Cortical Processing Differences in Attention-Deficit Hyperactivity and Normal Control Subjects

Nagel S.M.[1,2], Bowyer S.M.[2,3,4], Moran J.E. [2], and Tepley N.[2,3]

[1]Saginaw Valley State University, USA; [2]Henry Ford Hospital, USA; [3]Oakland University, USA; [4]Wayne State University, USA.

ABSTRACT

Magnetoencephalography (MEG) was used to investigate the cortical activity differences in cognitive processing in subjects with Attention-Deficit Hyperactivity Disorder (ADHD) and normal controls. Using MR-FOCUSS, we compared MEG images of the localization of cortical activity measured from the ADHD patients and control subjects. Although the results should be interpreted cautiously, this study suggests the presence of functional defects in the frontal and parietal cortex in ADHD patients. Analysis of one subject pair 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 ADHD.

KEY WORDS Attention-Deficit Hyperactivity Disorder, ADHD, MEG, MR-FOCUSS.

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood and continues into adulthood for approximately 30% of the cases. 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 ***[http://consensus.nih.gov/cons/110/110_statement.htm]***. 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. We present here the results of one 49 year old male diagnosed with ADHD-Combined Type compared with the results of an age, sex, and IQ matched normal control 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.

METHODS

To date, seven patients diagnosed with ADHD (4 with Combined Type, 2 with Inattentive Type, and 1 Hyperactive Type) and two normal control subjects have been recruited via an ad placed in a hospital publication and then tested. Mean age of the ADHD participants was 26 years old, range was 18 – 48, 4 males and 3 females. ADHD diagnosis (DSM-IV criteria) was assessed through multiple methods [American Psychiatric Assoc, 1994]. 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). The participants were prepared for studies in the lab's customary way [Bowyer, 2003].

A Visual Continuous Performance Test (Visual-CPT) [Ricco, 2002] 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.

The Stroop Interference Test (SIT) [Stroop, 1935] 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. Condition 2 involved reading the names of colors written in the congruent color text. 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.

Each participant was asked to have an 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 subject the latency (in ms.), location (x,y,z coordinates), and average amplitude of response (nanoAmp-meter) were extracted from the MR-FOCUSS [Moran, 2001] imaging results for each cognitive process step. VECMF's were analyzed at the time of data collection by ECD.

RESULTS

The results collected during the Visual-CPT and the SIT distinguished a 49 year old male ADHD patient and matched normal control (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 [Nagel-Leiby, 1990]: L=Left, R=Right, B= Bilateral, F= Frontal Cortex, P= Parietal Cortex, I= Inferior, S= Superior, D= Dorsolateral.

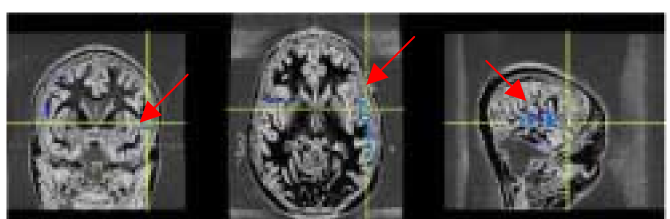

Figure 1A Coronal (L), Axial (Center), and Sagittal (R) views of Left Inferior Frontal and Parietal activation in NC at 303 ms following a cue to attend.

<u>Visual Continuous Performance Test:</u> In Condition 1 (vigilance) the NC showed greater activation overall of the L hemisphere (Amp=-16.7, Time= -47.7ms), whereas the ADHD showed greater activation overall of the R hemisphere (Amp= +10.7, Time= +28.3ms). The NC showed activation in LIF (238-334 ms) with a shift to RIF activation at 442 ms (some LIFactivation remained at 442 ms). Conversely, the ADHD showed activation in BSP at 300 ms with a shift to the LDF and RIF at 344 ms. In Condition 2 (selective attention) the NC showed activation of LF (204 ms), followed by

activation of LIF and LP at 303 ms (FIG 1A). LIF remained activated until 338 ms. RSF was activated at 436 ms. Conversely, the ADHD showed activation of RIF from 318 - 360 ms (FIG. 1B). In Condition 3 (response preparation) the NC showed activation of RIF from 218-318 ms with anterior movement, and activation of LIF at 413 ms. Conversely, the ADHD showed activation of LSP and LSF at 301 ms, followed by activation of RDF, RP, and BIF at 350 ms.

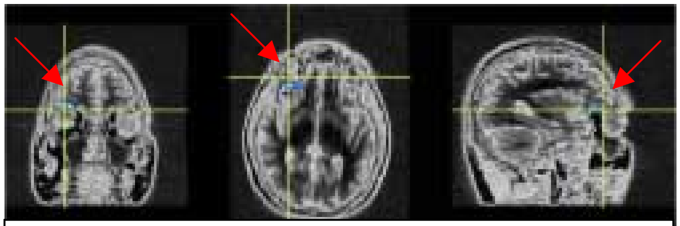

Figure 1B Coronal (L), Axial (Center), and Sagittal (R) views of activation in ADHD at 320 ms following a cue to attend.

Stroop Interference Test: In Condition 1, the NC showed activation of L > RIP (179 ms.), followed by activation of BIP and RSF from 323 – 423 ms. Conversely, the ADHD showed no activation of P or F. In Condition 3a (high error rate reflecting poor executive control), the NC showed BIP and BSP activation at 220 ms. BIF was activated at 320 ms. The ADHD showed activation of LF at 405 ms. and LIP at 482 ms. In Condition 3b (low error rate reflecting good executive control), the NC showed activation of LIF at 209 ms (FIG 2A), followed by LIP activation at 258 ms (FIG. 2B). The ADHD showed activation of the LSF at 313 ms (FIG. 2C).

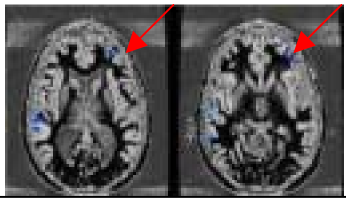

Figure 2A Axial view of Left Frontal Activation in NC at 209 ms. during challenged but effective response control.

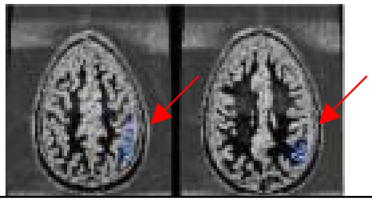

Figure 2B Axial view of Left Inferior Parietal Activation in NC at 258 ms in same condition shown in Figure 2A.

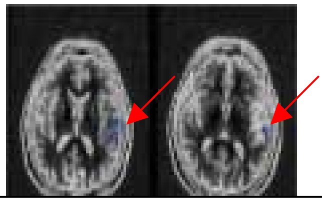

Figure 2C Axial view of Left Superior Frontal Cortex in ADHD at 313 ms during challenged but effective response control.

DISCUSSION

ADHD may be associated during vigilance (CPT-Condition 1) with right rather than left hemisphere activation and a lack of activation of the Left Inferior Frontal and Bilateral Parietal Cortex at ~300 ms. relative to normal. When selective attention is engaged (Condition 2), ADHD may be associated with a lack of activation of Left Frontal Cortex at ~200 ms. relative to normal. Normal activation of Left Frontal and Parietal Cortex at ~300 ms. (Fig. 1B) may be associated with activation of Right Frontal Cortex in ADHD (Fig. 1B). ADHD may also be associated during selective attention with an absence of normal Right Frontal Cortex activation at 400 ms. When a response is prepared to a cued target (Condition. 3), ADHD may be associated with a lack of Right Frontal Cortex activation at ~200 ms relative to normal. In addition, ADHD may be associated with a greater activation of Left Parietal and Frontal Cortex at ~300 ms. relative to normal, as well as more widespread activation in Right Frontal and Parietal Cortex at 400 ms, when only the Left Inferior Frontal Cortex is activated in normal processing.

The SIT findings suggest that ADHD may be associated with a lack of activation of attention processing in Bilateral Inferior Parietal Cortex (~300 ms) and Right Superior Frontal Cortex (~300-400 ms.) relative to normal. When the executive control of responses is dysfunctional due to task demands, ADHD may be associated with a lack of normal activation of Bilateral Inferior and Superior Parietal Cortex at ~200 ms. In addition, ADHD may be associated with a lack of normal activation of Bilateral Inferior Frontal Cortex at ~300 ms, as well as late (~350 – 480 ms.) activation of Left Frontal Cortex and Left Inferior Parietal Cortex. When the executive control of responses is functional, ADHD may be associated with reduced overall right hemispheric activation. Normal activation of Left Inferior Frontal Cortex at ~200 ms may be absent or reduced in ADHD. Finally, there may be a delay (from ~200 ms in NC to ~300 ms in ADHD) and shift (Inferior in NC and Superior in ADHD) of Frontal Cortex activation in ADHD relative to normal during the executive control of responses under challenging circumstances.

This study establishes the efficacy of specific MEG imaging techniques 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, leading to selective and more effective behavioral and pharmacological treatment of these subtypes. In addition, MEG studies may help to elucidate the generators of the neurophysiological event-related potentials.

ACKNOWLEDGEMNT: Supported by NIH/NINDS Grant RO1-NS3091.

REFERENCES

Committee on Nomenclature and Statistics: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, D.C.: American Psychiatric Association; 1994.

Bowyer SM, Mason K, Tepley N, Smith BJ, Barkley GL. MEG validation parameters for clinical evaluation of interictal epileptic activity. J Clin Neurophysiol 2003; 20(2):87-93.

Ricco, CA, Reynolds, CR, Lowe, P, Moore, JJ. The continuous performance: a window on the neural substrates for attention? Archives of Clinical Neuropsychology 2002;17:235-72.

Stroop, JR. Studies of interference in serial verbal reactions, Journal of Experimental Psychology 1935; 28: 643-62.

Moran JE, Bowyer SM, Tepley N. Multi-resolution FOCUSS source imaging of MEG data. 3rd International Symposium on 7 Noninvasive Functional Source Imaging within the Human Brain and Heart, Biomedizinische Technik 2001;46: 112-14.

Nagel-Leiby, S, Buchtel, HA, Welch, KMA. (1990). Cerebral control of directed visual attention and orienting saccades. Brain 1990;113:237-76.