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Ear of stimulation determines schizophrenia-normal brain activity differences in an auditory paired-stimuli paradigm

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Abstract

Schizophrenia patients have abnormalities of auditory information processing, theoretically associated with dysfunction of neuronal excitation. Auditory paired-stimuli (S1–S2) paradigms are used to evaluate the nature of these abnormalities. It is unknown whether patients' abnormalities during S1–S2 paradigms are attributable to specific hemispheric differences in cortical processing. The present studies used whole head magnetoencephalography and monaural or binaural versions of the paired-stimuli paradigm to evaluate auditory processing among 38 schizophrenia and 38 normal subjects. The strengths of auditory-evoked brain responses over time were quantified using distributed source reconstructions with L2 minimum norm constraint and realistic head models. For left ear stimuli, schizophrenia and normal groups did not differ on either left or right hemisphere activity over auditory cortex. For right ear and binaural stimuli, schizophrenia patients had less activity over left auditory cortex from 80 to 120 ms post-stimulus but did not differ from normal on activity over right auditory cortex. Additionally, in response to monaural stimulation, schizophrenia patients had significantly less activity than normal over right temporal parietal junction from 60 to 120 ms post-stimulus. These data are consistent with four propositions about schizophrenia: (i) right auditory cortex is functioning normally; (ii) processing of simple auditory stimuli is abnormal in left auditory cortex, probably specifically in supra-granular layers; (iii) auditory localization abilities are deficient; and (iv) auditory cortex abnormalities are not a function of deficient hemispheric communication because they are evident early in processing as long as stimuli are delivered directly to left hemisphere.

Introduction

Auditory hallucinations and difficulties differentiating signal from noise in the auditory environment are important features of schizophrenia patients' clinical presentation (Andreasen & Flaum, 1991; Light & Braff, 1999). A popular theory is that problems with auditory information processing are related to both the symptoms and essential neuropathology of schizophrenia (Light & Braff, 1999). Of the methods used to study auditory information processing in schizophrenia, paired-stimuli (S1–S2) paradigms are particularly popular (Clementz, 1998). During the simplest version of a paired-stimuli paradigm, identical clicks are presented in close proximity (e.g. 500 ms interstimulus intervals), with the pairs separated by long inter-trial intervals (e.g. 8–10 s). Evoked brain responses are measured, and the magnitudes of responses to the first (S1) and second (S2) stimuli are compared. Initial use of these paradigms (Adler *et al*., 1982) was motivated by theories that schizophrenia patients have difficulty filtering irrelevant stimuli, resulting in sensory overload, cognitive fragmentation and perceptual distortions.

Despite its seeming simplicity, the paired-stimuli paradigm literature has numerous ambiguities (Hillyard & Kutas, 2002), clarification of which could facilitate understanding of auditory information processing in schizophrenia. First, under a parsimonious version of the 'poor sensory gating' theory, schizophrenia patients should not differ from normal on auditory-evoked responses (AERs) to S1, but should have larger AERs to S2. In several studies, schizophrenia-normal group differences were at least partially caused by patients exhibiting smaller responses to S1 (e.g. Blumenfeld & Clementz, 2001; Clementz & Blumenfeld, 2001). These findings are consistent with other data, suggesting that S1 but not S2 responses should differentiate schizophrenia and normal subjects. For instance, Shelley *et al*. (1999) demonstrated that schizophrenia and normal subjects differ on AERs when stimulus trains have long (4000 ms) but not short (500 ms) interstimulus intervals, with patients having smaller AERs than normal in the former condition.

Second, schizophrenia is characterized frequently as being a disorder of left hemisphere dominance and/or dysfunction (e.g. Crow, 1997). Such a theory is certainly consistent with work on information processing of language stimuli (e.g. Bruder *et al*., 1999; Wexler *et al*., 2002), schizophrenia patients' difficulties with thought and speech (e.g. Barch & Berenbaum, 1996), and structural and functional brain imaging findings (e.g. Tiihonen *et al*., 1998; Kwon *et al*., 1999; Niznikiewicz *et al*., 2000; Rockstroh *et al*., 2001; Rojas *et al*., 2002). At present, it is unclear whether hemispheric differences in auditory information processing account for schizophrenia-normal AER differences during paired-stimuli paradigms.

The present study was conducted to facilitate understanding of the paired-stimuli paradigm literature in schizophrenia by addressing

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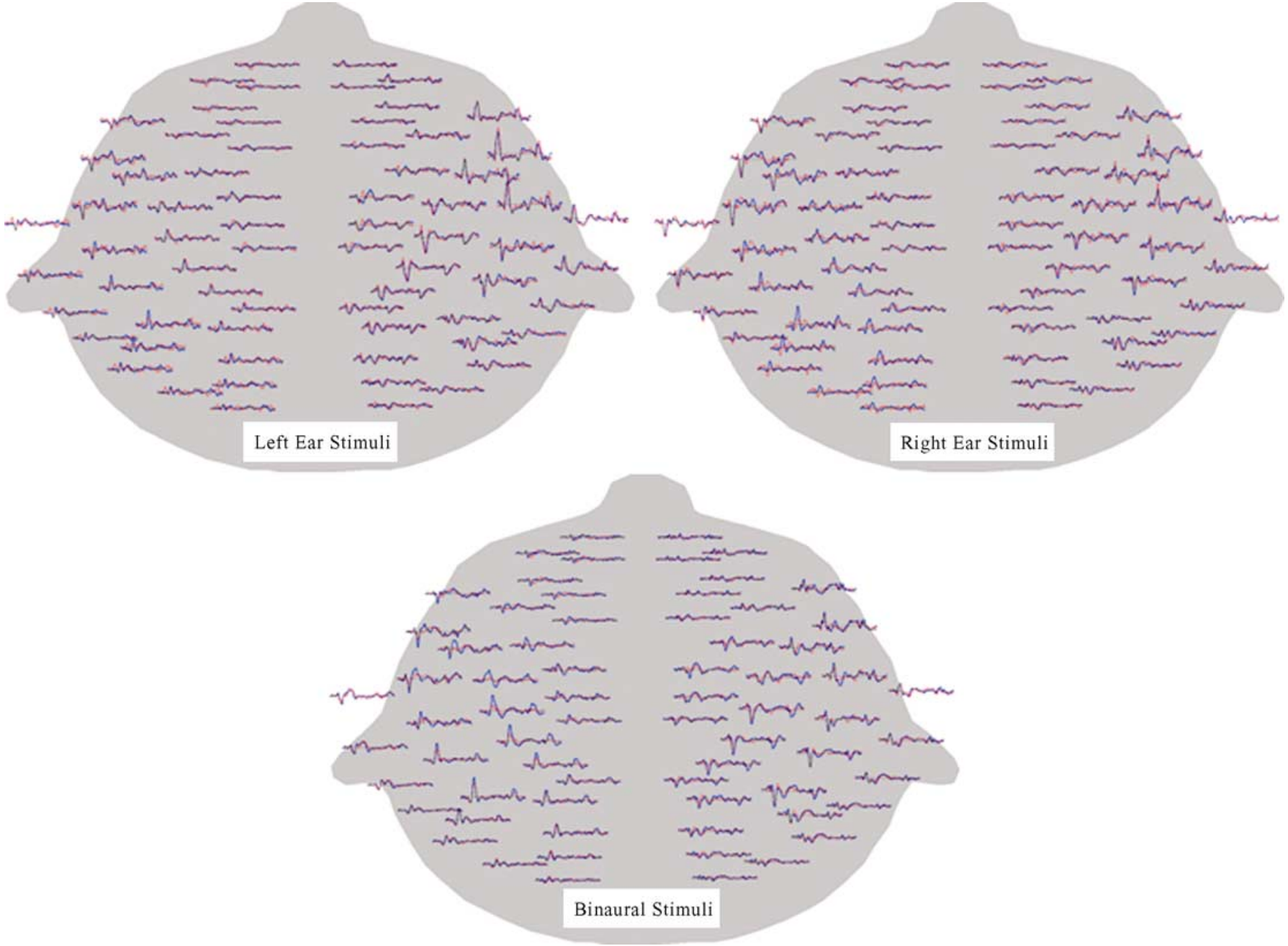

FIG. 1. Position plots of grand averaged MEG activity for normal (blue lines) and schizophrenia subjects (red lines) in response to left ear, right ear and binaural stimuli. Plots are shown from 50 ms before S1 to 250 ms after S2. The amplitude ranges from −200 to +200 fT, and the scale is the same for all plots.

the above issues. Whole-head magnetoencephalography (MEG) was used to measure AERs in an auditory paired-stimuli paradigm. To more clearly evaluate possible schizophrenia-normal hemispheric differences on AERs during this paradigm, two studies were conducted during which stimuli were presented either monaurally (Study 1) or binaurally (Study 2). Simultaneous assessments of activations over the entire cortex were estimated using L2 minimum norm (Fuchs *et al*., 1999; Hauk *et al*., 1999) and realistic head models (Fuchs *et al*., 2002).

Materials and methods

Experimental subjects

In the monaural study, 18 DSM-IV (First *et al*., 1995) chronic schizophrenia outpatients (mean age = 37.8 years, SD = 9.4, six females, two left-handed, GAF score range = 30–48) and 18 normal persons (mean age = 35.4 years, SD = 10.4, six females, two left-handed) served as subjects. In the binaural study, 20 DSM-IV chronic schizophrenia outpatients (mean age = 36.9 years, SD = 9.6, four females, two left-handed, GAF score range = 30–50) and 20 normal persons (mean age = 33.6 years, SD = 9.7, four females, two left-handed) served as subjects. Patients were recruited from psychiatric facilities, and normal persons were recruited from advertisements placed in the community. All subjects provided informed consent. Participants were absent of known neurological hard signs, potentially confounding treatments (e.g. electroconvulsive therapy) and current psychoactive substance use disorders. All but four of the patients (one in the monaural study and three in the binaural study) had a history of auditory hallucinations. In the monaural study, 12 patients were receiving clinical doses of atypical antipsychotics, one was receiving a clinical dose of a typical antipsychotic, and five were not taking any antipsychotic medication at the time of testing. In the binaural study, 14 patients were receiving clinical doses of atypical antipsychotics, two were receiving clinical doses of typical antipsychotics, and four were not taking any antipsychotic medication at the time of testing. Antipsychotic medications have little effect on AERs in the time ranges we evaluated (e.g. Umbight *et al*., 1998; Iwanami *et al*., 2001; Kähkönen *et al*., 2001).

Auditory stimuli

A paired-stimuli paradigm (0.04-ms broad-band square-wave clicks at 83 dB SPL from a Grass Click-Tone Generator) with an inter-click interval of 500 ms and pairs separated by an average of 9 s (range of 8–10 s) was used. For the monaural study, stimuli were presented in two blocks of 120 trials each (counterbalanced order of presentation within-groups). For the binaural study, stimuli were presented in one block of 200 trials. Subjects were asked to keep their eyes open, remain awake, minimize movements and listen intently to the stimuli. Subjects were allowed breaks as needed.

Data acquisition

Recordings were obtained in a magnetically shielded room using a 148-channel whole head biomagnetometer (4D Neuroimaging, San Diego, CA, USA). Blinks were recorded with electrodes placed above and below the left eye. MEG data were recorded for 1000 ms beginning 100 ms before the initial stimulus at 1017.25 Hz with an analogue filter bandpass of 1–400 Hz. Head shape was digitized using a Polhemus Fastrak (Polhemus, Colchester, VT, USA) for co-registration of head position relative to MEG sensor locations. Head motion was continuously monitored during data collection, and no subject demonstrated movement of more than 3 mm in any plane from the beginning to the end of testing.

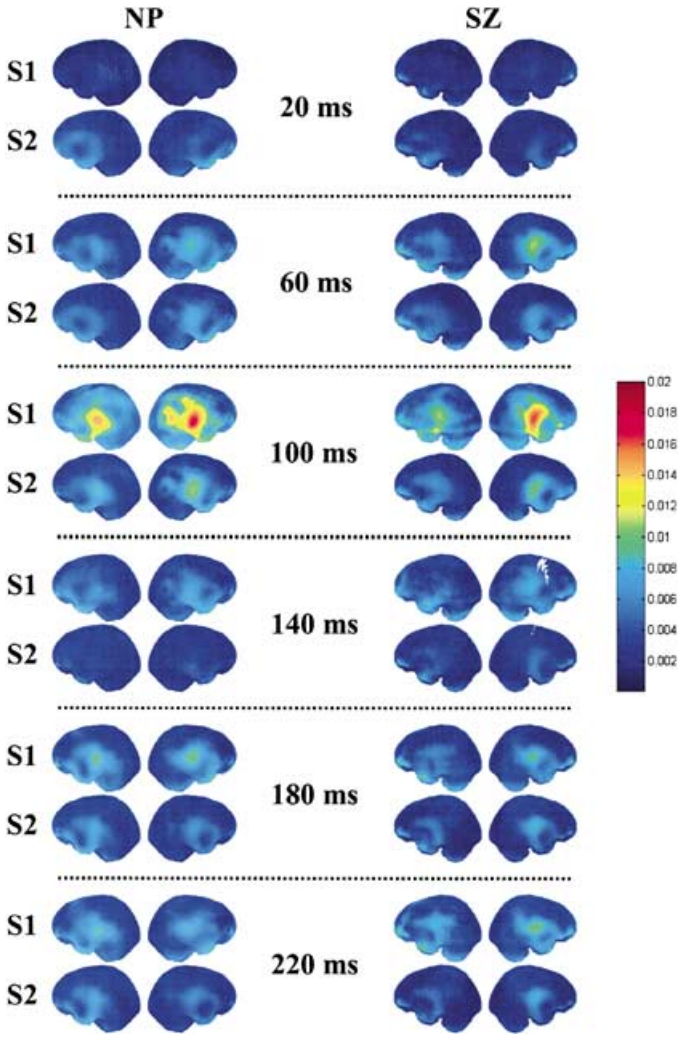

FIG. 2. Average minimum norm solutions in 40-ms segments for S1 and S2 responses averaged over left ear, right ear and binaural stimulation. The colour scale (in nA/mm^2) is shown to the right.

Data analyses

MEG data were screened to remove trials with blinks and/or other artefacts (i.e. trials with either EOG greater than 100 μV or MEG activity greater than 3 pT were automatically eliminated). The total number of usable trials was similar between-groups in both the monaural (schizophrenia M = 178.9, SD = 14.2; normal M = 191.4, SD = 16.0) and binaural studies (schizophrenia M = 165.2, SD = 27.2; normal M = 158.2, SD = 20.0). Data were averaged and digitally filtered from 1 to 40 Hz with a third-order Butterworth filter (Fig. 1).

Averaged 'normal' and 'schizophrenia' MRIs were constructed from 15 normal subjects (eight from the monaural study and seven from the binaural study) and 16 schizophrenia patients (eight from the monaural study and eight from the binaural study), respectively. Images were obtained using a 3D MPRAGE protocol (TR = 11.4 s, TE = 4.4 ms, flip angle = 10°, FOV = 256 mm, 1 mm isotropic resolution) across a 128-mm axial slab. Individual MRIs were averaged, and three-compartment realistic head models were constructed from these averaged images using Curry (Version 4.0, Neurosoft, 1999). The non-intersecting surfaces of the skin, skull and liquor were segmented, triangulated and entered into a Boundary Element Method volume

conductor model. The cortical grey matter was also segmented from the averaged MRIs.

A subject's digitized head shape was co-registered to the averaged segmented skin surface of their respective group. Activations were estimated for fixed cortical source locations (6423 rotating dipoles for the normal brain; 7064 rotating dipoles for the schizophrenia brain) at each time point using L2 minimum norm with optimal regularization determined by the L-curve criterion as implemented in Curry. Noise estimates were obtained from the 100-ms pre-stimulus baseline. Use of an averaged brain yields source modelling solutions that are very close to solutions found when using subjects' individual MRIs (Fuchs *et al*., 2002).

Statistical analyses

Source results were averaged over 20-ms segments and were smoothed by averaging over each source location and its nearest neighbours (average of six neighbours for each source location; Fig. 2). There were three distinct regions of activation: left and right auditory cortex and right temporal parietal junction (TPJ). For each 20-ms segment, therefore, peak activity was identified in each of these regions. The activity across time for each region was then quantified by calculating the average activity for the point of peak activation and its nearest neighbours. Activity over time was analysed using mixed design ANOVAs with Huynh–Feldt-adjusted degrees of freedom when necessary. Helmert contrasts and *t*-tests were used to further evaluate significant effects from the ANOVAs.

Results

Auditory cortex activity

In response to left ear stimuli, there were no significant differences between-groups in either left or right auditory cortex (Fig. 3). In response to right ear stimulation, there was a significant group by stimulus (S1, S2) by hemisphere interaction, $F_{1,34} = 6.78$, $P = 0.014$ (see Fig. 3). This interaction was accounted for by two factors: (i) normal subjects showed a left hemisphere advantage from 80 to 120 ms after S1 that was absent among patients, $F_{1,34} > 6.50$, $P < 0.015$; and (ii) normal subjects, 80–100 ms after both S1 and S2, had larger left hemisphere responses than patients, $F_{1,34} = 5.48$, $P = 0.025$. In response to binaural stimulation, there was a significant group by stimulus by latency by hemisphere interaction, $F_{10,380} = 3.10$, $P = 0.025$. This interaction was accounted for by two factors: (i) normal subjects had larger amplitude responses than patients from 80 to 120 ms after both S1 and S2, $F_{1,38} > 4.63$, $P < 0.038$; and (ii) normal subjects had larger amplitude responses over left hemisphere from 80 to 120 ms specifically after S1, $F_{1,38} > 4.08$, $P < 0.050$. The location of peak activations (from 80 to 120 ms after S1) in the anterior–posterior dimension (in Talairach coordinates) did not differ significantly between-groups in either left (schizophrenia M = −17.0, SD = 8.7; normal M = −18.3, SD = 7.5) or right (schizophrenia M = −15.8, SD = 5.4; normal M = −15.6, SD = 6.5) auditory cortex.

TPJ activity

There was a significant group by latency interaction on right TPJ activity (Talairach coordinates for normal subjects = 56, −58, 12) in response to left ear stimuli, $F_{10,340} = 10.45$, $P < 0.001$, and a significant group by stimulus by latency interaction in response to right ear stimuli, $F_{10,340} = 5.50$, $P < 001$. There were no significant effects involving group membership on binaural stimulation (Fig. 4). For left ear stimulation, the interaction was the result of normal subjects having higher right TPJ activity than patients in response to both S1 and S2 from 60 to 120 ms post-stimulus, $F_{1,34} > 12.66$, $P < 0.001$, For right ear stimulation, the interaction was the result of normal subjects having higher TPJ activity than patients from 80 to 120 ms only after S1, $F_{1,34} > 9.39$, $P < 0.004$.

Discussion

Three conclusions about brain functioning as measured with MEG among schizophrenia patients can be drawn from this study. First, patients have lower activations than normal in left auditory cortex when left hemisphere is directly presented with non-verbal stimuli, although the temporal pattern of activation is similar between-groups. Second, patients have normal right auditory cortex functioning when right hemisphere is directly presented with non-verbal auditory stimuli. Third, normal subjects have significant activation of right TPJ in response to monaurally presented non-verbal auditory stimuli, an activation that is largely absent among patients.

Consistent with previous results, differences between schizophrenia and normal subjects on auditory cortex responses are most evident after long (e.g. 9 s) not short (e.g. 500 ms) inter-stimulus intervals (e.g. Shelley *et al*., 1999; Blumenfeld & Clementz, 2001; Clementz & Blumenfeld, 2001; see also Javitt *et al*., 2000), and appear to be specific to left hemisphere. Although not statistically significant, there was an indication that patients' left auditory cortex was more anterior than normal (e.g. Tiihonen *et al*., 1998). Because the activity difference was mostly clearly manifest in a limited time range (from about 80–120 ms post-stimulus), it seems possible that this abnormality is associated with deficient NMDA-related supragranular layer cortico-cortical communication (see, e.g. Javitt *et al*., 1996; Reser *et al*., 2000) and/or structural deviations of left auditory cortex (e.g. Tiihonen *et al*., 1998). Furthermore, the pattern of brain activations within-groups, and the difference between-groups, was highly similar for both the right and binaural stimulation conditions, suggesting that this abnormality is a specific consequence of a breakdown in intra- and not inter-hemispheric communication.

Abnormalities of inferior parietal lobe have been previously implicated in the neuropathology and cognitive abnormalities observed among schizophrenia (e.g. O'Leary *et al*., 1996; Niznikiewicz *et al*., 2000; Grunwald *et al*., 2002). Right hemisphere typically is dominant for attention to and processing of non-linguistic auditory stimuli (Pardo *et al*., 1991; Pugh *et al*., 1996; Tzourio *et al*., 1997). Right TPJ specifically is hypothesized to support the ability to identify salient features and determine the task relevance of sensory events (e.g. Tzourio *et al*., 1997; Downar *et al*., 2001; Corbetta & Shulman, 2002). An association between right TPJ activity and sustained attention and/or identification of stimulus salience could explain why schizophrenia patients have a subnormal increase in AER amplitudes with increasing time between auditory stimuli. With short inter-stimulus intervals, there is less demand on sustained attention, so the main determinant of global AER amplitude is auditory cortex response, where schizophrenia and normal subjects show relatively

FIG. 3. Plots of mean auditory region activations (with standard error bars) in response to left ear (left column), binaural (middle column) and right ear (right column) stimulation for S1 (top row) and S2 (bottom row).

FIG. 4. Plots of temporal parietal cortex activations (with standard error bars) in response to left ear (left column), binaural (middle column) and right ear (right column) stimulation for S1 (top row) and S2 (bottom row).

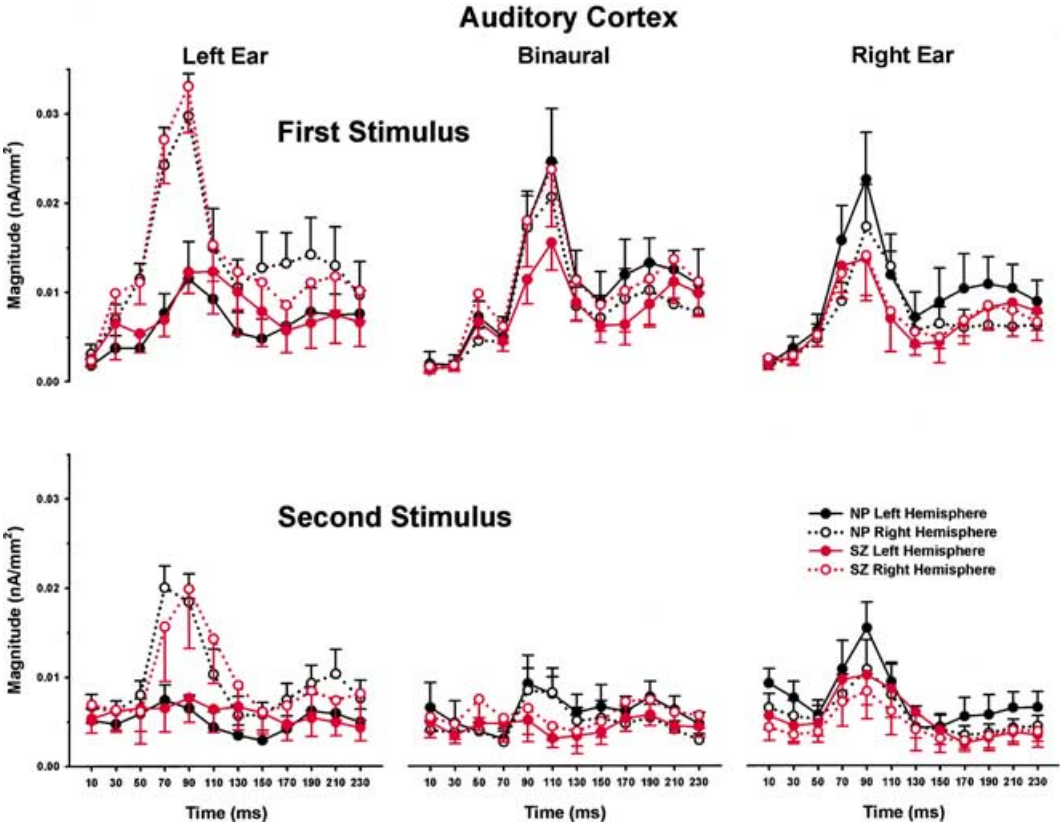
Auditory Cortex
Left Ear
Binaural
Right Ear
First Stimulus
Second Stimulus
Magnitude (nA/mm²)
Time (ms)
NP Left Hemisphere
NP Right Hemisphere
SZ Left Hemisphere
SZ Right Hemisphere

FIG. 3.

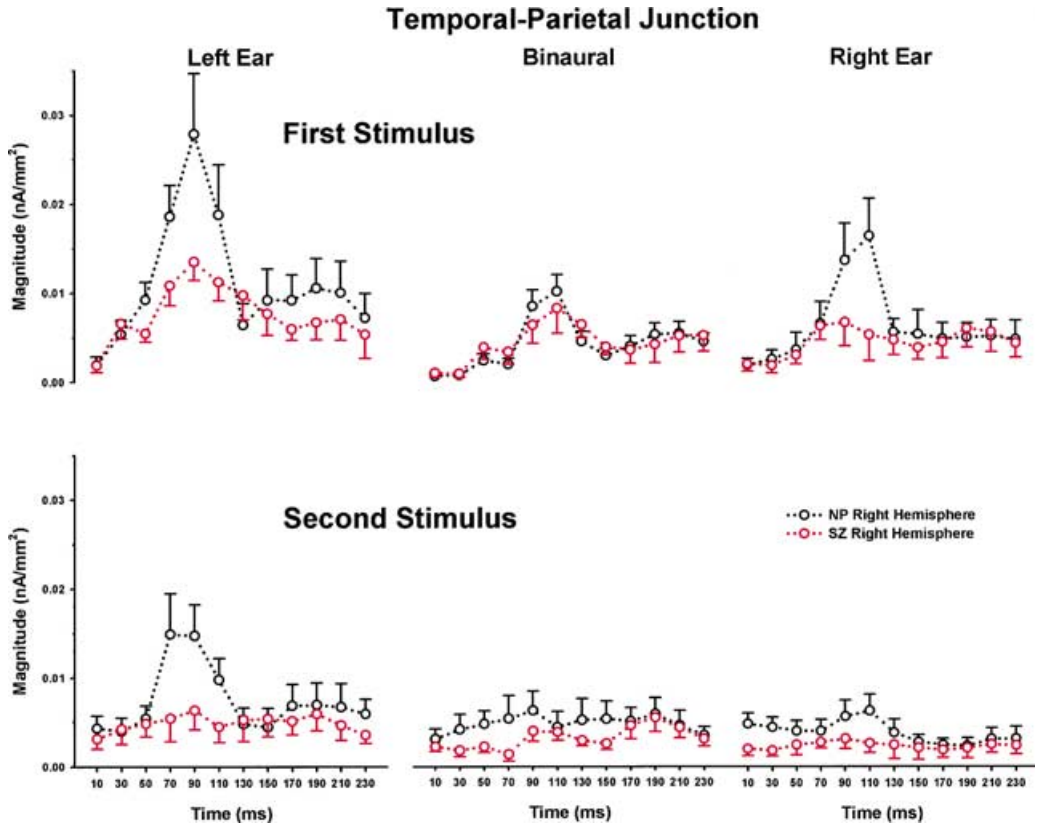
Temporal-Parietal Junction
Left Ear
Binaural
Right Ear
First Stimulus
Second Stimulus
Magnitude (nA/mm²)
Time (ms)
NP Right Hemisphere
SZ Right Hemisphere

FIG. 4.

similar functioning. The longer the temporal delay between stimuli, the greater the demands on sustained attention and/or identification of stimulus salience. These cognitive functions are associated with increased right TPJ activity, which is a brain response that is noticeably deficient among schizophrenia patients.

Right TPJ also is important for localizing stimuli in space (e.g. Clark *et al*., 2002). Because low TPJ activity among schizophrenia patients was only observed during the monaural stimulus conditions, it may be the case that lower right TPJ activity among schizophrenia patients indexes a more general problem with auditory localization abilities among these patients, especially those with auditory hallucinations, a symptom that characterized the present patient samples (Olsson & Nielzen, 1999).

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Abbreviations

AER, auditory-evoked response; MEG, magnetoencephalography; TPJ, temporal parietal junction.

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