Children and Adolescents with Autism Exhibit Reduced MEG Steady-State Gamma Responses

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Background: Recent neuroimaging studies of autism have indicated reduced functional connectivity during both cognitive tasks and rest. These data suggest long-range connectivity may be compromised in this disorder, and current neurological theories of autism contend disrupted inter-regional interactions may be an underlying mechanism explaining behavioral symptomatology. However, it is unclear whether deficient neuronal communication is attributable to fewer long-range tracts or more of a local deficit in neural circuitry. This study examines the integrity of local circuitry by focusing on gamma band activity in auditory cortices of children and adolescents with autism.

Methods: Ten children and adolescents with autism and 10 matched controls participated. Both groups listened to 500 ms duration monaural click trains with a 25 ms inter-click interval, as magnetoencephalography was acquired from the contralateral hemisphere. To estimate 40 Hz spectral power density, we performed time-frequency decomposition of the single-trial magnetic steady-state response data using complex demodulation.

Results: Children and adolescents with autism exhibited significantly reduced left hemispheric 40 Hz power from 200-500 ms post-stimulus onset. In contrast, no significant between group differences were observed for right hemispheric cortices.

Conclusions: The production and/or maintenance of left hemispheric gamma oscillations appeared abnormal in participants with autism. We interpret these data as indicating that in autism, particular brain regions may be unable to generate the high-frequency activity likely necessary for binding and other forms of inter-regional interactions. These findings augment connectivity theories of autism with novel evidence that aberrations in local circuitry could underlie putative deficiencies in long-range neural communication.

Key Words: ASD, auditory, autism, connectivity, gamma, MEG

Autism is a developmental disorder defined clinically by a triad of deficits comprising impairments in communication, social interaction, and behavioral flexibility (Wing and Gould 1979). The broad spectrum of autistic disorders is also associated with prominent attentional and perceptual abnormalities, and often mental retardation. In recent times, numerous theories have attempted to explain this range of impairments in terms of a single deficient cognitive construct. For example, autistic disorders have been diversely characterized as a deficit of theory of mind (Baron-Cohen *et al.* 1985), central coherence (Frith 1989), executive function (Ozonoff *et al.* 1991), complex information processing (Minshew *et al.* 1997), and empathic capacity (Baron-Cohen *et al.* 2002). Central coherence theory proposes that cognitive abnormalities associated with autism can be interpreted as the product of a reduction in contextual information integration along with a bias toward local versus global processing. In other words, people with autism exhibit detail-oriented processing in which object features are emphasized at the expense of global configurations and contextualized meanings. While central coherence theory has been consistent with most experimental observations in visual perception (Jolliffe and Baron-Cohen 1997; Shah and Frith 1983), visuospatial construction (Shah and Frith 1993), and even language processing research (Eskes *et al.* 1990; Frith and Snowling 1983; Happé 1997; Jolliffe and Baron-Cohen 1999), negative findings have also emerged (Happé 1999) and it has been criticized along with other available theories as descriptive rather than explanatory (i.e., for failing to address the neural mechanisms mediating the disorder).

A recent surge of neurological studies, however, has illuminated candidate abnormalities that may underlie the symptomatology of autism, and present attempts at a theoretical synthesis are focusing on aberrations in neuronal connectivity (Belmonte *et al.* 2004; Brock *et al.* 2002; Just *et al.* 2004). The three most prominent neurological theories are highly inter-related and share many conceptual similarities with central coherence, along with the distinct advantage of being more empirically refutable. These theories propose long-range neural connectivity is deficient in autism, which manifests into fragmented behaviors consistent with the diagnostic triad and impairments in central coherence. In short, functional neuroimaging studies have repeatedly shown simple cognitive tasks are associated with activation in multiple brain areas, and that successful performance is contingent upon interactions amongst these neural regions. Thus, long-range neural disconnectivity theories predict abnormally reduced neuronal interactions between cortical areas in autism, with eventual alterations in region-specific activation (e.g., hypoactivation in higher-level cortices) due to anomalous input-output dynamics. Initial evidence for this pattern has been obtained by correlating inter-regional activation magnitudes using positron-emission tomography (PET), with studies in autistic adults demonstrating reduced intra- and inter-hemispheric correlations of frontal and parietal cortices during rest (Horwitz *et al.* 1988), and lower connectivity between occipital and temporal cortices during a theory of mind task (Castelli *et al.* 2002). More recently, Just and colleagues correlated the voxel time series of functional-magnetic resonance imaging (fMRI) measures during a language processing task. These data showed reduced functional connectivity between Broca's and Wernicke's areas in autistic participants relative to IQ-matched controls (Just *et al.* 2004). Thus, in regard to inferior long-range connectivity, these

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three neurological theories share substantial empirical support from functional imaging studies and are also consistent with initial reports of white matter tract disruptions emerging from diffusion tensor imaging in autism (Barnea-Goraly *et al.* 2004).

On the other hand, there is also short-range intra-regional connectivity, and on this issue there is less empirical evidence and theoretical agreement. For example, abnormal brain connectivity theory (Belmonte *et al.* 2004) and the temporal binding deficit hypothesis (Brock *et al.* 2002) both propose that local over-connectivity may accompany regional under-connectivity in autistic disorders. However, Belmonte and colleagues (Belmonte *et al.* 2004) argue such over-connectivity may underlie the substantial comorbidity of epilepsy in autism (Ballaban-Gil and Tuchman 2000), whereas Brock *et al.* (2002) believe local over-connectivity may subserve feature processing enhancements also associated with autism. By comparison, under-connectivity theory (Just *et al.* 2004) makes no strict assertion on the presence or absence of local over-connectivity, but cites seminal but not yet replicated anatomical work on this issue demonstrating cortical minicolumns are more numerous and possess less compact cellular configurations in autistic brains (Casanova *et al.* 2002a). Whether this translates into over or under local connectivity remains to be determined, but the abnormal cellular configuration results in less peripheral neuropil space per minicolumn, suggesting a potential decrease in local inhibitory circuitry (Casanova *et al.* 2002a). Such a reduction in inhibitory interneurons could explain the increased incidence of seizure disorder in autism, as well as abnormal gamma band oscillations and putative temporal binding problems (Casanova *et al.* 2003

In this study, we investigate local connectivity by focusing on the gamma band of auditory magnetic steady-state responses (SSR) in children and adolescents with autism and a matched-sample of control participants. The magnetic SSR is most often elicited by click trains or amplitude-modulated tones, and substantial evidence suggests 40 Hz modulation rates evoke the strongest SSR in humans (Boettcher *et al.* 2001, 2002; Hari *et al.* 1989; Stapells *et al.* 1984). Prior studies have also shown the magnetic 40 Hz SSR localizes to primary auditory cortices and displays hemispheric asymmetry (right anterior to left) in normal adults (Teale *et al.* 2003). In the present application, we perform time-frequency analysis of magnetoencephalography (MEG) signals to quantify gamma band power per hemisphere elicited by a series of pulse trains (40/s) presented to the contralateral ear. Based on the inhibitory interneuron findings of Casanova *et al.* (2002a), we hypothesized that participants with autism would show reduced auditory SSR gamma power bilaterally relative to age- and gender-matched controls.

Methods and Materials

Subject Selection

Ten participants with autism (ages 7–17) and 10 controls (ages 8–16) participated in this experiment. All participants with autism met clinical criteria for DSM-IV autistic disorder (American Psychiatric Association 1994), as well as criteria for autism on the Autism Diagnostic Interview–Revised (ADI-R; Lord *et al.* 1994) and Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord *et al.* 2000) as assessed by a researcher trained to research criteria. Two subjects from each group were classified as left-handed or ambidextrous, and all other participants were right-handed as determined by the Annett Handedness Scale (Annett 1985). The control group had significantly higher IQ than the group with autism, and IQ was considered a possible covariate in early analyses (see Results). Additional demographic information is provided in Table 1. Exclusionary criteria included any medical illness affecting CNS function, neurological disorder, history of head trauma, and current substance abuse. Control subjects met the same exclusionary criteria, but had no personal or familial history of psychiatric or neurological disorders. Participants were recruited from the Denver region, and individually matched on chronological age and group matched on handedness. All 20 participants were male, although this was not an inclusion criterion for the study. Prior to study, informed consent was obtained in accord with the guidelines of the Colorado Multiple Institutional Review Board.

Table 1. Demographic Information

	Autism	Control	t-statistic
Age (years)	12.35 ± 3.02	11.96 ± 2.49	.31 n.s.
Education (years)	7.60 ± 1.58	7.20 ± 1.93	.51 n.s.
Handedness	.54 ± .87	.61 ± .52	.22 n.s.
Full Scale IQ	92.40 ± 25.47	120.80 ± 11.25	3.23[b]
Verbal IQ	90.70 ± 25.64	122.00 ± 12.78	3.46[b]
Performance IQ	96.00 ± 22.93	115.30 ± 9.26	2.47[c]
ADI-R Social[a]	16.67 ± 5.70	n.a.	
ADI-R Non-Verbal[a]	9.56 ± 1.94	n.a.	
ADI-R Verbal[a]	9.11 ± 1.36	n.a.	
ADI-R Stereotypy[a]	4.11 ± 1.62	n.a.	
ADI-R Onset[a]	2.11 ± 1.45	n.a.	
ADOS-G Communication	4.40 ± 2.32	n.a.	
ADOS-G Social	9.40 ± 3.13	n.a.	
ADOS-G Creativity	.90 ± .88	n.a.	
ADOS-G Stereotypy	2.30 ± 1.16	n.a.	

[a]ADI-R data from one autistic adolescent were lost.
[b]($p < .01$).
[c]($p < .05$).

Stimuli

Acoustic trains consisting of 2 ms duration bi-phasic pulses were delivered every 25 ms for a total of 500 ms, as measured at the earpiece. These pulse trains were repeated every 1500 ms until 150 trials per hemisphere had been collected. Recordings were made from the hemisphere contralateral to the ear stimulated with subjects lying on a nonmagnetic bed within a magnetically shielded room. All stimuli were produced using E.A.R. TONE 3A (Cabot Safety Corporation, Indianapolis, Indiana) transducers with 2 m of polyurethane tubing (3 mm inner diameter) and foam earpiece inserts with 30 dB attenuation to exterior noise. Sound amplitude was 65 dB SPL as measured by a Bruel & Kjaer 2209 SPL meter and 4157 artificial ear. All participants watched a silent video throughout the recording session to promote a consistent state of alertness.

MEG Recordings

Magnetic field data were obtained with a 37-channel Magnes I biomagnetometer (4-D Neuroimaging) equipped with concentric rings of first-order axial gradiometers (coil diameter = 2 cm, baseline = 5 cm). Data were collected over a 1 s window, including a 200 ms pre-stimulus period (initial pulse onset = 0 ms), using a 16-bit analog-to-digital converter with a sampling rate of 1041.7 Hz. Analog filters were set at 200 Hz low-pass and 1 Hz high-pass during all data acquisitions, and the raw data were also notch filtered at 60, 120 and 180 Hz using a custom-built tracking fourth-order elliptic filter with 40 dB of attenuation. The 4-D Neuroimaging Magnes SCP software (Version 1.6) was used for all recordings, and the fiducial points (i.e., left and right