Lack of tonotopic organization of the auditory cortex in schizophrenia.

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PeerJ PrePrints | http://dx.doi.org/10.7287/peerj.preprints.226v1 | CC-BY 4.0 Open Access | received: 30 Jan 2014, published: 30 Jan 2014

Abstract

Background: Disorganization of tonotopy in the auditory cortex has been described in schizophrenia. Subjects with schizophrenia show little to no spatial organization of responses to different tone frequencies in the auditory cortex. Previous studies have called into question the use of MEG and the M100 response to assess tonotopy. This study seeks to replicate prior results of tonotopic disorganization in schizophrenia compared to healthy controls.

Methods: The tonotopic organization for 400 Hz and 4,000 Hz sound in 19 patients with schizophrenia and 11 comparison subjects was determined using MEG by examining the M100 auditory-evoked magnetic field dipole in primary auditory cortex. The equivalent current dipole locations were then mapped and compared.

Results: The previous result of a lack of tonotopy in subjects with schizophrenia was partly replicated. In control subjects, the 400 Hz tone auditory evoked field was found anterior to the 4000 Hz in the primary auditory cortex.

Conclusions: The lack of tonotopic organization of the auditory cortex is replicable in patients with schizophrenia and suggests that the architecture underlying tonotopy in the auditory cortex is disordered. This result suggests possible alteration in the organization of the auditory cortex, which may in turn influence higher order cognitive processes by altering the perception of incoming auditory stimuli.

Key words: Magnetoencephalography; evoked potentials; auditory cortex; schizophrenia; M100

Introduction:

Schizophrenia is a chronic psychiatric illness characterized by prominent auditory hallucinations, delusions and a host of cognitive symptoms such as impaired attention and executive functioning. Disturbances in auditory processing and structure of auditory areas in the brain are a hallmark of schizophrenia and are thought to be partially responsible for some of the characteristic deficits of the disease (Crow, 1997). A number of groups have suggested that patients with schizophrenia have increased difficulty with auditory perception (Rabinowicz et al., 2000; Holcomb et al., 1995). Magnetoencephalography (MEG) allows for real-time auditory responses to be examined non-invasively with excellent spatial and temporal accuracy. One of these auditory responses, the M100 (a wave peaking at 100 ms), is the most prominent evoked magnetic response to auditory stimuli. Because of the temporal and spatial accuracy of MEG and the prominence of the M100 response, the functional organization of the auditory cortex has been examined using the estimated source location of this component.

The M100 component appears to be generated on or near the transverse gyrus of Heschl on the superior temporal gyrus (Godey et al., 2001; Reite et al., 1994). Auditory association areas near Heschl's gyrus such as the planum temporale may also be contributory to the M100. Structurally, Heschl's gyrus volume may be negatively impacted in schizophrenia (Kasai et al. 2003; Hirayasu et al. 2000). In addition, reduced planum temporale asymmetry has also been reported as disturbed in schizophrenia (Shapleske et al., 1999). In terms of functional localization, the M100 auditory evoked field exhibits anomalous anterior-posterior source location asymmetry in patients with paranoid schizophrenia. The neuroanatomic localization of the M100 in normal adults is further anterior in the right hemisphere (Baumann et al., 1991). We and others have previously shown that patients with schizophrenia demonstrate disturbed interhemispheric asymmetry of the M100 generator location (Reite et al., 1989; Reite et al., 1997; Rockstroh et al., 2001; Tiihonen et al., 1998). Specifically, subjects with schizophrenia do not exhibit the same extent of left-right difference in the anterior-posterior location of the M100 compared with control subjects.

In addition to source lateralization, the M100 response has been used to estimate the tonotopy, or the spatial mapping of frequency within the auditory cortex. The estimated source the M100 localizes more medially and/or posteriorly for higher frequency tones (Pantev et al, 1988; Pantev et al, 1995; Huotilainen, 1995; Arlinger et al, 1982; Pantev et al., 1998; Rosburg et al, 2000; Rojas et al, 2002), in contrast to lower frequency tones, which tend to localize more anteriorly and laterally. compared to lower tones. Our group first reported MEG data suggesting that M100-based tonotopic mapping may be disturbed in patients with schizophrenia (Rojas et al., 2002). In that study, particularly for frequencies lower than 2 kHz in the left hemisphere, we reported that there was a lack medial-lateral spacing (i.e. a tonotopic gradient) between frequency representations in subjects with schizophrenia. Separately, we also reported that patients with schizophrenia exhibit significantly broadened frequency tuning of the M100 response (Rojas et al., 2007). These studies suggest that there might be significant changes in the representation of frequency in the auditory cortex in schizophrenia. This may, in part, explain the reported pitch perception problems in people with schizophrenia (Rabinowicz et al., 2000; Holcomb et al., 1995).

Nevertheless, some have criticized the use of the M100 auditory evoked field to determine tonotopy as unreliable for individual subjects (Lütkenhoner, 2003), particularly when using the single moving dipole approach. In our prior experiment demonstrating altered tonotopy

in schizophrenia, we used a 37-channel instrument with poor spatial coverage and only assessed one hemisphere at a time. Because of this, the experiments took much longer to perform and were more susceptible to error and noise due to movement and subject fatigue. In the current study, we sought to replicate the altered tonotopy finding from our previous study in subjects with schizophrenia (Rojas et al., 2002) using a spatiotemporal multiple dipole model and a whole-head, 248 channel MEG instrument. We also seek to replicate results from ours and others' experiments that the primary auditory cortex exhibits a medial to lateral and posterior to anterior tonotopic organization with high tones represented medially and/or posteriorly. We predicted that subjects with schizophrenia would not exhibit medial-lateral or anterior-posterior differences in location of the M100 response to difference tone frequencies.

Methods:

Subjects

Twenty participants with DSM-IV schizophrenia (19 subjects) or schizoaffective disorder (1 subject) diagnoses were recruited for the study (4 female) as well as 13 participants (2 female) with no history of psychiatric or neurologic illness meeting Research Diagnostic Criteria for never mentally-ill [17]. The schizophrenia and comparison groups did not differ significantly in age, mean years of education, or socioeconomic status ($p > 0.05$). The schizophrenia and comparison groups did have a significantly different full scale IQ ($p = 0.001$). All subjects gave informed consent to participate in this research in line with the requirements of the Colorado Multiple Institutional Review Board (approval #03-793) and the principles for ethical research contained in the Declaration of Helsinki.

Sample characteristics (mean +/- SD)		
	Schizophrenia	**Control**
Age	38.1 +/- 7.33	39.1 +/- 8.32
Education (years)	13.1 +/- 2.10	14.3 +/- 2.69
SES (Hollingshead*)	40.1 +/- 15.0	37.9 +/- 11.5
Full scale IQ	96.2 +/- 14.9	112.6 +/- 15.7
BPRS total	46.6 +/- 11.2	NR
BPRS positive	11.4 +/- 6.27	NR
BPRS negative	8.79 +/- 4.21	NR
BPRS depression	13.3 +/- 5.35	NR
BPRS disorganization	13.1 +/- 4.54	NR

Table 1: Subject characteristics. NR = not reported. *Hollingshead's 4-factor Index of Social Position (Hollingshead, 1975), based on parental education and occupational status.

Persons with schizophrenia were re-diagnosed for the study using the Structured Clinical Interview for the DSM-IV (SCID) (First et al., 1994). To further assess the clinical presentation we also administered the Brief Psychiatric Rating Scale (Overall & Gorham, 1962)

Task and Stimuli

MEG recordings were made to monaural, contralateral ear stimulus presentations of 400 Hz and 4000 Hz sine-wave acoustic stimuli for 200 ms. Stimuli were delivered via foam insert earphones (ER 30, Etymotic Research, Elk Grove Village, IL). Prior to MEG recording, a hearing threshold test (method of constant stimuli) was administered to each participant and the level of presentation for each frequency was adjusted individually to 50 dB above hearing threshold to control for the effect of stimulus frequency on perceived loudness. No differences were detected in hearing threshold at any frequency between schizophrenia and comparison subjects. Separate blocks of 400 Hz or 4000 Hz pure tones were delivered either to the right or left ear, with ear order randomly determined for each subject. The interstimulus interval between tones was 4000 ms. A total of 285 trials were delivered to the subject. There was no significant difference between groups in number of trials delivered in any condition ($p > 0.05$).

MEG recordings

MEG data were acquired with a 4D-Neuroimaging (San Diego, CA) Magnes 3600WH neuromagnetometer system with 248 axial first-order gradiometers. Recordings were made inside a Lindren magnetically shielded room. Participants were recorded lying supine on a comfortable recording bed during recordings, watching a silent movie of their choice to maintain an alert state. MEG data were digitized continuously at 24-bits quantization and a sampling rate of 1041.7 Hz within a pass band between 0.1 and 200 Hz.

The location and orientation of the MEG coils relative to each subject's head were determined prior to recording by digitizing a set of fiducial reference points on the head with a magnetic digitizer (Polhemus 3SPACE, Colchester, VT). The left and right preauriular points (LPA and RPA) and the nasion were used to establish a right-handed Cartesian coordinate system, where the line between LPA and RPA is the x-axis (positive at right ear). The y-axis is the line normal to the x-axis at the midpoint with positive y towards the nasion, and the z-axis is normal to x and y at the origin (positive z exits the top of the head).

Data processing and magnetic source localization

After acquisition further data processing included reducing eye movement and blink artifact using the FieldTrip (Oostenveld et al., 2011) interface to EEGLAB's (Delorme & Makeig, 2004) ICA routines (binica algorithm, extended precision option, initial PCA to reduce dimensionality to 25 components). Epochs of 450 ms duration, including a 200 ms pre-stimulus period, were then defined relative to stimulus onset. Baseline corrected epochs were then excluded automatically based on amplitude criteria of exceeding +/- 2 pT. Remaining trials were visually inspected for any additional artifact, and artifact free trials were then averaged and digitally low-pass filtered at 20 Hz (phase-invariant, 24 db/octave, Butterworth characteristic). Source analyses were completed on the filtered averages using the Brain Electrical Source Analysis (BESA) software package, version 5.3.8 (Megis GmBH, Germany). A 2-source spatiotemporal multiple dipole model was fit to the data between 60 and 120 ms post-stimulus. Only individuals with dipole fit residual errors less than or equal to 10 percent for both 400 Hz and 4000 Hz for both hemispheres were included in the statistical analyses.

Statistical methods

Statistica 6.0 (Statsoft, Tulsa, OK) was used for all statistical computations. All significance tests were two-tailed and conducted at 0.05 alpha. Type III sums of squares were used in all ANOVA designs, which were implemented using the general linear model module.

Results:

For the tonotopy and cerebral asymmetry data and statistics below, only subjects with complete data sets at both frequencies in both hemispheres were included. This left 11 participants in the schizophrenia group and 6 in the control group. All subjects that were dropped were missing data from one of the two frequencies (400 Hz or 4000 Hz) in any of the conditions. In all of these instances, these missing data sets were due to failure in the ECD model to account for 90 percent or more of the observed data. The mean 3-dimensional coordinates for each group and condition are reported in centimeters in Table 2 with their associated standard error on the mean values

Column1	Condition	Mean # trials	SD	x-location	SEM	y-location	SEM y	z-location	SEM x
Controls	400 Hz left	273	13.7	0.556277	0.056226	0.018450	0.036711	0.144791	0.031923
	400 Hz right	274	12.9	-0.543777	0.055329	-0.093285	0.095289	0.015974	0.076946
	4000 Hz left	267	19.8	0.545778	0.025095	-0.085954	0.071478	0.031877	0.072101
	4000 Hz right	273	12.9	-0.562650	0.048956	-0.119898	0.028897	0.125669	0.048996
Schizophrenia									
	400 Hz left	248	56.9	0.576704	0.041526	0.025865	0.027113	0.148087	0.023577
	400 Hz right	238	60.7	-0.489453	0.040864	-0.224468	0.070376	-0.092775	0.056829
	4000 Hz left	239	61.6	0.564232	0.018534	-0.092384	0.052790	-0.034496	0.053250
	4000 Hz right	242	56.8	-0.519516	0.036157	-0.070004	0.021342	0.062820	0.036186

Table 2: Mean three-dimensional coordinates for all AEF in both groups and conditions in cm with standard error on the mean.

To determine whether the predicted relationship between frequency and depth differed by group, a 2 x 2 x 2 ANOVA (group by hemisphere by frequency) was performed using MEG x coordinate (depth) as the dependent variable. In this condition there was no difference between groups, $F(1,15)=0.021$, $p=0.886$. Hemisphere and frequency were treated as repeated measures and group was a between subjects variable. All other group, hemisphere, and frequency main effects were non-significant.

Tonotopy can also be expected to be observed in an anterior-posterior gradient in the human auditory system, here represented by the ECD y-coordinate. There was a significant group by frequency interaction, indicating that for control subjects, there exists a posterior-anterior location gradient, with the 4000 Hz tone represented posteriorly, that does not occur in subjects with schizophrenia, $F(1,15)=4.4817$, $p=0.051$ (Figure 1). The group, hemisphere and frequency main effects were all non-significant ($p > 0.05$). Additionally, there was no significant correlation between BPRS positive symptoms score and dipole location ($p > 0.05$).

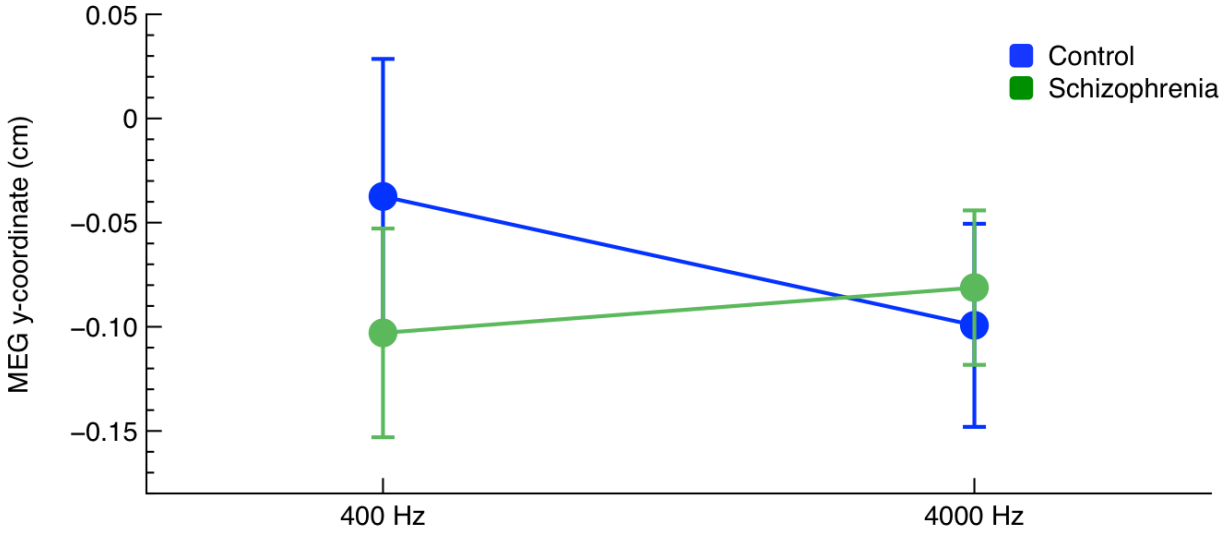

Figure 1: Control auditory evoked fields exhibit posterior to anterior location with higher frequency tones represented posteriorly, in contrast to schizophrenia subjects, F(1,15)=4.4817, p=0.051. Error bars standard error on the mean.

Finally, when analyzing the z-locations, a 2 x 2 ANOVA comparing hemisphere and frequency in all control and experimental subjects, a significant interaction between hemisphere and frequency was noted, with right hemisphere sources exhibiting a more inferior location for the 400 Hz dipole and a superior location for the 4000 Hz condition. The reverse finding was observed in the left hemisphere, $F(1,15) = 9.3417$, $p = 0.008$. All other z-coordinate effects on hemisphere, frequency, and condition were non-significant.

Discussion:

We investigated whether the tonotopic organization of the auditory cortex in schizophrenia is altered compared to controls. The results partially replicate previous data from our own laboratory that during passive listening to pure tone stimuli, schizophrenia subjects do not show the expected relationship between M100 dipole location and frequency, as do healthy subjects. In the current study, we observed that the tonotopic gradient for the healthy controls was significant only in the anterior-posterior direction. This group difference along the anterior-posterior dimension of the dipole location differs from our earlier study where we reported medial-lateral tonotopy differences compared with controls. As tonotopy can normally be observed in both the medial-lateral as well as anterior-posterior gradients, as discussed below, this result might imply that the control subjects in the current study had slight differences in their underlying functional anatomy. Our main result for control subjects is therefore more in line with the findings of Rosburg et al. (2000), who also observed anterior-posterior tonotopy in the M100 response location. In that study, however, there were no significant differences between control and schizophrenia groups in M100 anterior-posterior location. It is possible that some differences in methods between the papers could be important. In our earlier paper (Rojas et al. 2002), a 37-channel system was used and each hemisphere was recorded separately, increasing the total recording time for the subjects and possibly introducing unwanted confounds such as motion or fatigue. Rosburg et al. (2000) employed a 31-channel MEG system. In the current study, we employed a whole head MEG system. In the current study, a 2-dipole model was used

for source analysis in contrast to the earlier single dipole model. Finally, in the current study only two tones, a single low frequency (400 Hz) and single high frequency (4000 Hz) tone, were used. In the previous study, 5 tones were employed spanning 500 to 4000 Hz. Taken together with our prior study, the current data suggests that a major auditory functional organizing principle, tonotopy, may disturbed in subjects with schizophrenia. The negative findings for tonotopy in the Rosburg et al. (2000) study contradict our own and a definitive conclusion regarding tonotopy disturbances in schizophrenia is not currently possible. Such a definitive study will require a much larger sample using a modern MEG system.

While the tonotopic organization of the auditory cortex has been well studied, there are a variety of different reports of its organization in the literature. Some of the earlier studies performed demonstrate a linear pattern wherein high frequencies are represented medially and low frequencies laterally (Wessinger et al., 1997). Others undertaken more recently (typically utilizing fMRI) have demonstrated that the cortex is arranged into two mirror-symmetric gradients extending in an anterior-posterior orientation (Humphries et al., 2010). Our previous studies using MEG and those of other groups report the former finding that, at least for M100, the responses are arranged from high to low tones, medially to laterally or posteriorly to anteriorly along Heschl's gyrus (Pantev et al, 1988; Pantev et al, 1998; Huotilainen, 1995; Arlinger et al, 1982; Rosburg et al, 2000). Importantly, the methodological differences between these studies on tonotopy may explain the variability between studies. With MEG we can focus on a particular response such as the M100, while fMRI does not have the temporal resolution separate evoked magnetic or electric components. The reverse is true for MEG, where spatial resolution is more questionable and the nature of the inverse solution warrants some caution in over-interpretation of dipole locations. Also, we must be cautious with the interpretation of M100 results to infer the tonotopic organization of the primary auditory cortex given conflicting results from other groups (Lütkenhöner et al., 2003). The specifics of whether and how the system are disturbed spatially in schizophrenia are unclear from MEG. Obtaining a better answer to the spatial specifics question will likely require a technology with better spatial resolution than MEG. Functional MRI (fMRI) has certainly been used successfully to resolve tonotopy (e.g., Talavage et al. 2000; Formisano et al. 2003), but to our knowledge has not yet been employed to examine disturbances in tonotopy in schizophrenia.

The results of our study along with previous studies from our group suggest that the functional organization of the auditory cortex might be fundamentally altered in schizophrenia. This could be due to a structural difference or a dysfunction in auditory inhibitory interneurons, which might reduce the ability of the auditory cortex to laterally inhibit near-by regions, undermining the physiologic conditions necessary for tonotopy. This mechanism is still speculative in nature, but there is growing support to the idea that alterations in inhibitory interneurons play a significant role in schizophrenia (for a review see Benes & Berretta, 2001) and alterations in these neurons may inhibit tonotopic organization. Other mechanisms could also explain the results include whether the organization of the auditory cortex could be altered by active hallucination during recording or by medication history. Finally, it is possible that if the architecture of the auditory cortex is fundamentally altered, it may influence higher-order cognitive processes by altering the perception of auditory stimuli. It is likely true that there are both "top-down" and "bottom-up" processing abnormalities in schizophrenia that contribute to the observed phenomenon. The disorganization of the auditory cortex in schizophrenia may contribute to the proposed "bottleneck" of sensory information (Leitman et al., 2010) that leads

to some of the cognitive deficits in schizophrenia whereby patients misinterpret incoming information because the initial cortical processing is altered (Javitt, 2009).

This study is not without significant limitations. Chief among them is the large number of subjects whose data was not usable due to large errors in source modeling. This is consistent, however, with the tonotopy study of Lütkenhoner et al. (2003). The high failure rate for modeling the spatial location for all frequencies and hemispheres suggests that M100 based studies of tonotopy are not adequate for moving beyond group level analyses to studies of individual differences in schizophrenia. Next, the majority of our subjects with schizophrenia are currently medicated with anti-psychotics, which could confound data interpretation. Future experiments could benefit both from studying medication-naïve populations in the same paradigm as well as from larger sample sizes. Also, attention is implicated in the tonotopic representation of pitch in the auditory cortex (Ozaki et al., 2004). Given the impairments in attention in schizophrenia (Fioravanti et al., 2005), it is possible that our experiment has not adequately controlled for this effect. Further, prefrontal cortical domains have been implicated in auditory processing in both animals and humans (Dittmann-Balçar et al., 2001; Romanski & Goldman-Rakic, 2002) and these domains as well as subcortical and limbic areas have also been reported to be altered during auditory attention tasks in schizophrenia (Liddle et al., 2006; Laurens et al., 2005; Kiehl et al., 2005). The results of these studies and others have been used to speculate that the changes in sensory behavior observed in schizophrenia are due to cognitive mechanisms relying on prefrontal cortical circuits and not the sensory cortical derangements we have reported. Rabinowicz et al. (2000) found that tone-matching performance in schizophrenia did not differ with the addition of a distractor condition. This suggests that prefrontal cortical control and working memory deficits do not fully explain the deficits observed in schizophrenia. Future experiments should seek to determine if attention to the tone stimuli has an impact on M100 tonotopy in schizophrenia. Finally, it is unknown whether this phenomenon of altered tonotopy is unique to schizophrenia. Future studies that include clinical controls with other types of psychosis or auditory hallucinations such as bipolar disorder or major depression with psychotic features would help determine if this effect is specific to schizophrenia.

Aknowledgements:

This work was funded by NIH grants R25 MH080859 and R01 MH60214.

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