

## Auditory Sensory Gating Deficit and Cortical Thickness in Schizophrenia

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### ABSTRACT

Both an EEG P50 sensory gating deficit and abnormalities of the temporal lobe structure are considered characteristic of schizophrenia. The standard P50 sensory gating measure does not foster differential assessment of left- and right-hemisphere contributions, but its analogous MEG M50 component may be used to measure gating of distinct auditory source dipoles localizing to left- and right-hemisphere primary auditory cortex. The present study sought to determine how sensory gating ratio may relate to cortical thickness at the site of the auditory dipole localization. A standard auditory paired-click paradigm was used during MEG for patients (n=22) and normal controls (n=11). Sensory gating ratios were determined by measuring the strength of the 50 ms response to the second click divided by that of the first click (S2/S1). Cortical thickness was assessed by two reliable raters using 3D sMRI. Results showed that: (1) patients had a P50 and left M50 sensory gating deficit relative to controls; (2) cortex in both hemispheres was thicker in the control group; (3) in schizophrenia, poorer left-hemisphere M50 sensory gating correlated with thinner left-hemisphere auditory cortical thickness; and (4) poorer right-hemisphere M50 auditory sensory gating ratio correlated with thinner right-hemisphere auditory cortical thickness in patients. The MEG-assessed hemisphere-specific auditory sensory gating ratio may be driven by this structural abnormality in auditory cortex.

### KEY WORDS

P50, Sensory gating, Cortical thickness, Electroencephalography, Magnetoencephalography, EEG, MEG

### INTRODUCTION

Schizophrenia is a disorder characterized by abnormal information processing. Reduced gating of the P50 component of the event-related brain potential is reliably found in patients with schizophrenia (e.g., [Adler et al., 1982]) and is generally considered to be a neurophysiological marker of attentional impairment. Clinical studies of M50 gating have shown that gating predicts performance on neuropsychological tests of attention, working memory, general memory, and executive function in schizophrenia. Right-lateralized M50 sensory gating ratio is correlated with severity of negative symptoms in schizophrenia [Thoma et al., 2005], whereas left-lateralized M50 gating ratio is related to positive symptoms [Irwin et al., 2003].

Temporal-lobe structural abnormality in STG areas, thought to be generators of P50 and M50, and atypical asymmetry of planum temporale (a possible generator of P50) have been well documented in schizophrenia. There is abundant evidence that a deficit in the cortical structure on the superior bank of the left temporal lobe contributes to symptoms in schizophrenia and that neurophysiological abnormality is related to the reduction. Thus, it was hypothesized that, to the extent that patients with schizophrenia

demonstrated impaired sensory gating, they would also have reduced cortical thickness measured at the source dipole on Heschl's gyrus and/or planum temporale. That is, auditory cortical thickness, as an index of cortical pathogenesis, would be negatively correlated with sensory gating ratio.

## METHODS

*Subjects:* Eleven normal control subjects and 22 patients with schizophrenia, matched on age and education, were solicited through ads in the local media and clinic referral. Following entry into the study, one normal control subject was excluded due to sMRI abnormalities. Patients had a minimum of three months on their current medication and had not had an inpatient stay for at least one year, were current outpatients with chronic schizophrenia, had been hospitalized at least once, and were well characterized by their providers. Time since first hospitalization ranged from 10 to 39 years ( $\mu = 23$ ,  $sd = 9$ ). Subjects were screened with the Structured Clinical Interview for DSM-IV Axis-I Disorders, Clinician Version (SCID-CV) to establish appropriate diagnosis, screen for co-morbid diagnoses, and screen for current substance abuse or history of drug dependence. Subjects were screened for history of neurological disorder or disease and serious medical illness. Control subjects were not included if they had a family history of a psychotic disorder in a first-degree relative. Screening procedures also included a "noise run," where subjects were placed in the MEG dewar to screen for metal-induced artifact. Prior to data collection, and after a complete description of the study to the subjects, written informed consent was obtained.

*Neuroimaging Data Collection:* MEG was recorded in a magnetically and electrically shielded room using a whole-brain, 122-channel biomagnetometer system [NeuroMag, Helsinki]. MEG amplifier gain was 2500 and Analog-to-Digital (A/D) conversion rate was 1000. At the start of each test session, subjects were fitted with an electrode cap to which three small coils were attached in order to provide specification of the position and orientation of the MEG sensors relative to the head. 150 uncontaminated tone-pair epochs were collected with the overall session lasting approximately 30 minutes. A bipolar oblique channel of electro-oculogram (EOG) was recorded simultaneously with MEG. Epochs were rejected if peak-to-peak signal strength exceeded 150  $\mu$ v in EOG and 3000 fT/cm in any MEG channel. MEG data were digitized at 500 Hz per channel for 1000 ms beginning 100 ms prior to S1. Separately, 3-D volumetric T1-weighted sMRI was collected with a 1.5 T Picker Edge Imager. The pulse sequence was a Field Echo 3-D Sagittal (Picker) with the following parameters: TR = 15 ms, TE = 4.4 ms, FOV = 256 mm, flip angle = 25 degrees, matrix 192 x 256, slice thickness = 1.5 mm, no gap.

*Stimuli and Data Analysis:* Stimuli were presented in pairs with 500 ms ISI and a random ITI averaging 10 s. Stimuli were binaural 3 ms clicks, created and delivered using NeuroStim software through Etymotic earphones placed in the subject's ear canal. Prior to data collection each subject's hearing threshold was determined, and peak click intensity was set 30dB above threshold. In order to minimize motion-related artifact produced by the plastic tubes connected to the Etymotic earphones, the tubes were taped to the subject's face and ear.

An equivalent current dipole model was used with the assumption that the neuronal sources were focal. Source locations were determined using NeuroMag (2001) software. To co-register MEG and MRI data, three anatomical landmarks (nasion and right and left preauriculars) were measured for each subject using the Probe Position Identification system [Polhemus] prior to data collection. The same three points were identified in the subject's sMRI, and a transformation matrix that involved rotation and translation between the MEG and sMRI coordinate systems was used. To increase the reliability of the MEG-MRI co-registration, approximately 50 points on the scalp were digitized with the Polhemus system, in addition to the three landmarks, to ensure that all points were located on the MRI scalp surface.

Using NeuroMag software, a 5 to 55 Hz bandpass filter and a -100 to -10 ms baseline adjustment were first applied to averaged MEG data. M50 was defined as the first upward-oriented dipole occurring prior to M100, 40 to 80 ms poststimulus. Determination of the strength, location, and peak latency of the M50 sources in left and right hemispheres was accomplished by fitting each dipole using subsets of 34 planar gradiometers over each temporal lobe. For modeling S1 M50, 4 ms of data before and 5 ms of data following the M50 peak were selected. Equivalent current dipoles (ECDs) were then determined separately for each hemisphere using NeuroMag source localization routines. Only ECDs with goodness-of-fit values exceeding 75% for S1 were accepted. Peak strength of the source over the 8 ms period was then determined. S2 M50 was identified using a procedure in which the location of the S2 dipole was assumed to be the same as that of the S1 dipole, and the strength of S2 M50 was determined for the 8 ms period surrounding the peak latency obtained for S1. M50 sensory gating for each hemisphere was expressed as a ratio similar to that of P50: S2 dipole peak strength divided by S1 dipole peak strength.

*Cortical Thickness Measure:* In all cases, the 50 ms magnetic source dipole localization fell on posterior Heschl's gyrus, on planum temporale, or within an expected 5 mm margin of error. NeuroMag MEG-MRI Integration Software [NeuroMag, 2001], designed to interact with dipole quantification and localization software, allowed linear measures of cortical thickness at the site of dipole localization. Two raters, blind to subject diagnosis and trained on NeuroMag source localization software, first achieved a 3-coordinate localization for the dipolar source (x, y, and z axes). The next task was to establish inter-rater reliability for cortical thickness measures. A tangent to the curve of the surface of the cortex at that localization was then approximated, and cortical thickness was measured as a linear distance perpendicular to that line. In cases where a fold in the cortex appeared to obscure the thickness, a similar procedure was used on a nearby area in which the thickness of cortex was more apparent. A level of 0.90 was set a priori as an acceptable level of inter-rater reliability.

## RESULTS

Inter-rater reliability (intra-class correlation) for cortical thickness measures was 0.92 ( $p < .0001$ ) and 0.91 ( $p < .0001$ ) for left and right hemispheres, respectively. Consistent with our previous studies, patients had higher M50 sensory gating ratios in left (ANOVA  $F(1,31)=6.63$ ,  $p=.02$ ) but not right ( $F(1,31)=.006$ ,  $p=.94$ ) hemispheres compared to control subjects. Patients had thinner cortex in both left ( $F(1,31)=90.68$ ,  $p < .001$ ) and right ( $F(1,31)=49.58$ ,  $p < .001$ ) hemispheres at the site of dipole localization compared to controls. To compare lateralized gating ratios with cortical thickness, left- and right-hemisphere M50 gating ratios were regressed on left STG cortical thickness and then on right STG cortical thickness.

The prediction of left STG cortical thickness for the schizophrenia group accounted for 50% of the variance ( $F(2, 21)=9.32$ ,  $p=.002$ ). Evaluating each predictor for the unique variance it contributed, there was a negative correlation between left ( $p=.001$ ; see Fig. 1) but not right ( $p=.23$ ) M50 gating ratio and left STG cortical thickness. The prediction of right STG cortical thickness for the schizophrenia group accounted for 40% of the variance ( $F(2, 21)=6.24$ ,  $p=.008$ ). Evaluating each predictor for the unique variance it contributed, there was a negative correlation between right ( $p=.01$ ; see Fig. 1) but not left ( $p=.10$ ) M50 gating ratio and right STG cortical thickness.

The prediction of left STG cortical thickness for the control group was non-significant. The prediction of right STG cortical thickness for the control group accounted for 71% of the variance ( $F(2, 9)=8.71$ ,  $p=.01$ ). Evaluating each predictor for the unique variance it contributed, there was a negative correlation between right ( $p=.01$ ) but not left ( $p=.09$ ) M50 gating ratio and right STG cortical thickness.



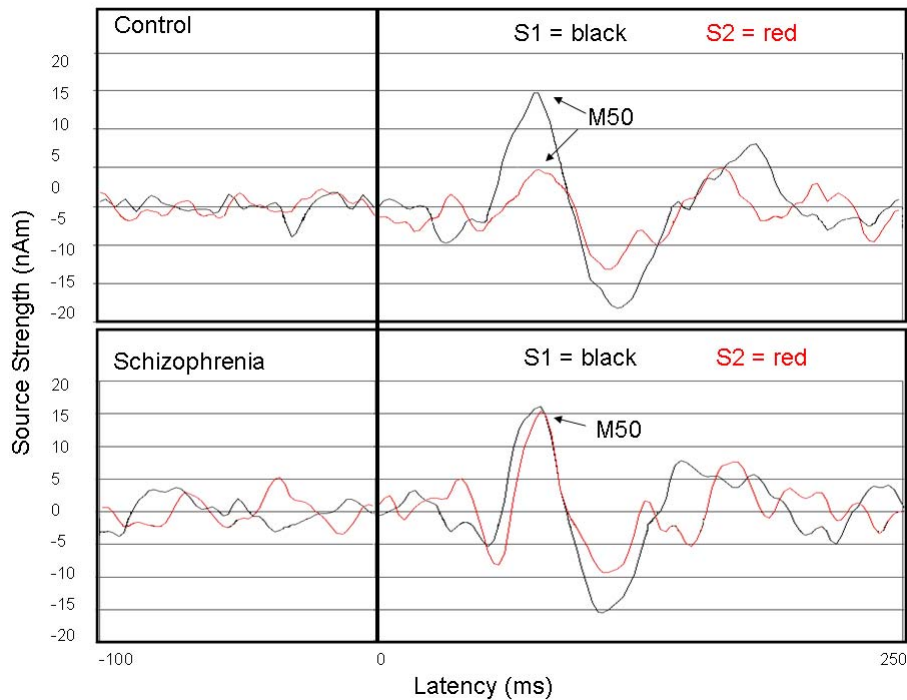
**Figure 1.** Scatterplots depict (a) the relationship between left hemisphere cortical thickness and left hemisphere M50 sensory gating ratio, and (b) the relationship between right hemisphere cortical thickness and right hemisphere M50 sensory gating ratios in the schizophrenia group.

Left and right STG thickness was correlated in patients ( $r = .71$ ,  $p < .001$ ) but the correlation was non-significant in controls ( $r = .51$ ,  $p = .10$ ), though there was no difference between these correlations ( $p = .67$ ).

## DISCUSSION

Patients with schizophrenia showed bilateral reductions in cortical thickness at auditory dipole localizations associated with M50 auditory sensory gating and a left-lateralized deficit in M50 sensory gating. For the schizophrenia group, there was a hemisphere-specific negative correlation between M50 gating ratio and cortical thickness; left-hemisphere gating ratio was negatively correlated with left-hemisphere cortical thickness but not right-hemisphere cortical thickness, and right-hemisphere gating ratio was negatively correlated with right-hemisphere cortical thickness but not left-hemisphere cortical thickness. No relationship between gating and thickness of cortex was expected in normal control subjects, and it was assumed that healthy cortex would be associated with unimpaired gating. This hypothesis held true for the left hemisphere, but an unexpected negative correlation was found in the right hemisphere. This unlikely result was not predicted and should be replicated prior to being interpreted.

Recent studies have documented reduced cell density [Chance et al., 2004; although also see Cotter et al., 2004] and significantly reduced cortical thickness in bilateral STG auditory regions in schizophrenia [Chance et al., 2004; Kuperberg, et al., 2003; Cannon et al., 2002]. In longitudinal studies, severe gray matter deficit in primary auditory regions was absent at disease onset but was associated with later stages of the course of the disorder [Thompson et al., 2004]. MEG studies have identified M50 as being generated from posterior areas of STG [Pelizzone et al., 1987; Reite et al., 1988; Mäkelä et al., 1994; Yoshiura et al., 1995; Huotilainen et al., 1998; Onitsuka et al., 1999]. Thus, it is not surprising that STG structural fidelity and STG-dependent functional measures are related. Both hallucinations [Barta, et al., 1990; Flaum, et al., 1995] and thought disorder/delusions [Shenton, et al., 1992; McCarley, et al., 1993]



**Figure 2.** Waveforms depict (a) a gating ratio of .33 in a normal control subject, and (b) a gating ratio approaching 1.0 in a schizophrenia subject. Gating ratios are computed as the amplitude at the peak of the 50 ms response to the first click divided by the amplitude of the response to the second click (S2/S1).

are associated with reduced volume of posterior STG, linking the clinical presentation of the disease with a reduction in cortex. More recently, McCarley and colleagues [2002] related reduced cortical thickness to neurophysiological function in schizophrenia, showing bilateral reductions of gray matter volume on posterior STG, left-lateralized impairment in P300 in schizophrenia, and a correlation between P300 and left cortical volume.

Abnormality in a P300 study is measured in terms of reduced response to oddball stimuli. Abnormality in a sensory gating study is generally considered as a relative increase in the amplitude of the response to a second (S2) stimulus. This seeming contradiction is illusory however, if one considers that impairment in either paradigm represents a failure of contextual association between temporally related stimulus events. In an oddball paradigm, the “odd” stimulus is defined by its disparity from temporally contiguous stimuli. Thus, normal responding is defined by an increase in the response to an odd stimulus and impairment in terms of a lack, or reduction, of that increase. Importantly, there is no increase in the response to the odd stimulus when it is presented in isolation or contiguously similar stimuli. In a gating experiment, successful “gating”, or reduction of the second stimulus, occurs only when that stimulus is presented in a specific temporal relationship to a first, identical stimulus--otherwise no “gating” occurs. It has been argued that gating represents the function of an active inhibitory network, designed to reduce the flow of redundant sensory information associated with sensory overload [Adler et al., 1982; Kisley et al, 2004]. Thus, in a theoretical sense, impairment of cortical structure may play a role in failure of association between stimuli, and consequent functional abnormality, whether measured as a failure to enhance P300 amplitude, or a failure to reduce M50 amplitude.

Thoma et al. [2003] linked impairment in auditory sensory gating with the function of a fronto-temporal network. Hanlon et al. [in press] showed that gating impairment is first seen at 50 ms in the left hemisphere and that by 100 ms is seen bilaterally, suggesting that a deficit that begins very early in the left hemisphere rapidly spreads to become a more generalized deficit. The authors of both papers emphasized the role of a network in transmitting pathological information processing both temporally and spatially. Based on the present data, it is tempting to conclude that the substrate for the overall gating impairment is in STG and that the signal measured there simply reflects abnormality of cortical thickness. However, present analyses should be interpreted with caution, as the results are preliminary, and the correlations found between gross cortical structure (sMRI) and impaired cortical function (MEG) in schizophrenia may both reflect a more complex and distal cause.

Abnormalities of temporal-lobe structures (e.g., Buchsbaum et al., 1997) and specifically STG structures (Dickey et al., 2002) have also been documented for those with schizophrenia-spectrum disorders. Gating impairment has also been noted in those with spectrum disorders. Although these studies do not address auditory sensory gating, it may be that to the extent that schizophrenia spectrum patients show a gating impairment, they also show left hemisphere STG abnormality. Future research examining STG temporal lobe structure in other gating-impaired populations may allow us to address the specificity of the relationship between STG structure and gating. Longitudinal research following possible changes in both cortex and sensory gating over the course of the disorder may also help to better define the apparent relationship between cortical structure and local cortical function.

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