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Functional Network Connectivity: Possible Biomarker for Autism Spectrum Disorders (ASD)

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Summary

Autism (ASD) is a complex neurodevelopmental disorder that affects social interaction and communication, often impairing individuals for a lifetime. In our study, we used magnetoencephalography (MEG), a non-invasive brain imaging technique, to identify possible biomarkers for ASD. We hypothesized that there would be significant differences in brain connectivity patterns between the ASD group and the controls. We recorded the brain activity of individuals looking at a stationary colorful image while in the resting state. The resting state refers to the brain activity of a subject when he or she is not engaged in any particular task. We found the ASD group had a high concentration of coherent brain activity in the frontal lobe, while the control group had a high level of coherence in the occipital lobe. Areas of high coherence indicate that the brain is well connected and communicating with many other areas of the brain. In controls, we expected high coherent activity in the occipital cortex, since they were looking at a colorful picture. In the ASD group, we found that the frontal lobe was unusually active. This area is typically used in higher-level cognition. These regions of abnormally high coherent brain activity indicate possible biomarkers for autism. Additionally, the ASD group had a significantly lower overall level of coherence than controls.

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Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that now affects 1 in 68 children (1, 2). Those diagnosed with ASD are afflicted by social impairment, communicative issues, and repetitive behavior. In addition to these symptoms, the ASD group also has difficulties in motor coordination, attention, and physical health issues. Studies have reported that only 56% of those with ASD are able to graduate from high school, and the majority of those with ASD end up being dependent on parents or caregivers for their entire lifetime (3, 4). Unfortunately, many of these problems are unknown to the general public.

Since the 1980s, the prevalence of ASD has been rapidly increasing. It is the fastest-growing serious developmental disability in the U.S (5, 6); however, scientists are still unable to find its exact cause. Though not fully responsible for ASD, genes affecting synaptic function and connectivity are theorized to play the largest role, while other factors, such as the environment, play a lesser but still important role (7). Although there is no cure for autism, its symptoms can be lessened through a combination of behavioral therapies and drugs (psychoactive and anticonvulsant medications) (8, 9). Many of these medications, however, often come with a wide variety of harmful side effects, discouraging the use of such drugs (10).

Currently, no imaging biomarker exists to identify autism in young children. Thus, there is no conclusive test to determine whether or not a child has the disorder, making the average age for a definitive diagnosis very late, averaging 5.7 years old (11).

Discovery of the underlying brain mechanisms that support or alter brain function in ASD would provide a basis for understanding how treatments or early interventions could reduce the severity of ASD. Over the past several years there have been many neuroimaging studies trying to better understand how the ASD brain works. It has been noted that the head is abnormally larger in some children with ASD compared to neurotypicals (12, 13). MRI was used to show that there is a generalized enlargement of the gray and white matter volumes in toddlers with ASD at age 2, compared to neurotypicals (14). Using functional magnetic resonance imaging (fMRI), it's been found that functional brain connectivity between the front and back of the brain is different in ASD compared to controls (15). In 2011, Kana et al. theorized that "disrupted connectivity," including both under-connectivity and over-connectivity, were responsible for the abnormal brain connections in ASD (17). These abnormalities are a possible cause of the behavioral and cognitive problems associated with autism.

Magnetoencephalography (MEG) is another non-invasive type of tool to image the brain connections by measuring the magnetic fields generated by the brain's neurons (13). MEG provides temporal resolution in the millisecond time range and spatial localization below 5mm so brain activity can be precisely localized (23, 24). The magnetic signals arising from the brain are exceedingly small (10^{-12} to 10^{-15} Tesla), so Superconducting Quantum Interference Devices (SQUIDs) are needed to detect these fields. MEG coherence imaging is often used to

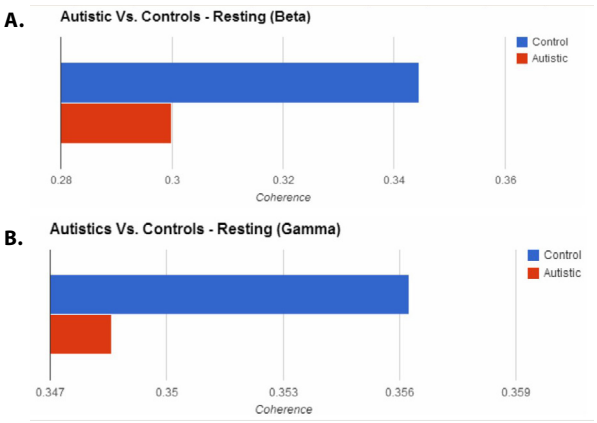

Figure 1: (A) Average level of beta band (14-30 Hz) coherence for each group during resting state with eyes open. There was a statistically significant difference between the groups. (B) Average level of gamma Band (30 – 80 Hz) coherence for each group during resting state with eyes open. Though there was a difference, it was not statistically significant.

look at connectivity and how different brain areas are communicating with each other (27). MEG has been used to investigate deficits in the auditory and somatosensory systems in ASD (18, 19). However, little MEG research has been done on the resting state brain differences between ASD and controls. While a person is at rest, their mind is not focused on or engaged in a specific task. Many fMRI studies have been performed on normal subjects to detect the default mode network (DMN), a well-established network of brain regions that is active during resting (20). FMRI has been used to detect a weaker connectivity in nine of the eleven areas involved in the default mode network in adolescents with ASD (21). Studying the resting state may be particularly useful because it is often difficult to engage very young children in a task, and many more children are able to participate in MEG recording during the resting state.

In this study, we used magnetoencephalography (MEG) to find key differences in the location of brain connection activity during rest between individuals with ASD and control participants. We hypothesized that there would be significant differences in coherence values and activity between the two groups. Our results indicate that an abnormal amount of functional connectivity occurs during the resting state in the frontal lobe in children with ASD. Coherent activity and functional connectivity are essentially measures of how much of the brain is activated and communicating. These results indicate that MEG may hold the key to an imaging biomarker for ASD that could be found in infant children. With the knowledge of these differences, MEG testing may provide an earlier diagnosis of autism. Research has shown that a baby's brain is 80% developed by the second year of life (26). If MEG testing can be used effectively prior to this age to detect and diagnose children on the ASD spectrum, then new treatments, such as drugs or remediation, may be tested to determine if they could prevent the development of autism.

Results

The highest coherent brain areas in the gamma band and beta bands were seen in the visual cortex in the control subject population during the 10-minute resting state brain scan. This was expected, since they were looking at a colorful picture on the ceiling. The occipital cortex receives information directly from the retina, so it is important in visual perception and color recognition. ASD subjects, on the other hand, had higher coherent brain areas concentrated in the frontal lobe, as opposed to the visual cortex. The ASD group also had an overall lower beta band coherence level (avg: 0.299 +/- 0.045) than did the control subjects (avg: 0.345 +/- 0.094) {p<0.05, t-test 2.317}, as seen in Figure 1A. In ASD, there was a slightly lower gamma band coherence level (avg: 0.349 +/- 0.063) compared to that of the control

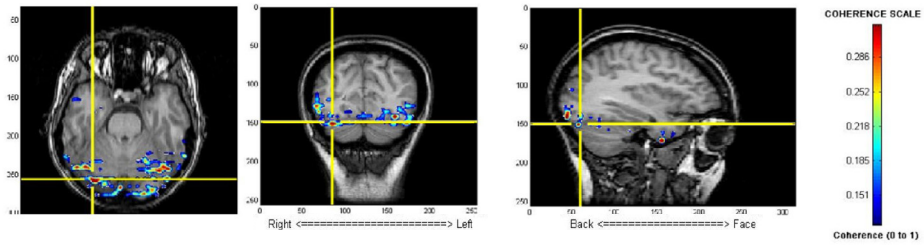

Figure 2: A control subject with the highest coherent activity located in the right inferior occipital gyrus during the resting state, measured by the beta band (14-30).

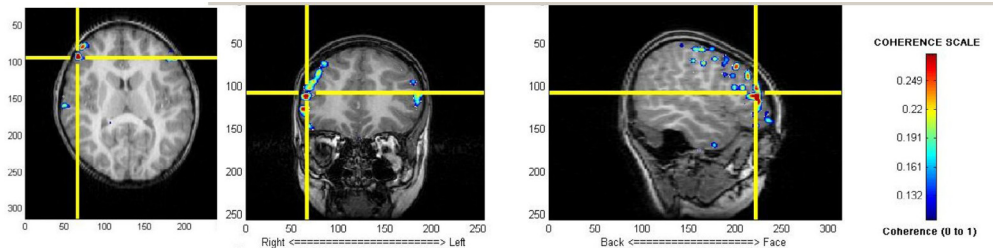

Figure 3: An ASD subject having the highest coherent activity in the right inferior frontal gyrus during the resting state, measured by the beta band (14-30 Hz).

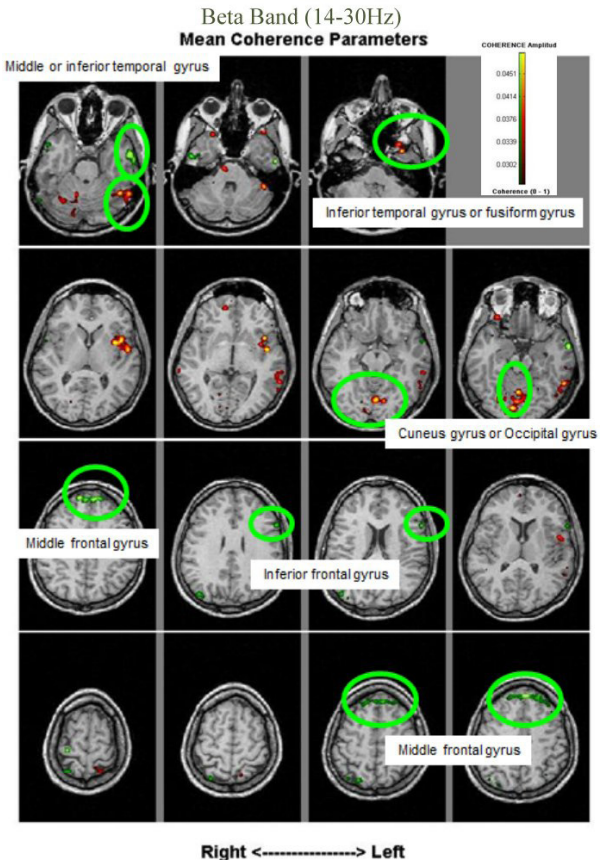

Figure 4: Comparison of controls and ASDs during the resting state in the beta band (14-30 Hz). 361 out of 4000 pixels were used to differentiate between the two groups, with a 95% discriminant performance level and p< 0.01. ASD subjects (green) have the most activity in the frontal lobe, while control subjects (red) have the most activity in the occipital lobe. Areas of significant coherence have been labeled.

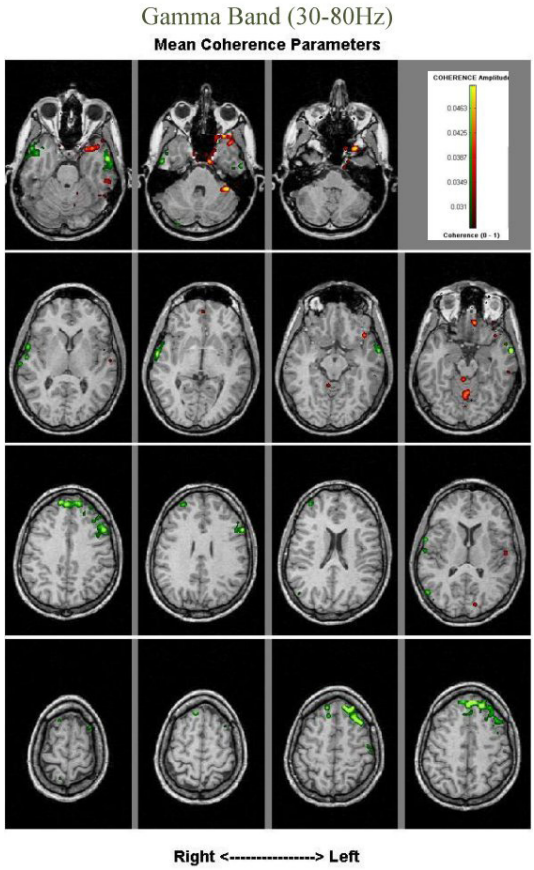

Figure 5: Comparison of ASD and control subjects during the resting state in the gamma band (30-80 Hz). 379 out of 4000 pixels were used to differentiate between the two groups, with a 95% discriminant performance level and p< 0.01. ASD subjects (green) have concentrated activity in the frontal lobe, similar to the beta band, and controls (red) have the most coherent activity in the occipital lobe.

subjects (avg: 0.356 +/- 0.123), which was not statistically different {p=0.768, t-test 0.3} (Figure 1B).

Discriminant analysis was performed to determine if the locations of brain activity could be used to discriminate between ASDs and controls. After performance of the coherence analysis across the entire brain for two frequency bands, the top coherent locations were put into a discriminant analysis. Figures 2 and 3 are examples of the individuals' top locations in the beta band for a control and an ASD subject. This type of analysis is used to determine if there exists a pattern of brain activity that is unique to each group and could be used on individuals' MEG image data to determine which group they would belong to. An overall group brain map was made for the ASD (N=13) and for the controls (N=11).

The discriminant analysis results indicated that 361 pixels out of 4000 pixels can be used to differentiate between the ASD and the control group, with a p-value of less than <0.05. Figure 4 shows the beta band locations where the resting state brain networks are different between groups. The control subjects have higher coherent activity indicated by areas in red, seen primarily in the occipital cortex and inferior temporal gyrus. In contrast, the ASD group has higher coherent activity indicated by green, seen primarily in the inferior frontal and middle frontal gyri. Figure 5 shows the gamma band results with similar coherent activation patterns.

Discussion

In the resting state, statistically significant differences were found between the beta band coherence level of ASD subjects and the coherence level of the control subjects. The control subjects had higher coherence values (0.345) than those with ASD (0.299).

All of the subjects were expected to have concentrated activity in the visual cortex, because they were looking at a colorful picture on the ceiling with their eyes open; this is our typical method for recording resting state brain activity. Another method for investigating the resting state brain activity is performed while the eyes are closed, but this method evokes a large amount of

alpha activity in the occipital cortex. This was seen in the previous MEG study (32) that was performed during rest with the eyes closed, where they found that there was more power in the alpha band in the ASD group. We cannot determine if there would have been group differences in an eyes-closed condition, and it is difficult to compare our results to studies that used the eyes-closed technique.

When the results of the discriminant analysis of the ASD group were compared to those in the control group, we discovered that the ASD subjects had a large concentration of functional brain connectivity in the frontal lobe, which consists of the middle frontal, inferior frontal, and superior frontal gyri. These parts of the brain collectively assist in problem solving, decision making, and controlling purposeful behaviors. This is in contrast to the concentration of brain activity in the occipital lobe seen in control subjects. When viewing a picture, control subjects primarily invoke only visual brain activation areas located in the occipital lobe. In the resting state eyes-open condition, we found potential biomarkers for ASD in the inferior frontal, middle frontal, and superior frontal gyri. There were also significantly lower coherence values for people with autism, indicating weaker connectivity between regions in the brain.

After performing a discriminant analysis in the gamma band frequency (30-80 Hz), coherent brain area differences were found for both groups. These findings suggest that ASD subjects may not actually be visually viewing their surroundings, but are internally engaging in some higher level of cognitive brain activity. The gamma band is associated with perceptual processing, attention, arousal, object recognition, and language perception (33), so this may suggest that subjects in the ASD group, instead of simply looking at the image, are doing some other internal cognitive task. Another possible explanation for these results is that children with autism use different brain networks than neurotypicals for basic tasks like looking at a picture. This may just be a disruption in one of the intrinsic connectivity networks (the DMN is only one of those), and this could easily reflect a disruption in either the DMN, Fronto-parietal Control Network, Dorsal Attention Network, or Salience Network – all having to do with attention focus. What we may be seeing is an inability to regulate between internal and external focus of visual attention, causing a disruption in top-down cognitive control, which may be reflected in the over-active frontal activation seen here. That is, the controls use the basic occipital lobe because they have “released” their frontal lobes from processing - the same may not be true in ASD.

The location of the lower coherence values seen in ASD during rest supports the hypothesis that ASD is a brain network disorder. These MEG imaging results display the connectivity networks between regions in the brain, as coherence is a measure of connectivity between brain regions. Despite the simple task of viewing a picture, the ASD group displayed a high level of coherent activity in the frontal lobe, which is normally active in higher-order functions. These novel results shed light on the differences in cortical brain activity between ASD subjects and controls. This innovative idea to use a resting state brain scan to determine if the brain networks can be used as a biomarker for distinguishing differences between these 2 groups has the potential to be a diagnostic tool and a research tool for looking at treatment responses in very young children, specifically those that cannot yet communicate. Previous studies of coherence using MEG or EEG in these two populations during resting have focused on the frequency content of the signals on each sensor, providing results in sensor space. Our method first images bursts of brain activity in the MRI (providing results in source space), then uses colors to identify the actual brain regions that are well connected to other areas, as opposed to just drawing a straight line connecting the EEG electrodes or MEG sensors that contain similar frequencies. This MEG coherence source imaging (CSI) method allows for a precise identification of the actual brain regions that are in use during the resting state.

The biomarkers found in our MEG experiment have the potential to lead to the testing for ASD at an extremely young age (i.e. less than 1 year old). With ASD becoming more widespread, it is imperative that methods are discovered to diagnose the disorder earlier. This study found significant MEG biomarkers for ASD during the resting state. Since our resting test is passive, we should be able to use the same type of scan on increasingly younger children to help determine at what point ASD can be detected by MEG. With MEG becoming a more popular tool for diagnosis, we hope to be able to use it to diagnose autism during infancy. This will allow treatment to be started earlier, which is more likely to lead to better outcomes. Additionally, the knowledge of these biomarkers allows for an expansion of research to be done, specifically on detecting changes in the functional network after treatment.

Future experiments can improve upon this research by testing increasingly younger children, until the point at which the children develop autism is found. In addition to earlier diagnosis, future work could be focused on obtaining therapeutic agents that suppress activity in the frontal lobe and strengthen neural connectivity, possibly ameliorating the symptoms of ASD. With the biomarkers, studies can be done to observe treatment responses. Researchers could test children with certain puzzles or antipsychotic drugs in the hopes of modifying the child’s brain waves. After completing the treatment, subjects could be brought back after a set amount of time to have their brain activity compared to the activity prior to treatment. For example, previous studies have shown that the chemical GABA is positively correlated with gamma activity (36, 37). There are certain antipsychotic drugs that are able to modify the amount of GABA in a person. Further investigation is required to find a similar chemical to change the brain patterns found in ASD. We hope that our research on the biomarkers of autism can provide a novel approach for bettering the lives of those with autism.

Methods

Participants

Thirteen participants with ASD (average age: 17.5 years) and eleven control subjects (average age: 15.2 years) completed the study. There were no significant between-group differences in intellectual functioning, as both performed in the Above Average range on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999), $t(17) = 1.08$, $p = 0.31$. Individuals were recruited from a nearby hospital, through advertisement, and by peer nomination. Subjects were diagnosed with ASD based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision and confirmed with the Autism Diagnostic Interview-Revised. All APA Ethical Guidelines were followed, and Institutional Review Board approval was obtained from all institutions participating in this study. The WASI was individually administered. Participation in the study was contingent on the individual functioning at least within the Low Average range of intellectual ability (>80 Full Scale IQ scores on the WASI). Exclusionary criteria for ASD and control participants included any known history of head injury with loss of consciousness or other neurological disorders and the presence of any metallic implant that would preclude the use of the MEG scanner, (e.g. braces on teeth, pace maker). Control subjects had no history of developmental delay, learning disorder, or ASD in a first-degree relative.

MEG Procedures and Protocol

Each participant underwent a MEG procedure. After signing informed consent, subjects changed into hospital gowns and removed all metal from their body. Three small electrode coils used to transmit subject location information to the neuromagnetometer probe were affixed to the forehead with two-sided tape. Two more coils were taped on each cheek, in front of the ear canal opening. A commercial videotape eraser was used to demagnetize dental work if needed. Participants then lay on a bed in a magnetically shielded room. The neuromagnetometer helmet containing the detector array was placed around the participant's head in close proximity to most of the cortical surface. The participant was asked to avoid both eye and body movements.

MEG Data Acquisition and Pre-processing

Brain activity was recorded non-invasively using a 148-channel whole head MEG system (4D Neuroimaging, Magnes WH2500) with magnetometer type sensors. This sensor is a Super Conducting Quantum Interference Device (SQUID), filled weekly with liquid helium to keep it at superconducting temperatures. During acquisition, magnetic field changes in tesla units were recorded at 148 locations around the head with a sampling rate of 508 times per second. The data were band-pass filtered from 0.1 to 100 Hz and continuously recorded for later analysis. A 10-minute resting state brain scan was performed with the subjects' eyes open. In post-processing, the data were then band-pass filtered from 3 to 85 Hz to reduce environmental artifacts. A notch filter at 60 Hz was used to eliminate the power line frequency. Additional noise artifacts due to heart and body movements were eliminated using an independent component analysis (ICA) algorithm on the data, if needed. This ensured that the MEG data only contained signals from the subject's brain. Data were then further band-pass filtered into two frequency bands: Beta (14-30 Hz) and Gamma (30-80 Hz). These two frequencies are frequently used in research, because of their association with consciousness and cognitive tasks, respectively. Beta brain waves are associated with normal waking consciousness, as well as logic and critical reasoning. Gamma waves are associated with high-level information processing.

MEG Coherence Analysis

Synchronization of oscillating neuronal activity can be quantified by calculating the coherence between different brain regions (27). The resting state brain activity was analyzed with our coherence source imaging (CSI) technique to identify active cortical networks. The cortical networks that were imaged contained sources that interacted or communicated strongly within the gamma and beta frequency ranges. A source model of the cortical brain surface was created from a standard MRI (from a child). The MRI was segmented, and the brain surface was represented by a cortical model of approximately 4,000 dipoles, each having an x, y, and z orientation at each site. This model was then morphed to fit the digitized head shape collected during the MEG acquisition. The accuracy of forward model calculations was enhanced by utilizing a spherical model of the head that exactly matched local skull curvature for 6 different regions of the brain, corresponding to the front, middle and back of each hemisphere. This multisphere technique has been demonstrated to be accurate for MEG solutions (28). To calculate coherence, the MEG data were first imaged on the MRI using the MR-FOCUSS, and a connectivity map was created for each of these locations (27). MR-FOCUSS, a current distribution source imaging technique, was used to image the high amplitude bursts of brain activity that occurred during the 10-minute resting state (29). The coherence between frequencies within each band across each of the 4,000 modeled locations was determined. Coherence quantifies the network connectivity that underlies the resting state brain activity. Statistical analysis of the cortical coherence level (0 to 1) was used to quantify differences in network connectivity between groups. A region-of-interest (ROI) tool was used to identify 54 regions in the brain (27 in each hemisphere). MEG Tools uses a nonlinear volumetric transformation of the brain to transform MEG coordinates to these standard brain coordinates [30]. This enabled the ROI tool to access an atlas of Brodmann area identifiers and an atlas of cortical structures (31).

Group Difference Testing and Discriminant Analysis

For each frequency band (beta and gamma), a t-test was used to assess the differences in average coherence

values between ASD and control subjects. The resting state brain activity was also subjected to a discriminant analysis for each frequency band. Brain regions with statistical significance were identified with a p-value less than 0.05. The Statistica program was used to perform the statistical analysis of the coherence levels between the ASD group and the control group of subjects. The t-test indicated that the results were significant, with a p-value less than 0.05, meaning that our results are highly unlikely to be due to chance.

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