 2007; Silk et al., 2005). The results confirm deficits in striatal and prefrontal activation, as well as changes in activation in parietal areas. The general findings emphasize the importance of fronto-striatal networks in ADHD. Although there is no definitive physiological model of ADHD, further evidence for fronto-striatal impairment in this population comes from the research into stimulant medications as well as animal models of hyperactivity that implicate dopamine pathways associated with these regions (Gainetdinov et al., 1999). This pathway is proposed to be heavily involved in saliency, reward, learning, and deciphering cues for motivation to appropriate behavior, among other things, all relevant dysregulation in the ADHD brain.

More recently, the mesolimbic reward system has been investigated specific to ADHD. Data indicate that regions differing between ADHD adults and controls for the dopamine D2/D3 receptor and for the dopamine transporter included the left ventral striatum (including accumbens and ventral caudate), left midbrain, and left hypothalamus (Volkow et al., 2009). Similar findings in studies of reward mechanisms have indicated that adults with ADHD showed less activity in ventral striatum to immediately available rewards, as has been previously reported in adolescents and adults with ADHD (Scheres, Lee, & Sumiya, 2008; Strohle et al., 2008).

The DMN is important to the study of ADHD brain function due to its functional components. These components comprise medial (medial prefrontal cortex, posterior cingulate/precuneus) and lateral (posterior parietal) brain regions that routinely exhibit coherent decreases in activity during attention-demanding cognitive tasks (Raichle et al., 2001). It has also been noted that attentional lapses have been found to occur shortly after periods of decreased deactivation of posterior DMN regions (Weissman, Roberts, Visscher, & Woldorff, 2006). ADHD is a diverse developmental condition with various potential loci of neural dysfunction. Recent data indicate decreased functional connectivity between the precuneus and other DMN regions in adults with ADHD (Castellanos et al., 2008). Further data indicate decreased DMN network homogeneity in the precuneus in ADHD as compared to controls (Castellanos et al., 2008). The precuneus is a prominent node in the DMN that has been receiving increasing attention in the ADHD neuroimaging literature, showing reductions in grey matter volume in ADHD samples (Carmona et al., 2005; Overmeyer et al., 2001). The precuneus has been shown to play an important role in cognitive and self-relevant processing (Enzi, de Greck, Prosch, Tempelmann, & Northoff, 2009; Northoff, 2005; Northoff & Bermanpohl, 2004; Northoff et al., 2006; Northoff et al., 2009). It may also play an important function in affect and self-regulatory functions given its widespread

connectivity with anterior cingulate, lateral prefrontal, inferior and superior parietal lobes, and subcortical connections including the thalamus, striatum, and brainstem regions (Cavanna & Trimble, 2006).

It is important to note that all network assemblages within the default network can be interpreted and/or monitored with quantitative electroencephalogram (qEEG) and LORETA methods (Cannon, 2009; Cannon, Congedo, Lubar, & Hutchens, 2009; Thatcher, North, & Biver, 2011). In addition, LORETA neurofeedback can be implemented in regions in both attentional networks and the DMN including the anterior cingulate gyrus and precuneus (Cannon, Baldwin, & Lubar, 2009; Cannon et al., 2009; Cannon et al., 2007; Cannon, Lubar, Sokhadze, & Baldwin, 2008). The current study utilizes center coordinates from the Raichle Raichle et al. (2001) DMN study. However, data suggest that attentional networks, including a dorsal attention system (Andrews-Hanna et al., 2007) operate differently than the DMN involving cingulo-frontal and posterior parietal regions.

Connectivity within this attention network in conjunction with middle frontal regions is suggested to be influenced by tasks involving conflict related modulation (Fan, Hof, Guise, Fossella, & Posner, 2008; Posner, Sheese, Odludas, & Tang, 2006). Another important finding indicates that the fronto-insular cortex plays an important role in the transition between the executive attention network and default network activity, or more simply the insula maintains a functional role in switching between executive attention and the DMN (Sridharan, Levitin, & Menon, 2008). It has also been shown that numerous syndromes may preferentially disrupt connectivity within the DMN including Alzheimer's disease; autism; and, relative to this work, ADHD (Andrews-Hanna et al., 2007; Fassbender et al., 2009; Kennedy & Courchesne, 2008; Liddle et al., 2011; Uddin et al., 2008; Weng et al., 2010).

Research utilizing diffusion tensor imaging (Silk et al., 2005; Vance et al., 2007) in ADHD has shown dysfunction of a larger, more extensive attentional, cognitive, and visuo-spatial

network that involves frontal, striatal, and parietal areas. The authors proposed, in agreement with others, that network integrity is of fundamental importance for attentional and cognitive control (Mesulam, 1990). The important network assemblages of significance were identified in the white matter underlying right occipito-parietal cortex, left inferior frontal cortex/striatum, and left inferior temporal regions. Connectivity nearing statistical significance was also reported in white matter underlying the right and left inferior parietal regions (Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2009).

We hypothesized that sLORETA would accurately localize the statistically significant source that corresponds with the fMRI signal (or activation) difference between adults with ADHD and controls. fMRI advises the difference in blood oxygen levels between rest and task states. However, this difference can mean more than one thing. For example, if there is little change in activation between both states, it could either mean low activation during task or an elevated (hypervigilant) resting state. Conversely a large difference in activity could mean the subject is overactivated (utilizing greater energy resources) during the task state or the mechanisms seen in a healthy DMN are not present in the ADHD brain. Thus, the shift in energy can be defined as under- or overarousal in the correct state (rest or task). Furthermore, the frequency of the current source density may explain the origin of the EEG activity. The current study examined the BOLD and LCSD in the DMN during eyes-open resting.

METHODS

A study, recently completed by Cynthia Kerson and her colleagues was performed at the Applied fMRI Institute in San Diego, California. Subjects were interviewed via phone or Skype following a script that ruled out suicidal ideation, traumatic brain injury, medication intake other than stimulants (which were ceased 3 days prior to the examination), claustrophobia, pregnancy, nonambulatory access, schizophrenia or other Axis III disorder,

and/or metal implants and verbally responded to the Mini International Neuropsychiatric Interview questionnaire (Dunbar, 1998), for inclusion into the ADHD or non-ADHD group. The participants also completed the Connors Adult ADHD Rating Scale Self-Report Short Version (CAARS-SS; Connors et al., 1999).

The participants were screened using a questionnaire specific to ADHD symptomology during the initial interview. The answer scale is *never, rarely, sometimes, often, and very often*. Should the subject answer mostly *often* or *very often* to these six questions, he or she would be admitted into the study as an ADHD subject (following congruent results on the CAARS). Conversely, those who answered mostly *never* or *rarely* would be included in the control group.

The verbally administered Mini International Neuropsychiatric Interview instrument was intended to rule out comorbid disorders, including major depressive disorder, mania, panic disorder, obsessive-compulsive disorder, social phobia, psychotic disorders, including schizophrenia, posttraumatic stress disorder, anorexia or bulimia, antisocial personality disorder, and/or other mood disorder with psychotic features. Alcohol or psychoactive substance abuse or dependence is also usually questioned during this interview, but we did not include those questions as they posed ethical issues. Two ADHD subjects reported history of mild depression and one reported anxiety, although neither was medicated. We accepted these subjects because they were not medicated and symptoms were not current. None of the controls reported symptoms from any of the aforementioned disorders during this interview.

There are 26 questions on the CAARS-SS that distinguish non-ADHD adults from ADHD adults. The answer scale is 0 (*not at all, never*), 1 (*just a little, once in a while*), 2 (*pretty much, often*), and 3 (*very much, very frequently*), and the answers result in scaling for inattention/memory problems, hyperactivity, restlessness, impulsivity and emotional lability, problems with self-concept, and an overall ADHD index. The six ADHD adults in this study had an average of 21.5 on the overall ADHD index (92 percentile; raw score was 22.33 for the women

[97 percentile] and 20.66 for the men [87 percentile]). This is contrasted by the average overall ADHD index of 10.5 for controls (41.14 percentile; 10.4 for the women [52 percentile] and 7 for the men [25.66 percentile]).

Twenty-four potential subjects were recruited through local practitioners and Children and Adults With Attention Deficit Hyperactivity Disorder. Of these, 10 non-ADHD and 9 ADHD subjects were recruited. Of the five who were excluded, three reported current major depressive disorder and were on selective serotonin re-uptake inhibitors, one reported recent history of suicide attempt, and one did not want to participate without pay. However, three non-ADHD recruited subjects did not complete the study (one became anxious in the MRI scanner, one cancelled due to time constraints, and one was physically unsuited), and three recruited ADHD subjects were disqualified (two became anxious in the scanner and the third rescinded consent after completing both the fMRI and EEG sections of the evaluation). Therefore, the total participants were seven non-ADHD and six ADHD adults. All participants in this study were right-handed. After signing the informed consent, each participant first underwent a qEEG or fMRI scan, depending upon a random assignment, and then proceeded to the respective imaging or qEEG device.

QEEG is the procedure in which the brain's electrical processes are recorded. QEEG comprises computerized imaging and statistical procedures to aid in the detection of abnormal patterns often associated with specific pathological conditions. It is a direct and reliable signature of neural activity and provides ideal temporal resolution in the millisecond time domain (Coburn et al., 2006; Hughes & John, 1999).

The subjects were seated in a quiet room away from any telephones and other ordinary office noise. Their scalps were prepped with NuPrep and alcohol to clean and abrade the skin at the 19 electrode sites as designated by the 10/20 international system (Jasper, 1958) and linked-ear reference. The subjects were then fitted with a spandex cap (ElectroCap International, Eaton, OH, USA) that contains

electrodes at the 10/20 sites, aligning the electrodes to the proper locations on the scalp. The subjects were briefly educated on artifact production and contamination (e.g., how the signal compared when calm and relaxed to during eye blinks and saccades and when shoulder, facial, and/or neck tension persisted) and asked to remain quiet and still during the recording session. The participants completed 5-min eyes-closed and eyes-opened resting baselines. ERP procedures were also conducted using the Stroop task; however, these results are not presented in this work.

EEG recordings were acquired using the Mitsar 202 (Mitsar Ltd, St. Petersburg, Russia) amplifier system. The EEG was sampled by 24-bit AD converter at 250 samples per second, and the low and high pass filters were set at 0.0 and 50.0 Hz, respectively. Data were acquired using the WinEEG acquisition program. Data were then transported into the Eureka software (NovaTech EEG, Mesa, AZ, USA), where it was plotted and carefully inspected using manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, jaw clenching, body movements, or electrocardiogram (EKG) artifact were removed from the EEG stream.

The fMRI scanner was a Siemens 3 T Tim Trio. The images were collected every 2 s. The scanner employed Syngo B15 software with the BOLD fMRI and Neuro3D packages. The RF transmitter contains one 35 kW narrowband RF transmitter and one 8 kW broadband RF transmitter. Its gradient strength/slew strength is $\leq mT/m / \leq 200 T/(m^*2)$ with 32 receiver channels. The stimuli delivery system was an Avotec Silent Scan 3100 research audio system and NEC NP 4000, XGA 1280 × 768 rear projection system. A luminit 75° diffuse screen and Presentation software were used for the task presentation. A fiber optic keypad was used for participant responses.

Each subject was instructed about the tasks they were to perform in the scanner. In this case, the FANTAB Neuropsychological Battery was used, which is a version of the CANTAB (Cambridge, England) Neuropsychological Test Battery that is fashioned to work in the scanner. After task instruction, the subject changed

into hospital scrubs. They were covered with a blanket and fitted for the head-motion cage. The keypad was positioned to their dominant hand. They were shuttled into the scanner, given time to acclimate, and began with cross-hair fixation to be used as the baseline comparator to the tasks, followed by the FANTAB battery. At the end they remained still, listening to music for 12 min to record the individual anatomical aspects of their brain. A T1-weighted anatomical image was also acquired for registration purposes (MP-RAGE, TR = 2500 ms; TE = 4.35 ms; TI = 900 ms; Flip angle = 8; 176 slices; FOV = 256 mm).

STROOP Observations

The Stroop (Stroop, 1935) task timing differed for the fMRI scan and the EEG recording due to differences in acquisition time (the fMRI records every 2 s vs. EEG, which samples at 250 per second). The participant viewed a screen that presented the word RED or GREEN at the top and the words RED and GREEN below. The top word could spell RED or GREEN and its letters could be colored either red or green. The bottom words' letters could also be either color, and either word could be left or right. The task is to identify the color of the letters of the top word and then decide which of the two words below accurately label the color while also inhibiting the urge to match the color of its letters. Figure 1 is an example screen in which the correct answer is GREEN. Last, in this trial, the subject would click the left

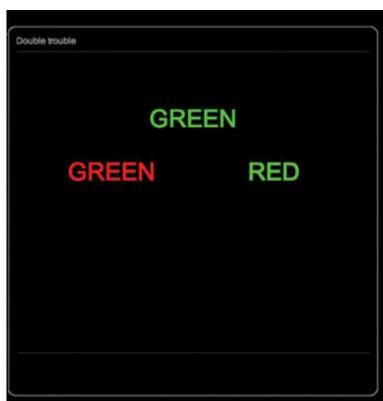


FIGURE 1. Example trial from Stroop Task. (Color figure available online.)

mouse while recording EEG or the #1 button in the fMRI scanner because the correct answer is on the left. The EEG task lasted 20 min (400 trials), and the fMRI task lasted 5 min.

The subjects were randomly assigned to either have the EEG recording or the fMRI scan first and then switch to the other during the same session on the same day. This random assignment was to account for confounding due to possible fatigue from either test during the other. One observation was that the ADHD subjects had more correct answers on the fMRI Stroop task if they did the EEG recording first as compared to those ADHD subjects who had done the scan first. Although this finding was not significant (possibly due to the very small sample size), it might be that during the EEG recording a rehearsal effect was evident. This phenomenon was not found in the control group.

fMRI Data Analysis

fMRI data were preprocessed using the SPM 2005 software package (Wellcome Department of Cognitive Neurology; <http://www.fil.ion.ucl.ac.uk/spm/>). Time-courses were motion and slice-time corrected, normalized to the standard Montreal Neurological Institute (MNI) template, smoothed with an 8 mm Gaussian kernel, and high-passed filtered prior to analysis (cutoff 180 s). Individual subjects data were modeled in SPM5 using the general linear model. Four predictor functions were included in the model corresponding to the onsets and durations of the four task event types convolved with the standard hemodynamic response function. Rotational and translational movement parameters within the x, y, and z planes were included as an additional six regressors. Blocks of rest were included in the task design, and these allowed the task regressors to be calculated relative to a constant that included resting baseline activity. Group-level analyses were carried out using the MarsBaR ROI toolbox for SPM, which calculates the average level of activation across all voxels within predefined ROIs.

sLORETA Data Analysis

The EEG stream was edited using Eureka 3 software (NovaTech EEG, Mesa, AZ, USA).

EEG resampling was obtained by means of natural cubic spline interpolation, as the EEG is a continuous signal constituted by oscillation of potential differences over time. All active task conditions and baseline data were processed with particular attention given to the frontal and temporal leads. All episodic eye blinks, eye movements, teeth clenching, jaw tension, body or neck movements, and possible EKG were removed from the EEG stream. Fourier cross-spectral matrices were then computed and averaged over 75% overlapping four-second artifact-free epochs, which resulted in one cross-spectral matrix for each subject for each discrete frequency. The EEG data were analyzed utilizing the following frequency domains: delta (0.5–3.5 Hz), theta (3.5–7.5 Hz), alpha 1 (7.5–10.0 Hz), alpha 2 (10.0–12.0 Hz), and beta (12.0–32.0 Hz).

To assess the electrophysiological differences between groups, sLORETA was employed to localize the generators of the scalp EEG power spectra. The sLORETA solution space is restricted to the cortical gray matter in the digitized MNI atlas with a total of 6,239 voxels at 5 mm spatial resolution (Pascual-Marqui, 2002; Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002). The average common reference was computed prior to the sLORETA estimations. The calculated tomographic sLORETA images correspond to the estimated neuronal generators of brain activity within each frequency domain (Frei et al., 2001). This procedure resulted in one 3D sLORETA image for each subject for each frequency range.

To evaluate the DMN regions between groups a region of interest (ROI) file with the MNI coordinates for the 12 seed points for the DMN regions was constructed (see Table 1). Each of the ROI values consisted of the current source density levels from each ROI seed and one single voxel (its nearest neighbor) for total voxel size 10 mm^3 . The resulting file produced log transformed average current source density across multiple EEG segments for all subjects for each seed (ROI). These data were organized into Microsoft Excel spreadsheets and then entered into SPSS 19 for analysis. Secondary analysis examined differences between groups

across the whole brain. sLORETA images corresponding to the estimated neuronal generators of brain activity within each given frequency range were calculated (Frei et al., 2001). This procedure resulted in one 3D sLORETA image for each subject for each frequency range. The significance threshold was based on a randomization test utilizing 5000 data randomizations. The mean current density for all frequencies between groups was compared and t values plotted onto a MRI template.

RESULTS

The sLORETA and fMRI resting state data localize activation and decreased current source density in medial BA 10 with increased activation/current source density levels extending to BA 32. As previously stated, one of the ambiguities associated with the fMRI signal and test results is that it does not provide information about the direction of differences. However, complimentary sLORETA data demonstrate the ADHD subjects show less activity in medial BA 10 than controls during the resting state in primarily the delta frequency. Figure 2 shows the voxel-by-voxel sLORETA comparisons for controls > ADHD. The maxim region of difference for total relative power is shown at $-15, 60, 25$ with $t = 1.25, p = .298$. However, in the comparison of medial BA 10 in the DMN specifically, the ADHD group shows less delta activity than controls. This was the only difference in all frequency domains and although not significant it is in the desired direction. On the other hand, the fMRI activation at medial BA 10 shows a significant difference between ADHD and control as shown in Figure 3. Other DMN areas showed similar effects but not at significant levels; these include ROI 5, 8, 10, and 11 as shown in Table 1. The primary frequency domains shown as deficit in the ADHD group were delta and alpha.

DISCUSSION

The agreement between sLORETA and fMRI for the differences between ADHD and control in medial BA 10 is robust. Of importance, it is

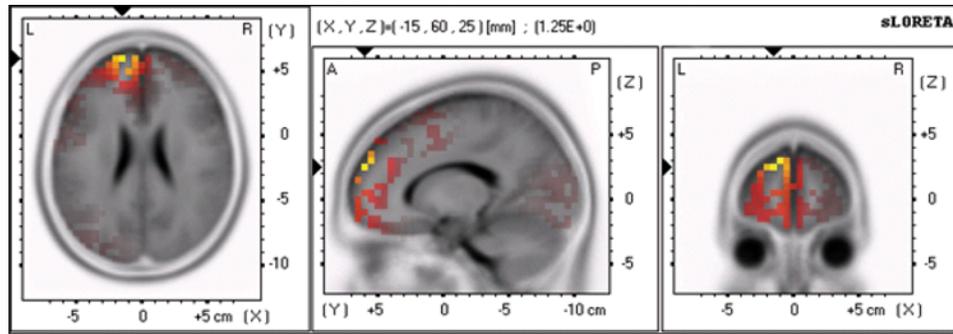


FIGURE 2. Differences for ADHD > Control for whole brain analysis with 5,000 data randomizations. Note. Medial BA 10 show at -2.51 , $p = .058$. (Color figure available online.)

questionable whether a single voxel of increase or decrease would explicate the network complexity associated with the symptoms of ADHD (Mazaheri et al., 2010). The effects shown in the data suggest that regions associated with salience, attention, and self-regulatory processes are dysfunctional in the ADHD population. Although not all identified regions reached significance, they were in the predicted direction.

At the core of these network deficits are the medial prefrontal cortices and its associations with the AC and regions known to be associated with affect regulation and monitoring the physical state of the body (e.g., insula and

inferior frontal cortex—BA 10 and 47). Left BA 40 was also identified by the data as an area of difference. It is a very important consideration for attentional maintenance and integrative processes. BA 40 has intricate connections to the posterior cingulate, precuneus, angular gyrus, and Wernicke's area and is functionally involved in somatosensory integration—which is a vital component in all variants of attentional maintenance (Uddin et al., 2008).

Similarly, left prefrontal deficits may reflect deficits in attention and regulatory processes and working memory. Of interest, this region is also associated with an inverse activity pattern in the right amygdala (Aguirre, Detre, & Wang, 2005; J. Wang et al., 2005). Perhaps this is relevant to the class of ADHD (e.g., inattentive or hyperactive). The first author tends to think the AC/prefrontal and parietal regions play a vital role in the direction of attention and its maintenance. Disruptions between these network assemblies produce negative effects in operant learning, and the behavioral result is disorganization, inappropriate response selection, and deficits in numerous neurocognitive domains.

Recent data have reported effective monitoring of the EEG in DMN regions and resting state networks (Babiloni, Marzano, et al., 2010; Babiloni, Pistoia, et al., 2010; Bluhm et al., 2009; Chen, Feng, Zhao, Yin, & Wang, 2008; Hlinka, Alexakis, Diukova, Liddle, & Auer, 2010; Jerbi et al., 2010; Koeda et al., 1995; Murias, Webb, Greenon, & Dawson, 2007; Putman, 2011; Stam et al., 2005). A more recent investigation proposed resting state

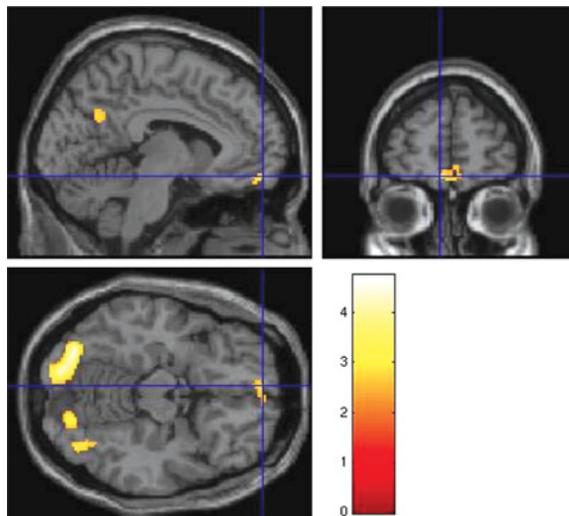


FIGURE 3. Differences for Attention Deficit Hyperactivity Disorder > Control for whole brain analysis with uncorrected p of .01 and a 100 voxel extent threshold. Note. The only ROI in the DMN to show significant difference is medial BA 10 with $t = -2.05$, $p = .05$. (Color figure available online.)

network and DMN activity reflect organized purpose in the EEG signals for monitoring environment and keeping multiple systems maintained at any point in time (Deco & Corbetta, 2011). It may very well be that during baseline, with the eyes closed or opened, we are observing a complex behavior consisting of self-regulation (for task compliance) and all its variants (e.g., attention, cognition, affect, and motor regulation) as opposed to nonrelevant, spontaneous noise. As such, in the case of the individuals with ADHD in this study, the deficits associated with medial BA 10 may also reflect deficient modulation of amygdala activation because delta and theta activity are the primary EEG frequencies in the human limbic system (Brazier, 1968) and it is these frequencies that EEG activity was most pronounced.

The methods of quantitative EEG and sLORETA are comparable to fMRI methods such that the spatial resolution for much of the fMRI data (1.5 Tesla) is 4 mm^3 under optimal conditions (Ozcan, Baumgartner, Vucurevic, Stoeter, & Treede, 2005; Yoo, Talos, Golby, Black, & Panych, 2004). Resolutions with LORETA across studies ranges in 7 mm^3 and consideration of maximum error can be as low as 1 cm and even reduced to 5 mm^3 or less with the updated s/eLORETA versions. It is however, unlikely that the brain would selectively synchronize 1 cm of neurons during any type of information processing; rather more widespread synchronization of network assemblages is more in line with our current understanding of the workings of the brain (X. J. Wang, 2010). Of interest, data indicate that deliberately diminishing negative affective responses yields increased activation in lateral and dorsal regions of the prefrontal cortex (PFC) and/or decreased activation in the amygdala (Phan, Fitzgerald, Nathan, & Tancer, 2006) suggesting that the PFC exerts a top-down, inhibitory influence through the medial PFC (e.g., BA 10 and 9) given its connections with the dorsolateral PFC and amygdala (Price, 2005). Studies of social stress have also shown a potential modulator role for the left PFC (BA 9 and 10) on the right amygdala (J. Wang et al., 2005). Activity between the amygdala and OFC as well as the

insula and parietal cortices have been implicated in extinction of conditioned fear, the mediation of aversive conditioning and associative learning in conjunction with the hippocampus (Buchel, Morris, Dolan, & Friston, 1998; Quirk, Likhtik, Pelletier, & Pare, 2003).

The current data are but a prelude to a larger study yet may have important implications. There are several limitations to the interpretation of the study data. First, sample size is low, and therefore important activations and current source density changes may not be detectable in our sample. Second, the fMRI facility and/or proximity to the operating MRI scanner may also have created emotional or EEG artifacts not yet realized. Third, due to this small sample size, the findings may not be generalized to the ADHD population. Fourth, due to its hostile environment, the MRI scanner may have created anticipatory and/or residual anxiety for these subjects.

Finally, the DMN like other novel concepts is not without controversy (Buckner & Vincent, 2007; Mason et al., 2007; Morcom & Fletcher, 2007). There is debate about what constitutes a "resting state," with some suggesting that it reflects internally directed mental activity (Gilbert, Dumontheil, Simons, Frith, & Burgess, 2007), whereas others posit it as mind wandering (Mason et al., 2007). Still other authors propose that a resting or default state is of no use as a processing baseline (Morcom & Fletcher, 2007). Resting with eyes open or closed is a subjective experience, dependent upon one's level of internal arousal, and thus less quantifiable. Whether it is resting and noncognitive or attention and self-regulation it is important to have a constant (or point of reference) in the study of the brain (Raichle et al., 2001). This is certainly one of the more compelling rationales for utilizing a baseline condition. It has been demonstrated that disruptions to the DMN and compromised functional connectivity within the DMN and between other network assemblages in the brain are implicated in numerous psychopathologies (Greicius, Srivastava, Reiss, & Menon, 2004; Sheline et al., 2009; Uddin et al., 2008). Thus, the current data support the accuracy of sLORETA

in monitoring the DMN with statistically similar results as fMRI, with the added information of the directionality of the contrast between groups and important information about the direct neural activity associated with the signal activation.

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