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Examining Neural Synchrony in Autism During Resting State With Magnetoencephalography (MEG)

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EXAMINING NEURAL SYNCHRONY IN AUTISM DURING RESTING STATE WITH MAGNETOENCEPHALOGRAPHY (MEG)

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ABSTRACT

Autism Spectrum Disorder (ASD) comprises a group of neurodevelopmental disorders associated with the functioning of the central nervous system (American Psychiatric Association, 2013). The symptoms experienced by individuals with this disorder include social impairment, communication difficulties, and repetitive and stereotyped behaviors. The etiology of ASD has yet to be determined, and it is typically diagnosed based on behavioral criteria of the Diagnostic and Statistical Manual-5th Edition (DSM-5; APA, 2013) and confirmed with "gold standard" assessment tools such as the Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview-Revised (ADI-R; Johnson Center for Child Health Development, 2014). Abnormalities in synchronous neural activity have been hypothesized to be a core pathophysiological mechanism (Cornew et al., 2012). Magnetoencephalography (MEG) can measure synchronous neural activity during resting state, when the brain is not consciously engaged in cognitive processing. Coherence is a measure of the synchronicity. We examined differences in coherence during resting state in ASD, compared to neurotypical developing individuals (NT), in an attempt to identify potential biomarkers and illuminate a core etiological mechanism.

INTRODUCTION

Neurodevelopmental disorders are disabilities associated with the functioning of the central nervous system, that affect language and speech, motor skills, behavior, memory, learning, or other neurological functions (Environmental Protection Agency, 2011). Autism Spectrum Disorder (ASD) is a family of neurodevelopmental disorders characterized by social impairment, communication deficits, and repetitive and stereotyped behaviors, with severity of impairment ranging from mild to severely debilitating. The Centers for Disease Control and Prevention recently estimated that 1 in 68 children suffer from ASD (The Centers for Disease Control and Prevention, 2014). Given the prevalence of ASD, coupled with the increasing resources needed to care for these individuals, it has become paramount to focus our effort on understanding the neurophysiological mechanisms that underlie this condition (Lajiness-O'Neill et al., 2014).

The etiology of ASD has yet to be determined, though one hypothesis suggests that an imbalance of excitation and inhibitory processes of the central nervous system may contribute to its cognitive and behavioral features (Cornew et al., 2012). Also, findings of abnormalities in total brain volume, regional changes in gray matter volume and abnormal white matter integrity have been hypothesized to reflect deficient integration of information at the neural level, and are consistent with reports of abnormal cortical connectivity in ASD when performing tasks that pose high cognitive demands (Tsiaras et al., 2011).

The extent of the abnormalities are yet to be determined, but the technologies of functional imaging and electrophysiological methodologies have the potential to reveal abnormal neurophysiological processes early in development, before the behavioral symptoms of ASD begin to emerge. Early identification of biomarkers relating to ASD could accelerate accurate diagnosis, identifying children in need of early intervention. This could lead to overall improved outcomes in these disorders upon reaching adulthood (Lajiness-O'Neill et al., 2014). We can examine patterns of neural oscillations, including abnormal oscillatory activity noninvasively during a *resting state* exam (Cornew et al., 2012).

The *resting state* occurs when the brain is not active in performing tasks but idles, allowing thoughts to wander. During resting state, the default mode network (DMN) of the brain is activated, which causes blood flow to the brain to generally decrease by 10-15%, due to lack of activation in certain areas of the brain (Buckner, Andrews-Hanna, & Schacter, 2008). Brain regions that are activated in the DMN include the anterior cingulate cortex (ACC), the medial prefrontal cortex (mPFC), the posterior cingulate cortex and precuneus (PCC), the medial temporal lobe (MTL) and the inferior parietal cortex (IPC), as illustrated in Figure 1. (Sandrone & Catani, 2013). It has been hypothesized in relation to ASD that disruption of the mPFC in the DMN results in a mind that is environmentally focused and lacks the capability to comprehend other people's thoughts (Buckner, Andrews-Hanna, & Shacter, 2008). This may contribute to an inability to interact with others in a social context, which is an expected behavioral consequence (Buckner, Andrews-Hanna, & Schacter, 2008).

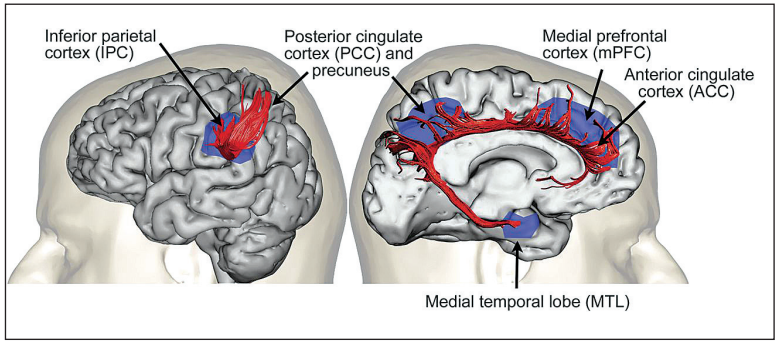

Figure 1. The Default Mode Network (Sandrone and Catani, 2013).

Another etiological hypothesis related to ASD is the Weak Central Coherence Theory (Noens & van Berckelaer-Onnes, 2008). Central Coherence refers to the normal tendency to process incoming information on a large scale, and with the context to allow an individual not only to make sense of received information, but also to structure it. People with ASD tend to process information on a small scale, instead of a large scale, which is considered "weak" central coherence (Noens & van Berckelaer-Onnes, 2008).

These purported etiologies may be reflected biologically in asynchronous neural firing. The synchronous firing of large populations of neurons is reflected by oscillatory activity, and illustrates the connectivity of cortical regions involving excitatory/inhibitory interactions (Cornew et al., 2012). Hemodynamic imaging with functional magnetic resonance imaging (fMRI) has demonstrated abnormalities in the patterns of neural connectivity over a wide range during resting state in ASD, as well as in other neurodevelopment disorders (Lajiness-O'Neill et al., 2014). Electromagnetic readings of Electroencephalography (EEG) have also shown support toward this claim during resting state. Over the past few decades, EEG has accumulated considerable literature exploring the abnormalities in electrophysiology in ASD, which have revealed high rates of epilepsy and epileptiform activity in ASD, which may be etiological rather than comorbid. Typically, the EEG studies in ASD report oscillatory anomalies (Lajiness-O'Neill et al., 2014).

Magnetoencephalography (MEG) provides researchers the opportunity to investigate neural functioning with high temporal and spatial resolution in ASD, because of its capability to record magnetic fields generated by the cortex (2014). Alternative methodologies provide either high spatial (fMRI) or temporal (EEG) resolution, but not both (Lajiness-O'Neill et al., 2014).

Similar to EEG, MEG allows for the investigation of the generation of evoked signals and neural synchrony by specific cortical regions, as well as coherence between signals generated by separate cortical regions (Lajiness-O'Neill et al., 2014). Coherence measures the correlation of signals with within a frequency or bandwidth using values from 0 to 1. A coherence value of 0 indicates that the signals are completely uncorrelated, while a coherence value of 1 indicates that the signals are completely correlated (Neurotraces, 2003). MEG also has some distinct advantages over EEG, allowing for better analysis of neurophysiological activities. One distinct feature of MEG is that the skull bones and soft tissues between the brain and the scalp do not distort the MEG signals, while EEG signals are highly affected by the skull and soft tissues (Lajiness-O'Neill et al., 2014). Another

distinct feature is that when used in research on epilepsy, it has been estimated that MEG can detect sources of spike-detection signals of synchronously activated cortical areas as small as 6-8 square cm. (Lajiness-O'Neill et al., 2014). However, in EEG, cortical areas of at least 10 square cm. must be synchronously activated in order to procure data on the sources of spike detection (Lajiness-O'Neill et al., 2014). MEG has also been noted as quiet, comfortable, and non-invasive. This is a remarkable advantage over the enclosed and noisy fMRI, or the invasiveness of PET in ASD studies, since by its very definition ASD includes symptoms of sensory sensitivity that can distort findings (Lajiness-O'Neill et al., 2014). With accumulating data supporting the effectiveness of MEG and its superiority over other methodologies in ASD studies, surprisingly few studies have investigated an excitation/inhibition imbalance on a macroscopic level of ASD using MEG during resting state (Lajiness-O'Neill et al., 2014).

MEG studies such as Tsiaras et al.'s network visualizations revealed that ASD has reduced interdependence synchronization marked by short range connections within bilateral frontal and temporal sensors, as well as between temporal sensors (Tsiaras et al., 2011). Tsiaras and colleagues used Graph Theory to examine resting state functional networks in a small group of adults with ASD. In a study by Cornew and colleagues (2012) using MEG, it was noted that in children with ASD there were regionally specific elevations in delta (1-4 Hz; suggesting a disconnection between gray and white matter, as well as thalamic abnormalities), theta (4-8 Hz), and high frequency (20-120; Hz beta and gamma) power. This study also demonstrated greater theta power in midline regions, as well as in parietal and occipital regions in ASD. Greater power in all high frequency bands was noted in ASD but was specifically noted in the temporal, parietal, and occipital regions (Cornew et al., 2012). The findings of this study also suggested that alpha power in the temporal and parietal lobes is associated with greater symptom severity in ASD (Cornew et al., 2012).

In the present study, we attempted to better understand the etiology of ASD by conducting *eyes open resting state* in ASD, using whole-cortex magnetoencephalography (MEG). We

hypothesized that the analysis would reveal decreased coherence in the DMN in frontal regions in ASD, compared to neural typically developed controls (NT'-s), suggesting less coherent activity in regions critical for theory of mind (e.g. taking another's perspective) in ASD, compared to NT. We further hypothesized that the analysis would reveal increased coherence in posterior (temporal, parietal, and occipital regions) brain regions in ASD, compared to NT, consistent with decreased connectivity between anterior and posterior regions in ASD.

METHODOLOGY

Participants

Participants were 10 male children (5 with ASD and 5 age-matched NT controls) aged 8-10 years old (mean = 9.0; SD = 1.0 for both the ASD and control groups). A Full Scale Intelligence Quotient (FSIQ) measured with the Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-2) ranged from 101-126 (mean = 112, SD = 9.29 for ASD with n = 3; mean = 110.8, SD = 12.7 for NT controls with n = 5). Autism Diagnostic Observation Schedule (ADOS-2) scores using ASD module 3 for the ASD children are displayed in Table 1.

Children screened for inclusion in the ASD sample group had been previously diagnosed with ASD according to the DSM-V criteria and had no history of a comorbid genetic disorder, seizure disorder, or other neurological disorder. Inclusion criteria for NT participants included no first-degree relatives with a history of ASD, no history of a learning disorder, a neurological disorder, or other psychopathology. Both groups had a Full Scale Intelligence Quotient (FSIQ) $\geq$ 70, and no head injury that resulted in loss of consciousness (LOC), or any metal implant that would interfere with MEG scanning.

	Social Affect	Restrictive Repetitive Behavior	Total	Comparison
Mean	8	2.75	11	6
Standard Deviation	6.8	3.6	7.5	3.6

Table 1. Mean and standard deviation of ADOS-2 scores of ASD Children.

Procedure

Research participants were involved in a single assessment session at Henry Ford Hospital. The session involved a one-hour clinical battery, during which diagnostic and neuropsychological tests were conducted. A licensed psychologist or clinical psychology doctoral candidate with expertise in ASD performed all assessments and confirmed ASD diagnoses. Assessments included the ADOS-2 (Lord et al., 2000), the Social Communication Questionnaire (SCQ; Rutter et al. 2003), and the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005), Vineland-II Adaptive Behavior Social scales (Sparrow et al., 2005), WASI-2 (Canivez & Watkins, 2001), NEPSY II developmental neuropsychological assessment (Korkman, Kirk, & Kemp, 2007), Clinical Evaluation of Language Fundamentals Fourth Edition (CELF-4; Paslawski, 2004), and the Comprehensive Test of Phonological Processing (CTOPP; Wagner, Torgesen & Rashotte, 1999). Following the one-hour clinical battery of tests, the participants' neural activity was assessed with MEG during an eyes open resting state.

MEG Preprocessing and Data Analysis

One-hundred forty-eight (148) channel whole head MEG (4D Neuroimaging, Magnes WH2500) collected cortical activity measuring magnetic field strength, associated with currents from populations of 50-100K cortical neurons. Electrocardiography (ECG) and movement artifacts were removed, using an Independent Component Analysis (ICA) technique. Data were band-pass filtered from 3 to 85 Hz. Synchronization of neuronal activity during eyes open resting state was quantified by calculating coherence between cortical sites from MEG imaged brain activations using the MR-FOCUSS Coherence method (Moran, Bowyer, & Tepley, 2005).

RESULTS

As shown in Table 2., the primary regions of coherence for NT's were predominantly in the frontal lobe (80%), compared to ASD, where only one of the subjects' primary region of coherence

was in the frontal lobe (20%). The other subjects' primary regions of coherent activation in ASD were in the parietal and temporal lobes. The second and third key brain regions of coherent activation in NT's were all in the frontal lobe, predominantly in the superior and middle frontal brain regions. The second key region of coherent activation for ASD was in frontal regions (precentral, middle frontal, and superior frontal; 60%). The third key region of coherent activation (80%) in ASD was also in frontal cortical regions (precentral, inferior frontal and middle frontal). Table 2. also shows the hemispheres of the coherent activity. In NT's, 67% of the coherent activity was in the left hemisphere, while 53% of the coherent activity was in the left hemisphere in AS.

Subject	Group	Coh Collapsed Top	Coh Collapsed Second	Coh Collapsed Third
6621	ASD	Left Fusuform Gyrus	Right Inferior Occipital Gyrus	Right Fusiform Gyrus
6622	ASD	Right Postcentral Gyrus	Left Precentral Gyrus	Right Precentral Gyrus
6624	ASD	Left Fusifrom Gyrus	Left Fusiform Gyrus	Left Inferior Frontal Gyrus
6626	ASD	Left Middle Frontal Gyrus	Right Middle Frontal Gyrus	Left Middle Frontal Gyrus
6630	ASD	Right Inferior Temporal Gyrus	Right Superior Frontal Gyrus	Left Middle Frontal Gyrus
6623	NT	Left Lateral Orbitofrontal Gyrus	Right Superior Frontal Gyrus	Left Middle Frontal Gyrus
6627	NT	Left Precentral Gyrus	Left Middle Frontal Gyrus	Left Superior Frontal Gyrus
6628	NT	Right Superior Frontal Gyrus	Left Middle Frontal Gyrus	Left Middle Frontal Gyrus
6629	NT	Left Middle Frontal Gyrus	Left Superior Frontal Gyrus	Right Middle Frontal Gyrus
6631	NT	Right Postcentral Gyrus	Right Superior Frontal Gyrus	Left Superior Frontal Gyrus

Key	ASD	Temporal	Frontal	Parietal	Occipital

Table 2. Activation of Brain Regions during coherence collapsed in NT and ASD.

Figures 2. and 3. display key regions of coherent activity in ASD predominantly in parietal and temporal cortical regions. Figures 4. and 5. display the top cortical regions of coherent activity in NT's, specifically in the middle, superior and precentral frontal gyri.

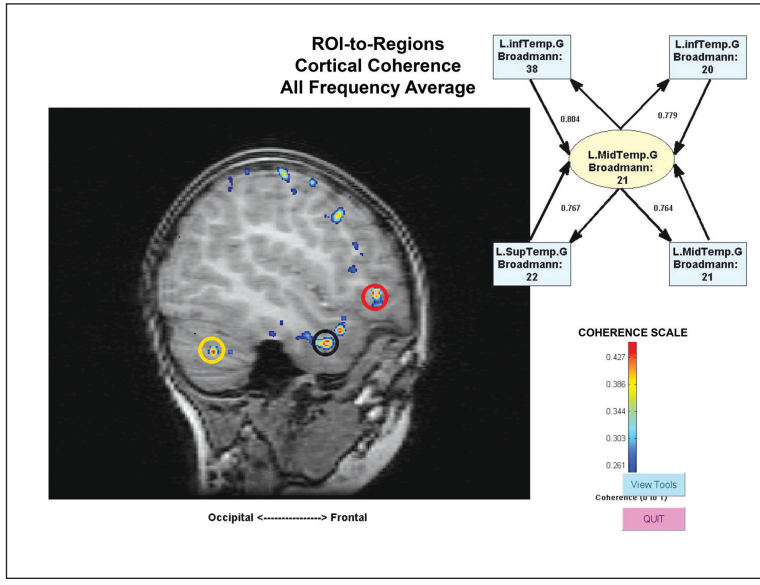

Figure 2. Top activation in ASD in the Left Middle Temporal Gyrus and in the Parietal and Occipital regions.

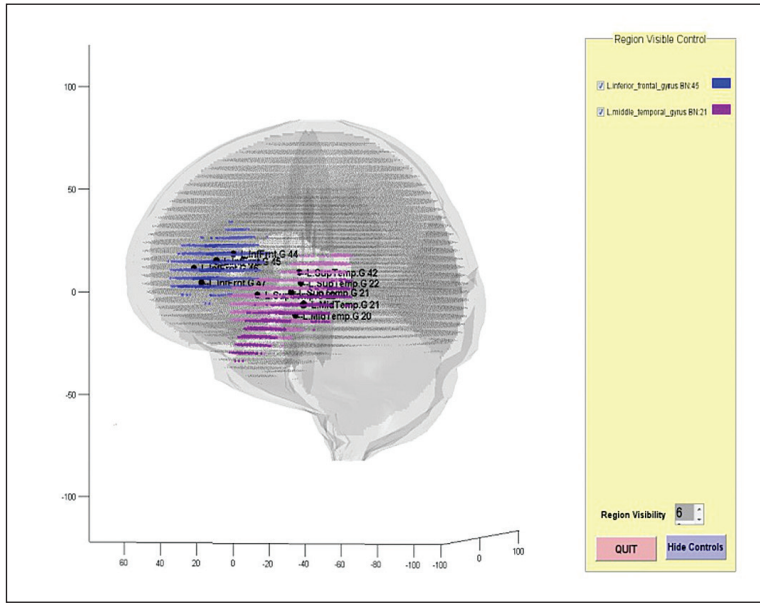

Figure 3. Top activation area in ASD in the Left Middle Temporal Gyrus.

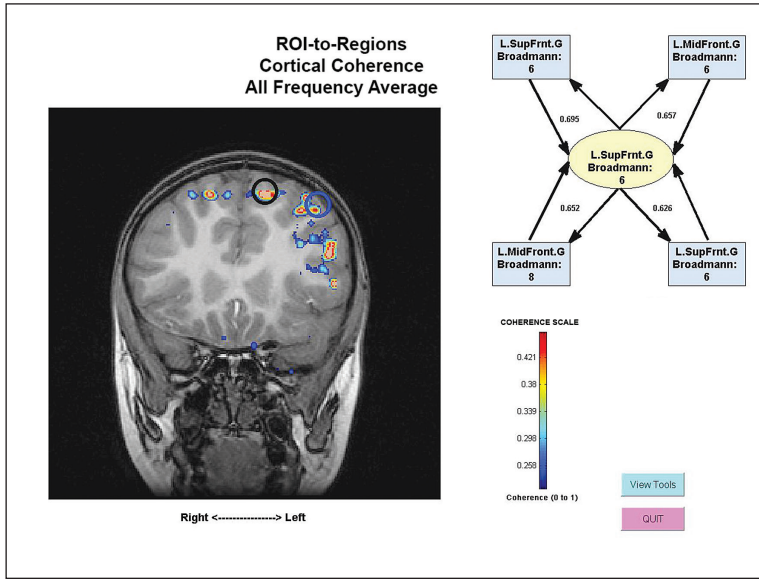

Figure 4. Top activation areas in NT's in the Superior Frontal Gyrus.

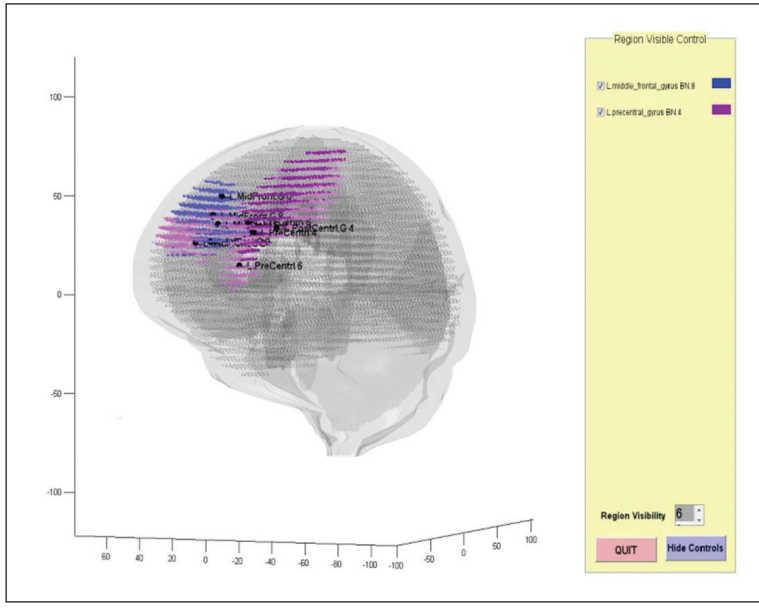

Figure 5. Top activation areas in NT's in the Left Middle Frontal Gyrus and Left Precentral Gyrus.

DISCUSSION

The goal of this pilot study was to better understand the etiology of ASD through the examination of neural oscillatory activation using MEG. The main regions of coherent neural brain activation in NT's were the left and right superior frontal gyri and the left and right middle frontal gyri. The superior frontal region is associated with working memory (temporary storage of information that can be manipulated to complete various tasks; Boisgeuheneuc et al., 2006). The middle frontal gyri is associated with the DMN, which is expected to be in effect during resting state, along with the superior frontal region of the brain (Buckner, Andrews-Hanna, & Shacter, 2008).

In ASD, the main areas of coherent brain activation were the left and right fusiform gyri (temporal cotex) and the right inferior occipital gyrus. Consistent with the NT's, increased coherent brain activation was noted in the right and left middle frontal gyri, as well as in the left and right superior frontal gyri and Broca's area. The fusiform and the inferior occicpital gyri are associated with facial recognition and detection, illustrating that in ASD the brain may be focused more on visual stimuli than higher-order cognitive thought, though it also includes working memory, but at lower levels of activation. The top regions of coherent brain activation in ASD are primarily responsible for basic sensory and visual perception.

The DMN is considered to be critical for behaviors such as self-referential thinking, reflection, taking on another's perspective (Buckner, Andrews-Hanna, & Shacter, 2008), and our data suggest that there may be possible disruptions in this network which contribute to the behavioral profile of ASD. Our data may also be consistent with the Executive Dysfunction hypothesis (Hill, 2004). Executive functions include but are not limited to planning, mental flexibility, and inhibitory controls (Hill, 2004). Many individuals with ASD demonstrate impairments in planning and mental flexibility, which supports the hypothesis of executive dysfunction.

Our results displayed that 53% of the areas of coherent brain activation in ASD were within the left hemisphere (only

slightly more than the right hemisphere). Two thirds of NT's primary regions of activation were in the left hemisphere. The left hemisphere of the brain is considered to be associated with speech and language processes. The lower amount of left hemisphere activation in ASD is likely consistent with known speech and language deficits observed in ASD.

FUTURE RESEARCH

Future research will consist of examining developmental patterns in the DMN, including assessing individuals early in the course of their illness. Following additional data collection, imaging data will be correlated with behavioral and psychometric data.

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