Hemispheric Differences in Neural Activation During Gaze Cueing in Autism Spectrum Disorder (ASD) Measured by Magnetoencephalography (MEG)

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Abstract- **Atypical hemispheric lateralization during language tasks has been reported in autism spectrum disorders (ASD). Six participants with ASD and eight neurotypical controls underwent MEG while performing a gaze cueing task. Participants indicated whether a character's gaze shifted congruently or incongruently to targets (asterisk), words, or faces. We hypothesized similar aberrant activity and contextual differences would be evident during joint attention (JA), suggesting fundamental cognitive processing biases in regions necessary for either verbal or nonverbal communication. Data were analyzed with MR-FOCUSS [1]. Results revealed higher mean amplitudes in left occipital and parietal brain regions during gaze shifts to both targets and faces in ASD while higher mean amplitudes in right inferior temporal and medial orbitofrontal regions was evident in controls. Pronounced amplitudes were noted in left angular regions during gaze shifts to faces in ASD. Latency data further reveals contextual differences and a possible double dissociation in brain regions recruited for joint attention. While controls displayed an earlier onset in activation to words in frontal regions and later activation to faces in inferior temporal regions, ASD demonstrated the opposite pattern; an earlier activation in inferior temporal regions and later activation in frontal regions to words. Results suggest atypical hemispheric specialization for joint attention with ASD recruiting left posterior hemispheric regions during gaze shifts to social stimuli while controls recruit right inferior temporal and medial orbitofrontal regions. Consistent with aberrant connectivity and a "crowding" hypothesis, ASD subjects appear to be using regions that underlie reading such as posterior parietal and occipital regions for joint attention. This is the first study to reveal these deficits in ASD children and adolescents with neuroimaging.**

Keywords- **MEG, Magnetoencephalography, Autism, Gaze Cueing, Joint Attention, Social Cognition**

I. Introduction

Socialization deficits are a major source of impairment in autism spectrum disorders (ASD) despite cognitive or language skills [2]. The research literature is replete in identifying the social impairments associated with ASD [3].

Early neurological models of the social deficits in ASD emphasized the presence of localized dysfunction within the social cognition network, with particular focus on the prefrontal cortex, temporal lobe, and the limbic lobe. Functional neuroimaging studies of individuals with ASD have found altered brain activity in these regions in response to the perception of social stimuli [4]. To date, research has not identified a "smoking gun" in the identification of a potential social biomarker in ASD; however, the early behavioral deficit in joint attention appears a highly plausible candidate behavior for which an enduring neural marker is likely to be evident.

During social interaction, a person's eyes convey information about their direction of attention, emotion, and mental state [5]. A specific form of gaze following behavior is joint attention (JA); a complex communicative mechanism that develops in early childhood. JA is a method of nonverbal communication that occurs when one individual follows another individual's eye gaze or gesture to an object or third individual [6]. It is a fundamental part of social functioning as it has been linked to both social and language development [7]. However, this pivotal skill fails to develop appropriately in infants with autism, and almost nothing is known about the persistence of these gaze-following deficits into adolescence or adulthood and their impact on social functioning.

The goal of this study is to accelerate the discovery of the neural correlates underlying the profound social impairment in ASD using MEG. We will attempt to demonstrate aberrant connectivity and differential activation in brain structures of individuals with ASD using a gaze cueing paradigm. We examined differential effects of stimuli attended to, such as faces and words, in children and adolescents with and without ASD. These stimuli were chosen as individuals with ASD do not appear to attend to faces any differently than other "objects." Moreover, clinically, individuals with ASD tend to display an affinity for attending to orthographs (i.e., words) and often display accelerated word reading abilities in early toddlerhood, despite impaired language [8]. The mechanisms of these processes and implications for social functioning are poorly understood.

II. Methods

Participants: Six participants with ASD (Mean age = 15 mean IQ = 120; Males = 4) and eight neurotypical controls (Mean age = 17; mean IQ = 115; Males = 4) underwent MEG while performing a gaze cueing task. Autism Diagnostic Interview-Revised [9] confirmed diagnoses.

Measures: Participants viewed a character projected inside the MEG apparatus and indicated whether the character's gaze shifted to a target (i.e. asterisk), word, or face. The target, word, or face stimuli were either in a congruent or incongruent location with the character's gaze. There were a total of 60 targets, faces, or words (30 congruent and 30 incongruent in each condition); hence, over the three conditions there were a total of 180 stimuli. Each set (targets: congruent and incongruent; faces: congruent and incongruent; or words: congruent and incongruent) contain 30 responses to determine the averaged evoked response. The subject was asked to press the button when the subject is looking toward something. 148 channel whole head MEG (4D Neuroimaging, Magnes WH2500) collected cortical activity. Evoked magnetic field data was used from -0.2 seconds prior until 0.65 seconds after the stimulus onset. Brain activity was analyzed with MR-FOCUSS, a current density technique (1).

An average normalized amplitude per active sources in 54 brain regions based on MNI coordinates was calculated. The left and right hemisphere ROIs were summed and averaged based on total active sources for that ROI to generate a normalized mean amplitude for the ROI over the 650 ms epoch to compare groups.

III. Results

Joint Attention to Targets: There were no differences with respect to the onset of activation during gaze shifts to targets, although a significant number of differences were noted in the amplitudes of activation across different brain regions in ASD compared to controls and a clear double dissociation was evident. Higher normalized mean amplitudes were noted in ASD predominately in the left posterior hemisphere including the left cuneus, $t(11) = 2.85$, $p = .02$, middle occipital, , $t(11) = 2.56$, $p = .03$, poscentral gyrus, , $t(11) = 2.66$, $p = .02$, superior parietal, supramarginal, , $t(11) = 2.44$ $p = .02$, and right cuneus, , $t(11) = 2.99$, $p = .01$. In contrast, higher amplitudes of activation were noted in the right inferior temporal, $t(11) = 2.59$, $p = .03$, and right middle orbitofrontal regions , $t(11) = 2.49$, $p = .04$, during gaze shift to targets in controls. See Figure 1.

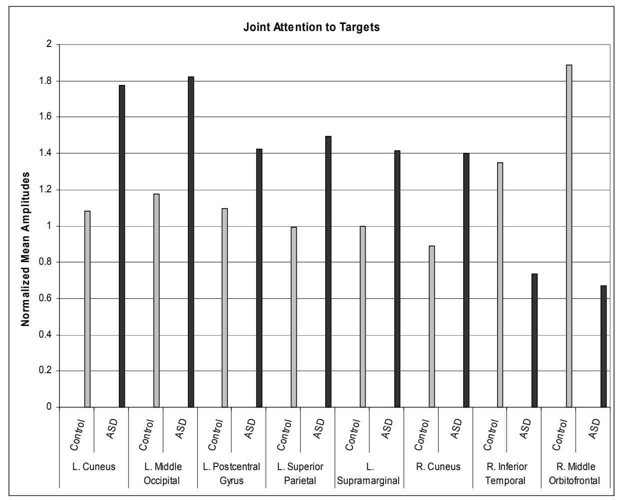

Fig. 1 Joint attention to targets. Note predominately left hemispheric activation in ASD and focal right frontotemporal activation in controls.

Joint Attention to Words: When ASD subjects engaged in gaze shifts to words, significantly higher normalized mean amplitudes were noted in the left superior occipital region in ASD, $t(11) = 3.53$, $p = .01$, while higher amplitudes were noted in the right putamen in controls, $t(11) = 3.12$, $p = .02$. See Figure 2. Significant differences in the latency of activation were noted in middle and superior frontal regions, $t(11) = 2.15$, $p = .04$; $t(11) = 2.48$, $p = .03$, as well as in supramarginal regions, , $t(11) = 3.24$, $p = .02$, with ASD subjects displaying a delay relative to controls with onset at ≈300-350 ms while controls displayed activation at about ≈200 ms. In frontal regions. See Figure 3.

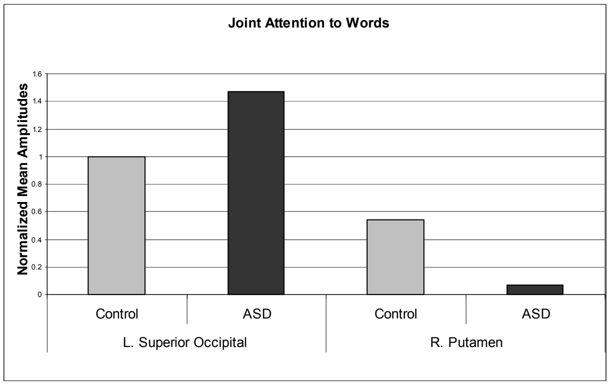

Fig. 2 Normalized amplitudes for joint attention to words with significantly higher left occipital activation noted in ASD.

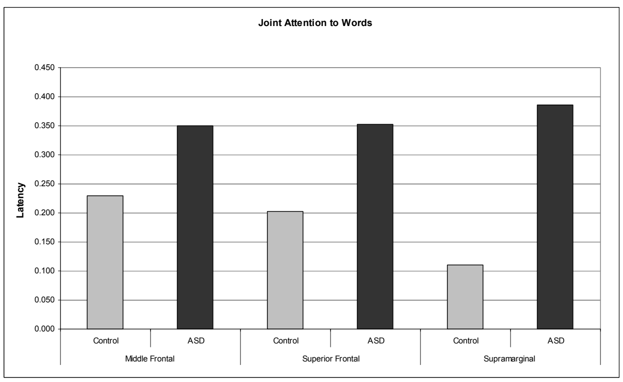

Fig. 3 Latency for joint attention to words. Note earlier latency in controls to words compared to later latency to faces in Fig. 6. The opposite pattern was noted in ASD.

Joint Attention to Faces: Significantly higher normalized mean amplitudes were noted in the left angular region in ASD compared to controls during gaze shifts to faces, $t(11) = 3.1$, $p = .01$. See Figures 4 and 5. In contrast, a significantly earlier latency of activation was noted in inferior temporal regions in ASD compared to controls, with control subjects displaying activation in inferior temporal regions at ≈300 ms, while ASD subjects onset of activation was at ≈200 ms, $t(11) = 2.48$, $p = .03$. See Figure 6.

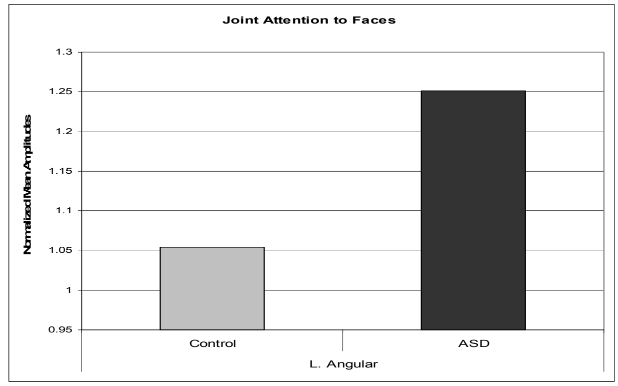

Fig. 4 Higher normalized mean amplitudes in left parietal regions during joint attention to faces in ASD relative to control.

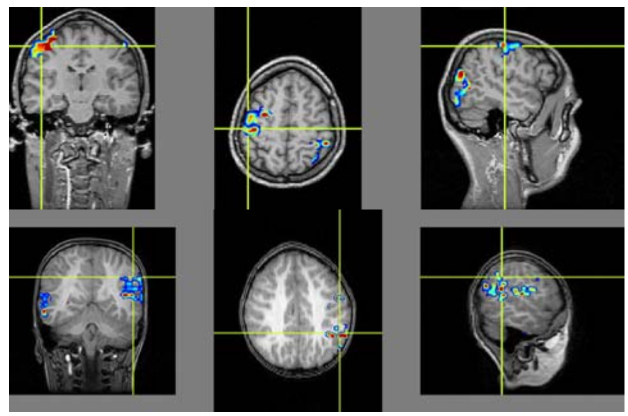

Fig. 5 Right frontoparietal activation in control subject at 194 ms (above) while ASD subject has significant activation in left parietal regions during face condition at 194 ms (below).

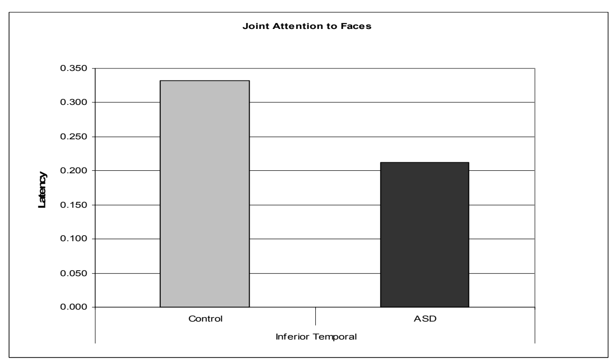

Fig. 6 Earlier latency of activation in ASD at ≈200 ms during joint attention to faces while controls activate later at ≈300 ms.

IV. DISCUSSION

The neurobiological underpinnings of gaze cueing in children and adolescents with ASD are poorly understood and could have significant implications for understanding the etiology of social impairment. Results of this study revealed higher mean amplitudes in left occipital and parietal brain regions during gaze shifts to both targets and faces in ASD while higher mean amplitudes in right inferior temporal and medial orbitofrontal regions was evident in controls, the latter of which has been implicated in the social cognitive network. Pronounced left angular amplitudes were also noted in left parietal, specifically angular, regions during gaze shifts to faces in ASD. Our preliminary findings suggest that there may be crowding in brain regions that underlie these processes which may be secondary to the recently reported atypical and rightward lateralization of language in ASD. Gaze cueing studies in ASD adults have revealed deficits in a number of brain regions believed to underlie social cognition such as the superior temporal gyrus and sulcus (STG and STS), inferior parietal lobule (IPL), middle temporal gyrus (MTG), and inferior and middle frontal gyri [10], though this is the first study to reveal these deficits in ASD children and adolescents with neuroimaging.

Latency data further reveals contextual differences and a possible double dissociation in brain regions recruited for joint attention. While controls displayed an earlier onset in activation to words in frontal regions and later activation to faces in inferior temporal regions, ASD demonstrated the opposite pattern; an earlier activation in inferior temporal regions and later activation in frontal regions to words.

V. Conclusion

Results suggest atypical hemispheric specialization for joint attention with ASD recruiting left posterior hemispheric regions during gaze shifts to social stimuli while controls recruit right inferior temporal and medial orbitofrontal regions. ASD subjects appear to be using regions that underlie skills necessary for reading such as posterior parietal and occipital regions for joint attention to gaze shifts. This may be due to “crowding” or altered hemispheric specialization in regions that underlie both social and speech perception, such as the right inferior parietal and superior temporal lobe (e.g. IP and STS). Moreover, we believe the crowding occurs not only due to competition in regions that underlie social and “speech” perception, but “language” perception in general, both oral and written.

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