Indications of Sex Differences in Cortical Activation in Adult Attention-Deficit Hyperactivity Disorder

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Abstract— **Magnetoencephalography (MEG) was used to investigate the cortical activity differences in cognitive processing in adult patients with Attention-Deficit Hyperactivity Disorder (ADHD) – Combined Type and normal controls. Using MR-FOCUSS, we compared MEG images of the localization of cortical activity measured from the ADHD patients and control subjects while performing a Visual Continuous Performance Test (CPT) and the Stroop Interference Test (SIT). Although the results should be interpreted cautiously, this study suggests the presence of functional defects in the frontal and parietal cortex in adult ADHD patients. Analysis of two subject pairs indicated an absence of frontal cortex activation in ADHD at ~200 ms during both selective attention and response preparation. A shift from left to right hemispheric activation in ADHD was indicated during vigilance, along with a difference in cortical activity at ~300 ms. Processing delays, hemispheric differences, and frontal and parietal cortex deficits were found during response error detection and response control in adult ADHD. These activation shifts from normal may differ based on sex.**

Keywords— **Attention-Deficit Hyperactivity Disorder, ADHD, MEG, MR-FOCUSS**

I. Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood and continues into adulthood for approximately 30% of the cases. ADHD is characterized by symptoms of inattention (Inattentive Type), impulsivity and overactivity (Hyperactive Type). Patients presenting with symptoms in both categories are diagnosed with ADHD – Combined Type. Attention to this public health problem has increased in recent years. In 1998, the National Institutes of Health held a consensus development conference on the diagnosis and treatment of ADHD [1]. The members of this panel called for research to improve the understanding of the diverse causes of ADHD to aid the prevention, diagnosis, and treatment. Although considerable research in neuropsychology, neurochemistry, and molecular biology indicate that multiple neurobiological factors underlie this disorder, current diagnostic practice is focused primarily on behavioral rating scales. This study seeks to expand knowledge of the neurosubstrates of ADHD. We present here the results of one 39 year old male and one 48 year old female, both diagnosed with ADHD-Combined Type, compared with the results of age, sex, and IQ matched normal controls in an attempt to begin to understand differences in the cortical activation associated with this diagnosis during vigilance, selective attention to visual stimuli, and the executive control over verbal responses.

II. Methods

Two patients diagnosed with ADHD-Combined Type, and two normal control subjects were recruited via an ad placed in a hospital publication and then tested. One male (39 yo) and one female (48 yo) were diagnosed using the DSM-IV criteria with the aid of multiple behavioral rating measures [2,3,4]. The exclusion criteria for all participants were a medical history of organ, mental, and neurological disease and/or medication use that could affect the test results. The Institutional Review Board of Henry Ford Hospital approved the protocol for this study and informed consent was obtained. The MEG data were collected using a whole-head neuromagnetometer (4D Neuroimaging WH2500) consisting of 148 magnetometers. The participants were prepared for studies in the lab's customary way [5].

A Visual Continuous Performance Test (CPT) [6] was used to measure the participant's MEG field responses while he/she maintained vigilance and engaged processes of selective attention. Random letters were shown for a brief 150 ms each with a 1.8 second inter-stimulus interval (4 blocks of 100 trials). The participant was instructed to respond as quickly possible by pressing a switch to the "X" target stimulus when it followed the "A" cue stimulus. Sixty percent of the trials were a letter other than "X" or "A" (Condition 1). Twenty percent of the trials in each block were cued, "no go" trials (Condition 2: "A" cue appears, but is not followed by the target "X") and 20% of the trials in each block were target, "go" trials (Condition 3: "A" cue is followed by the "X" target.

The Stroop Interference Test (SIT) [7] was used to measure the participant's MEG field responses during a task that necessitates the use of higher executive control over behavior. Stimuli were presented individually for 500 ms, with a 1.5 second inter-stimulus interval (3 Conditions, 40 trials each). Condition 1 involved the verbal identification of color stimuli, which was performed twice. Condition 2 involved reading the names of colors written in the congruent color text, was also performed twice. In

Condition 3, words were presented in a text color that was incongruent to the name of the color, and the color of the text was identified. The results in this report compare the participants' brain activation during an early run when numerous response errors occurred (Condition 3A) with brain activation during a later run when few response errors occurred (Condition 3B). This condition was run on average 5 times.

Each participant was asked to have a MRI scan performed. The MRI scans were used to co-register the MEG data to specific locations in the cortex of each participant. This allowed for a precise localization of the anatomical landmarks and cortical activation areas associated with the tasks (0-650 ms following stimulus presentation). All MEG study data were digitally filtered 1-50 Hz. For each condition 0-650 ms of averaged data (60-80 trials) was analyzed with MR-FOCUSS. All four blocks were averaged for the analysis of the data in Conditions 2 and 3 of the CPT study. For each subject the latency (in ms), location (x,y,z coordinates), and average amplitude of response (nanoAmp-meter) were extracted from the MR-FOCUSS [8] imaging results for each cognitive process step. VECMF's were analyzed at the time of data collection by ECD.

MR-FOCUSS [8, 9], a current density source imaging technique, was applied to the data to locate possible extended areas of cortical activation associated with these tasks. The MR-FOCUSS technique employs a discrete model of approximately 3000 x, y, and z oriented current dipole source locations matched to the distribution of cortical gray matter derived from each subject's MRI volumetric slice sequence. The accuracy of forward model calculations is enhanced by utilizing a spherical model of the head exactly matched to local skull curvature for 6 different regions of the brain, corresponding to the front, middle and back of each hemisphere. Typically, current density imaging techniques are characterized by poor resolution of compact source activity. However, MR-FOCUSS overcomes this weakness of generalized current density imaging filters by performing a recursive refinement of an initial estimate of cortical activity at each time point of data. The mathematical optimization performed by the MR-FOCUSS algorithm is designed to avoid imaging of noise contained in the data. Noise insensitivity is further enhanced because MR-FOCUSS uses a multiresolution wavelet representation of cortical activity as well as a conjugate gradient solution of the imaging equations to avoid inversion of ill-conditioned matrices. In addition, the MR-FOCUSS wavelet representation of cortical activity is used to control both the global and focal distribution of imaged activity. Cortical activity is efficiently calculated using a least squares solution for a small set of wavelet amplitudes rather than the weighted minimum norm technique used in the FOCUSS [10] iterative algorithm. MR-FOCUSS, like all MEG imaging techniques, incorporates mathematical constraints that limit the distribution of imaged sources. Therefore, to achieve statistical robustness against initialization bias, random amplitudes were incorporated in source initialization and twenty solutions were generated and averaged for MEG data, at each time point. Thus, activity common to most or all twenty solutions dominate the final average MR-FOCUSS images of activity.

Selection of significant activation is determined by setting the display threshold to 25% of the maximum cortical source amplitude (color coded blue, in figures), which accounts for 5 to 10 percent of the cortex. Similarly locations for which the amplitudes are above 80 % of maximum amplitude are color coded red. These sites represent 0.3 percent of the cortex (9 out of 2900 sites). For the MR-FOCUSS solution in this study, approximately 60 percent of all source locations have amplitudes less than 0.5% of the maximum amplitude. At these setting, MR-FOCUSS preferentially images signal over noise.

III. Results

The results collected during the Visual-CPT and the SIT distinguished a 39 year old Male ADHD patient and a 48 year old Female ADHD patient from their matched normal control subjects (NC) along several dimensions of cortical activation. The following results highlight the findings for Frontal and Parietal cortical regions known to be involved in the control of attention and executive control [11]: L=Left, R=Right, B= Bilateral, F= Frontal Cortex, P= Parietal Cortex, I= Inferior, S= Superior, D= Dorsolateral.

A. Visual Continuous Performance Test

During the state of maintained vigilance in Condition 1, both the Male and Female NC subjects showed greater activation (250-450 ms post-stimulus) of left hemispheric processing (LIF). The ADHD patients showed more widespread cortical activation with greater activity in the right hemisphere during this interval. The Male and Female NC subjects showed LIF activation with a brief spread to RIF at the end of this interval. The Male ADHD patient showed activation of attention resources in BSP, LSF, and RIF cortex, whereas the Female ADHD patient showed a prolonged activation of resources in BIF, LDF, and BSF cortex.

In Condition 2 during the allocation of selective attention, both the Male and Female NC subjects showed greater activation of left hemispheric processing (LIF) versus greater right hemispheric activation in the ADHD patients during the 250 – 350 ms post-stimulus interval. The Male NC subject showed mainly LIF activation during this interval with a brief activation of RIF at the end. The Female NC showed only activation of LIF cortex. The Male ADHD (Fig. 1) patient showed activation of attention resources in RIF cortex (287-360 ms) and LDF (318 ms), whereas the Female ADHD patient (Fig. 2) showed activation of RSF cortex (291 ms) followed by activation in BIF (329-356 ms).

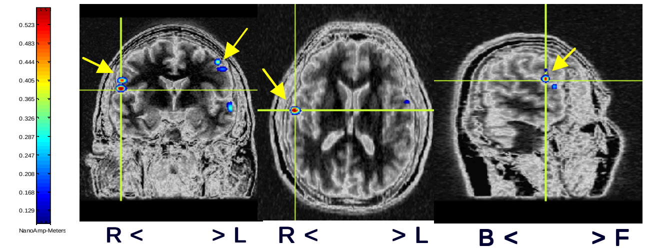

Fig. 1. Activation of Right Inferior Frontal and Left Dorsolateral Frontal cortex in Male ADHD patient at 318 ms post-stimulus of CPT- Condition 2.

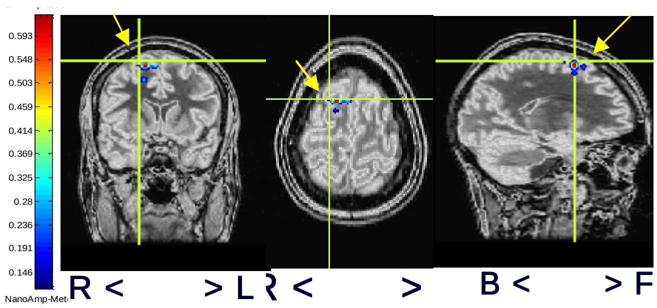

Fig. 2. Activation of Right Superior Frontal cortex in Female ADHD patient at 291 ms post-stimulus of CPT – Condition 2.

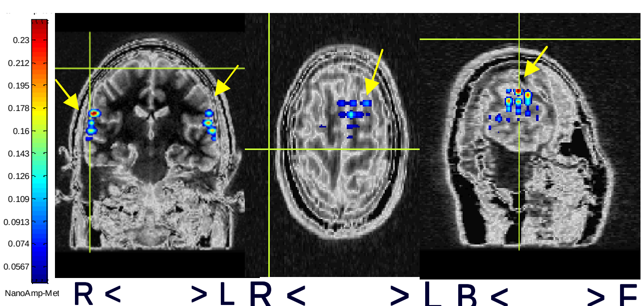

Fig. 3. Activation of Right and Left Inferior Frontal and Right Superior and Dorsolateral Frontal, and Right Parietal cortex in Male ADHD at 350 ms post-stimulus of CPT- Condition 3.

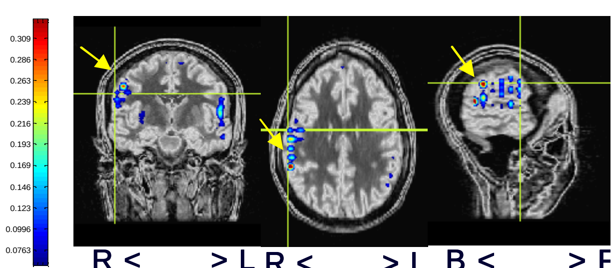

Fig. 4. Activation of Right Inferior Frontal cortex in Female ADHD patient at 376 ms post-stimulus of CPT – Condition 3.

During the preparation of a response in Condition 3, both the male and female NC subjects showed greater activation of the left hemisphere during the 300 – 400 ms post-stimulus interval, whereas the ADHD patients showed greater right hemispheric activation. The Male NC showed activation restricted to LIF, LDF, and LSF cortex, whereas the Female NC showed brief RF cortical activation along with the same regions in LF cortex. The Male ADHD patient (Fig. 3) showed activation of RSF, RDF, and RIF cortex, as well as LSF, LIF and LSP cortex in Condition 3. The Female ADHD patient (Fig. 4) showed less diffuse activation, which was limited to RIF and LIF cortex.

B. Stroop Interference Test

In Condition 3A (high error rate reflecting poor executive control), both the Male and Female NC subjects showed wide-spread bilateral activation during the 200 – 500 ms post-stimulus interval. This activation occurred in the BIP, BSP, and BIF cortex of the Male NC, whereas it occurred in the BIF, LSF, LDF, and RIP cortex of the Female NC. Conversely, the Male ADHD patient showed only a delayed activation of LF and LIP cortex. The Female ADHD patient showed activation of RIF cortex at the same time as the Female NC (266 ms versus 272 ms, respectively), but the Female ADHD patient showed activation of no additional cortical resources during this challenging condition.

In Condition 3B (low error rate reflecting good executive control), the Female NC subject and both Male and Female ADHD patients showed activation of right hemispheric processing (RIF). In each case, the LF and LP activation found in the 200-450 ms post-stimulus interval found for the high error Condition 3A ceased. The Male NC subject was unique by showing activation of the left hemisphere (LIP and LSP). The activation of right hemisphere processing (RIP, RSP, and RIF) that was found in the high error Condition 3A ceased for the Male NC.

IV. Discussion

ADHD may be associated during vigilance (CPT-Condition 1) with right rather than left hemisphere activation and a lack of activation of Left Inferior, Left Superior, and Left Dorsolateral Frontal cortex and Bilateral Parietal cortex at ~300 ms relative to normal. There may be a sex difference in the processing activated within the right hemisphere patients, with Right Superior Parietal and Right Inferior Frontal activation in Male ADHD and Right Superior and Inferior Frontal activation in Female ADHD. When selective attention is engaged (CPT-Condition 2), ADHD may be associated with a lack of activation of Left Inferior Frontal Cortex relative to normal. Right Frontal processing may be uniquely characteristic of the ADHD brain during the 250 – 350 ms interval following a stimulus attended to selectively. This Right Frontal cortical activation may be prolonged beyond 400 ms in Female ADHD. When a response is prepared to a cued target (CPT-Condition 3), ADHD may be associated with a lack of right hemispheric activation relative to normal. In addition, Male ADHD may be associated with a greater activation of Left Parietal and Left Frontal cortex at ~300 ms relative to normal, as well as more widespread activation in Right Frontal and Parietal cortex at 350 ms, when only the Left Inferior Frontal cortex is activated in normal processing. Female ADHD may be uniquely characterized by the activation of Right Superior Frontal cortex during selective response preparation, whereas Male ADHD may be uniquely characterized by activation of Right Dorsolateral Frontal and Right Inferior Frontal processing during the 250 – 375 ms post-stimulus interval.

The Stroop Interference Test results suggest that ADHD in both males and females may be associated with a reduced level of activation of attention processing in Bilateral Parietal and Frontal cortex (~200-320 ms) relative to normal. When the executive control of responses (Condition 3A) is dysfunctional due to challenging task demands, Male ADHD may be associated with a lack of normal activation of Bilateral Inferior and Superior Parietal cortex at ~200 ms In addition, Male ADHD may be associated with a lack of normal activation of Bilateral Inferior Frontal cortex at ~300 ms Female ADHD may be associated with a decrease in executive control relative to normal, with only brief activation of Right Inferior Frontal cortex at approximately 275 ms post-stimulus. When the executive control of responses is functional (Condition 3B), ADHD may be associated with Right Inferior Frontal activation. The activation of Left Inferior and Superior Parietal cortex at ~258 ms in the normal male may be absent or reduced in both Male and Female ADHD, as well as in normal females.

V. CONCLUSION

Due to the limited number of subjects tested so far the results should be interpreted cautiously. This study suggests**,** however, that MEG imaging techniques may be used in determining the structure, activation sequence, and strength of neuronal interaction during visual attention and the executive control of responses. In addition, this study indicates that MEG should increase the understanding of how attention and other forms of executive control occur in those diagnosed with ADHD. MEG studies may help refine the diagnosis of subtypes of ADHD, as well as sex differences in the pattern of ADHD, leading to selective and more effective behavioral and pharmacological treatment of these subtypes. Sex differences in cortical contributions to the control of attention [11] may be relevant to consider in research focused on the neurosubstrates of ADHD. In addition, MEG studies may help to elucidate the generators of the neurophysiological event-related potentials, both normal and those affected by ADHD [e.g., 12, 13].

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