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

pre-auriculars and the nasion) were determined using a Polhemus 3SPACE digitizer (Colchester, Vermont, USA).

Coil locations and orientations were then expressed in the coordinate system defined as follows: X-axis along the line between the preauricular points, positive to the right; Y-axis perpendicular to the X-axis at the midpoint with positive values toward the nasion; and Z-axis perpendicular to the same plane, starting at the midpoint with positive values in the upward direction. The instrument was positioned such that the center channel was over the zero-field crossing between the ingoing and outgoing magnetic flux extrema of the averaged auditory evoked field, which typically corresponded to a Y-coordinate of 0 cm and a Z-coordinate of near 5 cm for the center channel of the array.

MEG Analysis

Following MEG acquisition, data files were converted to Scan data format (Version 4.0; NeuroSoft, Inc., El Paso, Texas, USA). All data were visually edited trial-by-trial for eye-blink, head movement, and other artifacts prior to spectral decomposition. For each subject, the artifact-free single-trial data for each hemisphere were transformed into the time-frequency domain using complex demodulation (Hoechstetter *et al.* 2004; Paap and Ktonas 1977). The resulting spectral density power estimations were then averaged over trials to generate time-frequency displays of complex cross spectral density (final resolution: 5.0 Hz at 10 ms). These data were then normalized by dividing the power value of each post-stimulus time-frequency bin by the respective frequency's baseline power calculated as the mean power from 140 to 20 ms pre-stimulus onset. Using such a temporal window functioned to minimize the influence of filtering artifacts on baseline power calculations. For each hemisphere, the channel with maximal relative power at 40 Hz was then chosen for subsequent analyses. The relative mean 40 Hz power from 200 to 500 ms post-stimulus was then determined per hemisphere for each participant. This post-stimulus window was chosen to focus analyses on the SSR rather than transient evoked components based on prior published data (Ross *et al.* 2002). The Brain Electrical Source Analysis software (BESA 5.1.0; MEGIS Software GmbH, Germany) was used for all MEG data pre-processing and time-frequency decompositions.

Statistical Analysis

SPSS for Windows (Release 11.0.1) was used for statistical analyses. Significance tests were two-tailed and evaluated at 0.05 alpha. For repeated-measures ANOVA/ANCOVA applications, type III sums of squares were used. Group differences on demographic variables were examined through independent-samples t-tests. Relative mean 40 Hz power estimations for the 200 to 500 ms post-stimulus window were analyzed in a two-by-two mixed-model ANOVA design, with group as a between-subjects variable and hemisphere as a within-subjects variable. To examine potential differences in SSR timing, we utilized a similar repeated-measures ANOVA model with latency of maximum 40 Hz power per hemisphere as a within-subjects variable.

Results

Demographic Variables

Our groups did not significantly differ on age ($p > .75$), handedness ($p > .80$), or education ($p > .60$). However, as shown in Table 1, autistic participants exhibited significantly lower scores on all IQ measures. To examine whether IQ was related to 40 Hz power, we computed Pearson-correlation coefficients using each IQ scale (verbal, performance, full) and relative 40 Hz mean power for each hemisphere (i.e., 6 total correlations). Our results showed no evidence of correlation between IQ and 40 Hz mean power (all p's $> .33$) when using uncorrected two-tailed significance tests, and IQ was therefore not used as a covariate in the remaining analyses.

40 Hz Power Estimations

The overall group effect of relative 40 Hz power was significant indicating higher power in controls $F(1,18) = 10.01$ ($p < .01$). The main effect of hemisphere was not significant $F(1,18) = .52$ ($p > .47$), but the group-by-hemisphere interaction term was significant $F(1,18) = 4.71$ ($p < .05$) and descriptive statistics illuminated that 40 Hz relative power estimations for the left hemisphere were significantly stronger in controls relative to patients. For the right hemisphere, relative 40 Hz power did not reliably distinguish between groups. The SSR peak latency analyses were less informative, as hemisphere and group main effects, and their interaction were all insignificant (all p's $> .53$). Bar graphs showing relative fluctuations in 40 Hz power per hemisphere and group are provided in Figure 1.

Discussion

We examined gamma band power of auditory SSR in a group of healthy children and adolescents, and an age-matched sample with autism. Our results indicated right hemispheric gamma power increases were relatively equal between control and autistic participants. Conversely, gamma power fluctuations for left hemispheric cortices showed significant disruption in participants with autism, as the series of pulse trains did not elicit a SSR of increased 40 Hz power (relative to baseline) as it clearly did in controls. This hemispheric asymmetry was not expected, but it could relate to structural aberrations of left planum temporale that we observed in past studies of autism (Rojas *et al.* 2002, 2005). Below, we discuss the implications of these findings for prominent neurological theories of autism, with especial regard to inhibitory interneuronal deficits suggested by Casanova and colleagues (Cassanova *et al.* 2002a, 2003) and the overall landscape of cortical connectivity in autism.

As discussed in the introduction, current connectivity theories

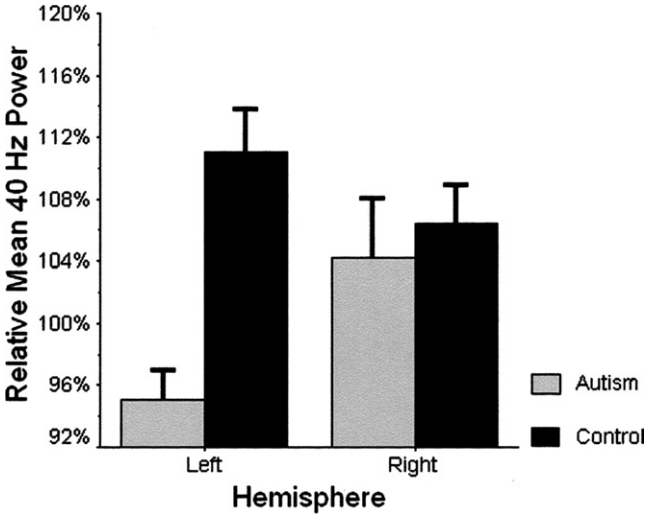

Figure 1. Auditory 40 Hz SSR power. Relative mean data for the 200-500 ms post-stimulus window are shown per hemisphere and group. Error bars depict one standard error of the mean.

(Belmonte *et al.* 2004; Brock *et al.* 2002; Just *et al.* 2004) have derived support from long-range disconnectivity evidence attained through PET and fMRI. However, it is important to acknowledge these methods only indicate functional disconnectivity, which could be attributable to anomalies in neural structure or function. In other words, two brain regions could be sufficiently connected but fail to functionally interact during stimulus processing. If this were the case, these methods would yield equivalent results, as they are unable to distinguish a lack of functional communication from a lack of structural connectivity. In light of recent micro-architectural work (Casanova *et al.* 2002a), we believe this is an important consideration as local circuit dysfunction could impair long-range communication over intact neuronal tracts (for further discussion, see Belmonte *et al.* 2004). Casanova and colleagues (Casanova *et al.* 2002a) observed smaller peripheral neuropil space in autistic minicolumns, and a class of inhibitory interneurons are known to occupy this space in normal humans and animals. These inhibitory cells are thought to be crucial to columnar function as they provide lateral inhibition processes necessary to distinguish the minicolumn as a quasi-independent functional unit (Casanova *et al.* 2003; Mountcastle 1997). Without such local inhibitory processes, groups of adjacent minicolumns are more apt to become synchronized, which in turn synchronizes the respective column and often neighboring columns triggering the onset of epileptic seizure (Casanova *et al.* 2003; DeFelipe 1999). In addition to explaining higher incidences of epilepsy in autism, a breakdown in inhibitory processes also holds value in accounting for advanced discrimination capacities in autism. Computational models of such deficits show reduced generalization along with enhanced discrimination (Casanova *et al.* 2002b; Gustafsson 1997), which is consistent with behavior studies indicating superior discriminatory performance in participants with autism (O'Riordan and Plaisted 2001; O'Riordan *et al.* 2001; Plaisted *et al.* 1998). Lastly, and of prime importance to current data, networks of such inhibitory interneurons are known to function as GABA-gated pacemakers for neocortical oscillatory activity, which are critical for both the production and maintenance of gamma oscillations (Bartos *et al.* 2002; Bragin *et al.* 1995; Grothe and Klump 2000; Porjesz *et al.* 2002; Traub *et al.* 1996).

Thus, although preliminary diffusion tensor imaging evidence has suggested disturbed white matter tracts in autism (Barnea-Goraly *et al.* 2004), we believe it may be premature to assume long-range connectivity disruptions in autism are exclusively structurally mediated, as abnormalities in local circuitry could manifest into long-range deficits in functional neural interactions. In this regard, anomalous local circuitry is not clearly at odds with connectivity theories of autism, as this issue is under specified in all current models. For example, Belmonte and colleagues (Belmonte *et al.* 2004) believe autistic circuitry may be over-connected locally and under-connected globally. In the sense of equilibrium, autistic circuitry could be considered locally over-connected due to a potential lack of excitatory-inhibitory balance (e.g., reduced interneuron counts and/or more synapses), which would compromise the integrity of high-frequency cortical activity (e.g., gamma oscillations) that is essential for long-range neuronal interactions. Although the under-connectivity theory of Just and colleagues (Just *et al.* 2004) takes no strict stance on local circuitry, it does propose the key deficit in autism involves the coordination amongst processing centers distributed across the cortical landscape, and uses strong fMRI and PET evidence to support this contention. A currently widespread belief in neurophysiology holds that gamma oscillations are crucial to coordinating information processing. Thus, impairment in generating high-frequency activity could be expressed as a failure to integrate neuronally disparate pieces of information, and if so the PET and fMRI data supporting aberrant cortical coordination in autism (Castelli *et al.* 2002; Horwitz *et al.* 1988; Just *et al.* 2004) may be reflecting a consistent underlying neural mechanism.

In conclusion, our data indicate abnormality in the production and/or maintenance of gamma band activity in left auditory cortices of children and adolescents with autism. We believe a lack of local inhibitory interneurons (Casanova *et al.* 2002a) may be the neural mechanism underlying this impairment due to the known role of such cells in generating high-frequency activity. Overall, these observations augment current connectivity theories of autism by adding novel information on the integrity of local circuitry. As for why 40 Hz reductions were limited to the left hemisphere, we can only speculate based on past observations of regional volumes and available physiological data. In two previous reports, we have shown that adults (Rojas *et al.* 2002) and children and adolescents (Rojas *et al.* 2005) with autism show significantly reduced left but not right planum temporale (PT) volumes. Since the known generators of 40 Hz magnetic SSR lie within the PT (Teale *et al.* 2003), we believe these observations may indicate a selective left hemispheric deficit in autistic disorder. Multiple studies of auditory physiology in autism have also shown deficits specific to the left hemisphere. For example, in a binaural sound intensity manipulation task, Bruneau *et al.* (2003) found that amplitude of late auditory temporal responses (i.e., N1c) scaled with sound intensity only in the right hemisphere of children with autism, which created a striking hemispheric asymmetry at the highest intensity level (i.e., 80 db SPL). By comparison, component amplitude scaled with sound intensity bilaterally in controls (Bruneau *et al.* 2003). There is also data showing earlier mismatch negativity (MMN) responses in left temporal cortices, as well as an abnormally preceding frontal response in children with autism (Gomot *et al.* 2002). Interestingly, neither component of the right hemispheric MMN distinguished typically-developing children from those with autism (Gomot *et al.* 2002). Additional evidence for an auditory functional asymmetry in autism comes from a recent MEG investigation showing left hemispheric mismatch field latency correlated with symptom severity in adults with autism (Kasai *et al.* 2005). Lastly, it is noteworthy that the findings of Casanova *et al.* (2002a) were based on only three brain regions, one of which was left auditory cortex. Thus, the potential lack of inhibitory interneurons may be limited to circumscribed regions of the autistic brain with other neural areas showing normal micro-architecture, but further research is necessary.

Finally, it is important to recognize limitations of this work including the small sample size, lack of data on female participants, lack of IQ matching in the groups, and relatively high functioning autism sample (only 2 participants with autism had a full scale IQ less than 70), all of which limit the generalizability of the findings. Another important consideration involves how the 40 Hz oscillations investigated here relate to the phase-locked gamma activity seen across cortical areas (e.g., occipital-frontal gamma phase-locking). The latter sort of gamma activity is clearly more often connected with temporal binding and other aspects of information processing, but we believe the basic neural mechanisms are likely quite similar. Essentially, if the neural machinery subserving the generation of high-frequency cortical activity is intact one would expect the sort of gamma examined here to be relatively normal, although the same is

unlikely true for region-to-region gamma synchrony as other factors and mechanisms are almost certainly involved. A final caveat to these data is 40 Hz aberrations cannot be considered specific to autistic disorder, as they have been reported in other conditions such as schizophrenia (Kwon *et al.* 1999; Spencer *et al.* 2003, 2004). Perhaps these anomalies are better understood as nonspecific risk factors for a variety of neurodevelopmental disorders.

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