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Frontal and superior temporal auditory processing abnormalities in schizophrenia

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ABSTRACT

Background: Although magnetoencephalography (MEG) studies show superior temporal gyrus (STG) auditory processing abnormalities in schizophrenia at 50 and 100 ms, EEG and corticography studies suggest involvement of additional brain areas (e.g., frontal areas) during this interval. Study goals were to identify 30 to 130 ms auditory encoding processes in schizophrenia (SZ) and healthy controls (HC) and group differences throughout the cortex.

Methods: The standard paired-click task was administered to 19 SZ and 21 HC subjects during MEG recording. Vector-based Spatial–temporal Analysis using L1-minimum-norm (VESTAL) provided 4D maps of activity from 30 to 130 ms. Within-group t-tests compared post-stimulus 50 ms and 100 ms activity to baseline. Between-group t-tests examined 50 and 100 ms group differences.

Results: Bilateral 50 and 100 ms STG activity was observed in both groups. HC had stronger bilateral 50 and 100 ms STG activity than SZ. In addition to the STG group difference, non-STG activity was also observed in both groups. For example, whereas HC had stronger left and right inferior frontal gyrus activity than SZ, SZ had stronger right superior frontal gyrus and left supramarginal gyrus activity than HC.

Conclusions: Less STG activity was observed in SZ than HC, indicating encoding problems in SZ. Yet auditory encoding abnormalities are not specific to STG, as group differences were observed in frontal and SMG areas. Thus, present findings indicate that individuals with SZ show abnormalities in multiple nodes of a concurrently activated auditory network.

1. Introduction

Using electroencephalography (EEG) and magnetoencephalography (MEG), a now large number of studies show smaller 100 ms auditory amplitudes in individuals with schizophrenia (SZ) than healthy controls (HC). In a review of studies examining N1 and M100 in schizophrenia, Rosburg et al. (2008) concluded that 100 ms auditory abnormalities are most commonly observed in studies using interstimulus intervals greater than 1 s and that an increase in N1 amplitude by allocation of attention is often lacking in individuals with SZ. Several large-sample studies provide examples. Examining N1 activity in the standard paired-click paradigm, Turetsky et al. (2008) observed a small first and a normal second N1 click response in SZ (N = 142) relative to HC (N = 221). Reduced N1 was also observed in the unaffected first-degree relatives of individuals with SZ without co-morbid psychiatric or substance use conditions, and N1 amplitude was observed to be a heritable measure

Abbreviations: DTI, diffusion tensor imaging; ECG, electrocardiogram; EEG, electroencephalography; EOG, electro-oculogram; ERP, event-related potential; ERF, event-related field; fMRI, functional magnetic resonance imaging; FDR, false discovery rates; HC, healthy controls; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; MEG, magnetoencephalography; PANSS, Positive and Negative Syndrome Scale; PFC, prefrontal cortex; S1, first click; S2, second click; SES, socioeconomic status; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; sMRI, structural magnetic resonance imaging; SSS, Signal Space Separation; STG, superior temporal gyrus; VESTAL, Vector-based Spatio-temporal Analysis using L1-minimum norm.

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and a better endophenotype than N1 gating. In another recent large-N study, Smith et al. (2010) used simultaneous EEG and MEG to examine 100 ms auditory processes in individuals with SZ (N = 79) and HC (N = 73) during a paired-click task. Patients had larger N1 Cz and left and right superior temporal gyrus (STG) M100 ratio scores (second-click/first-click), with EEG and MEG ratio score group differences due to a smaller first click (S1) response in patients, suggesting a deficit in encoding auditory information rather than a deficit in filtering redundant information.

N1 (EEG) and M100 (MEG) are the most prominent deflections of the adult auditory event-related potential (ERP) or field (ERF) (Hari, 1990). In an early study, Naatanen and Picton (1987) argued that the electric N1 reflects contributions from up to 6 distinct cortical areas: dipoles in or near the primary auditory cortex as well as prefrontal cortex (PFC) sources. Later studies showed connections between STG and PFC. For example, several studies have demonstrated bidirectional connections between STG and PFC in the rhesus monkey (Knight et al., 1999). Combined tracing and immunohistochemistry studies have revealed that projections from PFC pyramidal neurons make synaptic contact with a subset of calbindin-positive GABAergic interneurons in auditory areas (Barbas et al., 2005). Through these connections, PFC pyramidal neurons may modulate the excitability of microcircuits within the monkey's auditory belt and parabelt (Barbas et al., 2005). Neural tracers infused into auditory cortex have also been found to emerge in PFC axonal terminal (Romanski, 2004; Romanski et al., 1999). Finally, anatomical studies in humans have identified white-matter tracks connecting auditory cortex with lateral and medial PFC. These observations have been corroborated via in vivo imaging (Catani et al., 2002). Taken together, monkey and human studies support the hypothesis that PFC pyramidal neurons modulate the flow of information in auditory cortices by controlling the activity of GABAergic interneurons, which in turn modulate the excitability of STG pyramidal neurons (Barbas et al., 2005). With regard to individuals with SZ, there is evidence of aberrant fronto-temporal connectivity: in a diffusion tensor imaging (DTI) study, Abdul-Rahman et al. (2012) showed that disruption of fronto-temporal white-matter tracks involving arcuate fasciculus may be associated with psychotic features and auditory hallucinations in SZ.

Although equivalent current dipole source localization techniques work well to examine 50 and 100 ms STG activity (Edgar et al., 2003, 2008; Huang et al., 2003; Smith et al., 2010), equivalent current dipole techniques are likely less optimal in terms of localizing auditory activity in non-STG areas, because activity in non-STG areas is often and thus non-dipolar. The present study reports findings using a lead-field-based source localization method, Vector-based Spatio-temporal Analysis using L1-minimum norm (VESTAL; Huang et al., 2006), to examine auditory processes throughout the brain in HC and in individuals with SZ. Given that our and others previous paired-click findings indicated group differences for the S1 but not the second click (S2)[1] (Smith et al., 2010; Turetsky et al., 2008), the present study focused on examining early S1 activity at 50 ms and 100 ms. The following predictions were made:

Hypothesis 1. STG activity would be observed in both groups, and VESTAL STG group differences would be analogous to those reported previous studies. In particular, 100 ms STG group differences would be observed bilaterally. If 50 ms group S1 differences were observed, the 50 ms group differences would be left lateralized.

Hypothesis 2. Given studies indicating prefrontal activation during simple auditory tasks, frontal activation was expected in both groups. Although prior literature does not provide evidence for making strong predictions about group differences in frontal activity, it was hypothesized that the spatial pattern of frontal activity would be different in patients and controls.

[1] Within-group and between-group VESTAL group statistics for S2 are provided in Supplementary Figs. 1–3.

2. Methods and materials

2.1. Subjects

Nineteen patients with chronic SZ (14 males, mean age 40.31 ± 11.7 years) and 22 age-matched HC (15 males; mean age 34.95 ± 10.2 years) were recruited. Selection criteria were (1) diagnosis of schizophrenia with no other Axis I diagnosis, determined by the Structured Clinical Interview for DSM-IV-Patient Edition (SCID-DSM-IV; American Psychiatric Association, 1994); (2) stable, continuous treatment with one antipsychotic medication for at least 3 months; (3) no history of substance dependence (determined during the SCID-DSM-IV interview); (4) no history of alcohol or other substance abuse in the past 3 months (determined during the SCID-DSM-IV interview); (5) no history of head injury with loss of consciousness for more than 5 minutes; and (6) no psychiatric hospitalization in the last 3 months. As shown in Table 1, groups did not differ in age, education, or parental socioeconomic status (SES, Oakes and Rossi, 2003; scores derived from individual's income, education, and occupation information, with lower SES score indicating higher socioeconomic status). Patients' SES was significantly lower than controls'. Mean total scores of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) were 20.00 for positive symptoms and 17.46 for negative symptoms (N = 13; PANSS scores were not available in 6 subjects). Additional recruitment procedures and additional information on inclusion and exclusion criteria are reported in Smith et al. (2010).

Five HC and 2 SZ were left-handed as assessed by the Waterloo Handedness Questionnaire (Bryden, 1977). Patients with SZ were medicated and clinically stable without change in medications for at least one month before MEG. In the patient group, 14 participants were treated with 2nd generation antipsychotics: 2 on aripiprazole, 5 on olanzapine, 3 on risperidone, 3 on quetiapine and 1 on ziprasidone. Two participants were treated with 1st generation antipsychotic halperiodol. Finally, 2 subjects were treated with both aripiprazole and clozapine and 1 with aripiprazole, clozapine, and halperiodol. The average of Chlorpromazine equivalent dosage for all patients was 587 mg/day (1 patient did not have medication dosage information). Six patients with SZ and 2 HC were smokers.

2.2. Paired-click paradigm

The paired-click paradigm followed the protocol of Adler et al. (1993), in which 3 ms binaural clicks were presented in pairs (S1 and S2) with 500 ms inter-stimulus interval and with inter-trial interval jitter between 7 and 11 s, averaging 9 s. Clicks were delivered through earphones placed in each ear canal. The peak intensity of the click was presented 35 dB above each subject's hearing threshold. Presenting 150 click trials, the duration of the task was approximately 25 minutes. As previously noted, the present study examined only S1 activity at 50 and 100 ms.

2.3. MEG and MRI data acquisition and coregistration

MEG data were recorded in a magnetically shielded room (Vacuumschmelze, Germany) using a 306-channel Vector-View MEG

Table 1
Demographic information of HC and individuals with SZ.

	HC (N = 22)		SZ (N = 19)	
	Mean	SD	Mean	SD
Age	34.95	10.2	40.31	11.7
Education (years)	13.7	1.16	13.5	2.15
SES *	57.4	12.68	64.83	7.51
Parental SES	44.45	18.46	44.64	19.92

* HC had higher SES, $t(36) = -2.22$, $p < 0.05$. Group differences in age, $t(39) = -1.57$, education $t(39) = 0.36$, and parental SES, $t(36) = -0.03$, were not significant ($ps > 0.12$).