Specific and Unspecific Auditory Hallucinations in Patients with Schizophrenia

A Magnetoencephalographic Study

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Key Words

Magnetoencephalography • Positive symptoms • Schizophrenia • Auditory hallucinations

Abstract

Background/Aims: Different neuroimaging techniques have indicated that auditory association and language cortices are active in patients with schizophrenia and auditory hallucinations. Auditory verbal hallucinations are thought to arise from a disorder of inner speech, but little is known about their origin. **Methods:** Spontaneous magnetoencephalographic (MEG) measurements were recorded with a 74-channel two-sensor system (BIOMAGNES II) in 16 patients with schizophrenia and 8 healthy subjects in frequency ranges from 2 to 6 and 12.5 to 30 Hz. Eight patients had auditory hallucinations during the MEG recordings. **Results:** The total group of patients with schizophrenia showed a statistically significant elevation of the number of dipoles and dipole density maxima in slow frequency ranges compared to healthy subjects ($p < 0.001$). Significant dipole activities in the fast frequency range were only found during auditory hallucinations ($p < 0.001$). Dipole localization was concentrated in frontal and temporal regions depending on differ-

ent qualities of hallucinations. In patients with external imperative voices we found a parallel activation of the dorsolateral frontal and temporal cortex. **Conclusion:** We conclude that various auditory hallucinations in schizophrenia are induced by different neuronal activities and may be represented by different cortical regions.

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Introduction

Spontaneous magnetoencephalographic (MEG) activity in schizophrenic patients has been investigated in numerous studies. The majority of these investigations revealed significant differences mainly in the temporal region between schizophrenics and healthy controls [1–5].

In the past, differentiated psychopathological and pathogenetical analysis concentrated on auditory hallucinations, which are a core feature of schizophrenia. In several new studies alterations in connectivity between frontal and parietotemporal speech-related areas were discussed in the pathogenesis of auditory hallucinations [6, 7]. A failure of corollary discharge, a mechanism for distinguishing self-generated from externally generated

percepts, has been interpreted in terms of reduced frontotemporal connectivity, which might contribute to the pathogenesis of auditory hallucinations [6, 7]. Diffusion tensor imaging was used to investigate whether previously described abnormal activation patterns observed during auditory hallucinations relate to changes in structural interconnections between frontal and parietotemporal speech-related areas. Recently, alterations of white matter fiber tracts were found in the left hemisphere in patients with auditory hallucinations [8]. In MEG studies, hallucinating participants demonstrated a network of different cortical activations, including bilateral auditory cortex, left limbic regions, and right medial and right prefrontal cortex [1, 5, 9, 10]. Other recent functional neuroimaging studies have confirmed the pattern of distributed structural abnormalities specific to hallucinations [11–14]. In a pioneering study, Dierks et al. [15] described activation of Heschl's gyrus during auditory hallucinations using event-related functional magnetic resonance imaging (functional MRI). Volumetric investigations found a significant correlation between the severity of auditory hallucinations and volume loss in the transverse temporal gyrus of Heschl (primary auditory cortex) and left inferior supramarginal gyrus, as well as middle and inferior frontal cortices on the right side [16].

However, the neural correlates of auditory hallucinations are still not well understood. Patients may experience hallucinations in more than one modality simultaneously or at different times and they may or may not emanate from a single source. Recently, neural correlates of tasks which involve inner speech have been examined in patients with schizophrenia who hear voices, using regional cerebral blood flow, single photon emission computed tomography (SPECT), positron emission tomography and functional MRI.

In patients with schizophrenia and hallucinations, blood flow was significantly greater during hallucinations than in the nonhallucinating state in Broca's area [17]. Activity was also higher during hallucinations in the left anterior cingulate cortex and regions in the left temporal lobe. The increased flow in Broca's area was not correlated with other clinical signs, or due to concomitant neuroleptic therapy. Auditory hallucinations may also be reflected in distinctive metabolic maps of the brain. Regional brain metabolism was measured by positron emission tomography. Compared to patients who did not experience hallucinations, patients experiencing hallucinations had significantly lower relative metabolism in auditory and Wernicke's regions and a trend to-

ward higher metabolism in the striatum and anterior cingulate regions [18]. Neuroleptic treatment resulted in a significant increase in striatal metabolism and a reduced frontal-parietal ratio, which was significantly correlated with a decrease in hallucination scores. In serial assessments with ^{123}I -IMP SPECT an increased accumulation of ^{123}I -IMP in the left superior temporal area was shown in patients with schizophrenia and auditory hallucinations. This corresponds to the auditory association cortex [19]. Within the context of MEG investigations in schizophrenic patients with auditory hallucinations, different results were found especially with regard to dipole distribution within the slow and fast frequency bands. While Ropohl et al. [10] described an increase in fast dipole activity over the left temporal lobe during auditory hallucinations, investigations by Wienbruch et al. [5] showed a left temporal increase in slow activity in schizophrenic patients with auditory hallucinations compared with healthy controls. On the basis of the variation in results, the inclusion of psychopathological differentiation appears to be decisive. Without doubt, the quality of auditory hallucinations is not uniform. Differentiation between unspecific noises (acoasms) and specific phonemes (imperative, dialoguing, and commenting voices) may provide a further basis for understanding neuronal correlates of auditory hallucinations. The hypothesis on which this is based refers to the differential activation of cortical centers depending on different hallucination qualities.

Methods

Magnetoencephalography

Cortical activity was recorded with the same dual 37-channel neuromagnetometer (Magnes II®; 4-D Neuroimaging, San Diego, Calif., USA) as used previously [4, 10, 20]. Sensor arrays were placed with the center above C3 and C4, according to the international 10–20 EEG system. Spontaneous neuromagnetic brain activity was recorded in data sets of 600 s duration from both hemispheres simultaneously at a sampling rate of 520.8 Hz. Online high-pass (1.0 Hz) and low-pass (100.0 Hz) filters were applied, and an ECG was recorded. For offline data analysis, an initial 50-Hz notch filter was applied and the magnetic field noise of the heart was removed by ECG-triggered digital noise reduction. All raw data sets were carefully checked for artifacts from eye and body movements, and affected sections were excluded from further analysis. Digital band-pass filters were applied to analyze slow (2- to 6-Hz) and fast (12.5- to 30-Hz) frequency bands separately. The filters applied for spontaneous measurements corresponded to the statistically significant frequency bands determined in schizophrenic patients in previous investigations [4, 20]. Previously, no anomalies were found for the frequency range 7–10

Fig. 1. Spontaneous MEG activity with/without auditory hallucinations in a 28-year-old male schizophrenic patient. P.B. = Press button.

Hz in schizophrenic patients with florid psychotic symptoms (including hallucinations) [4, 10]. Therefore, the respective filter was not applied in the present investigation. A principal component analysis was used to select a 10-second period minimum from the whole measurement where one component was predominant in the signal [4]. In selected time sections >90% of the signal variance could be attributed to the dominant component and a single source model was considered to be an adequate mathematical model. Single equivalent current dipoles were calculated every 2 ms over the selected data segments using a locally fitted spherical head model. Only dipoles showing statistical correlations between estimated and measured magnetic field distributions of $r > 0.9$ were accepted for data evaluation. The spatial distribution of dipoles was determined by a three-dimensional convolution with a Gaussian-shaped envelope, for which the variance was the localization uncertainty of individual dipole localizations yielding a dipole density plot [4]. MEG localizations were inserted into an anatomical three-dimensional T₁-weighted image using a contour fit technique. The dipole maxima (red lines) were shown in the MR image and a localization specification was performed in accordance with the dipole density plot method [4] by additional 3-dimensional projection. Spontaneous neuromagnetic activity

was quantified by calculating the total dipole number (D_{total}) and the concentration of dipoles within the area of the highest dipole density (density maximum, D_{max}). To visualize the results of this analysis with respect to brain anatomy, dipole locations were superimposed on MR images acquired with a 1.5-tesla Magnetom (MagnetomTM, SiemensTM, Germany). During recording, patients were instructed to use a response device system: to press a button at the beginning ('on') and at the end ('off') of any auditory hallucination with their right hand positioned on a stable desk in order to reduce the rate of motor artifacts (fig. 1). In each patient, already during the first recordings of spontaneous activity (first 30 s), the instruction to maintain a calm reclining position was used as an acoustic stimulus via an integrated loudspeaker in the MEG. In addition, during the 'start' phase, the instruction was given to keep the button pressed for 10 s as a test if the subject did not perceive any auditory hallucinations during this time. Neither of the two instructions produced evidence of spontaneous activity altered by acoustic stimuli (loudspeaker instruction) or motor stimuli (pressing the button) in the form of a change in frequency in the measured ranges of 2–6 Hz and 12.5–30 Hz.

The signals of these response devices were recorded in addition to the spontaneous MEG activity. Therefore time epochs dur-

Table 1. Clinical and sociodemographic data in patients with schizophrenia

	Male patients with hallucinations	Female patients with hallucinations	Male patients without hallucinations	Female patients without hallucinations
Patients	5	3	4	4
Age, years	35 ± 2.3	30 ± 2.6	34 ± 3.2	34 ± 1.7
Age at onset of manifestation, years	27 ± 1.6	28 ± 3.2	25 ± 2.4	29 ± 0.8
Duration of illness, years	8 ± 2.8	2 ± 1.2	9 ± 3.1	5 ± 2.1
Hallucinations ¹	specific 2/5 unspecific 3/5	specific 1/3 unspecific 2/3	–	–
CPZ equivalents	270 ± 60	230 ± 50	190 ± 40	190 ± 20
Medication	typical: 1/5 atypical: 4/5	typical: 0/3 atypical: 3/3	typical: 3/4 atypical: 1/4	typical: 2/4 atypical: 2/4

Means ± standard deviations are given for age, age at onset, duration of illness, and chlorpromazine (CPZ) equivalents.

¹ Specific hallucinations: imperative voices, dialoguing voices. Unspecific hallucinations: noise, music.

ing auditory hallucinations could be analyzed separately by the dipole density plot method. The whole data analysis was done by 2 MEG specialists, who were kept naïve about specific psychopathological findings in the group of schizophrenic patients by the medical staff.

Subjects

Spontaneous slow and fast MEG activity was measured in 16 right-handed patients (9 men, 7 women, mean age 33, SD 2.8 years), of whom all met the ICD-10 criteria for schizophrenia. The patients were selected independently by 2 specialist psychiatrists on the basis of the ICD-10 and PANSS scales. In order to achieve subtype-specific homogenization within the group of patients with schizophrenia, only patients of the subtype of paranoid hallucinatory schizophrenia (ICD-10, F20.0) were admitted to the investigation by the 2 independent specialists. Eight patients had a P3 score (according to the PANSS scale, the P3 score assesses hallucinatory behavior and is rated from absent to extreme: 0–6 points) of above 5, and 8 below 2 (for sociodemographic and clinical data, table 1). Before MEG recordings, all patients were treated with typical and atypical neuroleptics. Three days before the measurement, neuroleptic medication was completely stopped to avoid medication interferences.

The control group consisted of 8 right-handed healthy test persons (4 men, 4 women, age 35 years; SD 8.2), who were exclusively recruited for this study. Exclusion criteria for patients with schizophrenia and control subjects were neurological disorders, organic psychoses, schizophrenia-like psychoses, addictive diseases, any electroconvulsive or repetitive transcranial magnetic stimulation treatment in the past or metal implants. Within the context of the psychopathological differentiation of auditory hallucinations, a categorization was performed according to first- and second-order symptoms. First-order symptoms in the sense of dialoguing, imperative, and commenting voices were categorized as specific, while noises corresponding to general sensory perceptions were classified as second-order symptoms and thus as unspecific.

Data Analyses

All variables were tested for normal distribution by the Kolmogorov-Smirnov test. Student's *t* test was used for comparison of the means of continuous variables and normally distributed data. Mann-Whitney *U* test was used otherwise. General linear models for repeated measures were used to test hemisphere effects. All statistical tests were two-sided, and a significance level of $\alpha \leq 0.05$ or less was used. Data were analyzed using SPSS™ for Windows™ 11 (SPSS™ Inc., Chicago, Ill., USA).

Results

Dipole Absolute Values

Table 2 shows the number of dipoles and the dipole density maximum for spontaneous slow and fast MEG activity during time segments with and without auditory hallucinations in patients and controls. In the intergroup comparison between patients and control subjects a statistically significant dipole elevation could be found for the slow dipole activities over both hemispheres in patients with schizophrenia ($p < 0.001$). Within the group of patients with schizophrenia, significant elevations of dipoles and dipole density maxima ($p < 0.001$) were found during time segments with auditory hallucinations in the fast frequency range (table 2). Using a general linear model to assess hemispheric differences, the number of dipoles differed significantly (general linear model; $F = 7.1$, $p = 0.018$) between patients with and without auditory hallucinations in the fast frequency range only. No statistically significant differences could be found in the dipole distribution in the slow frequency range between time segments with and without auditory hallucinations in patients with schizophrenia.

Table 2. Spontaneous MEG activity in patients with schizophrenia: dipole analysis of segments with and without auditory hallucinations

	2–6 Hz, left		2–6 Hz, right		12.5–30 Hz, left		12.5–30 Hz, right	
	dipoles	D _{max}	dipoles	D _{max}	dipoles	D _{max}	dipoles	D _{max}
Auditory hallucinations (n = 8)	2,350 ± 484	45 ± 6.6	2,040 ± 446	40 ± 12.5	4,410 ± 979	76 ± 29.6	2,930 ± 742	44 ± 10.1
Dipole localization	temporal lobe (n = 8)		temporal lobe (n = 8)		STG (n = 5), STG + DPC (n = 3)		STG (n = 8)	
Without hallucinations (n = 8)	2,210 ± 307	52 ± 11.9	1,720 ± 394	54 ± 13.2	2,200 ± 450	45 ± 15.3	1,720 ± 394	30 ± 13.8
Dipole localization	temporal lobe (n = 8)		temporal lobe (n = 8)		STG (n = 8)		STG (n = 8)	
p value	0.502	0.168	0.332	0.051	<0.001	0.019	0.001	0.036
Patients total (n = 16)	2,280 ± 389	48 ± 10.0	2,130 ± 359	47 ± 14.3	3,310 ± 1,358	61 ± 27.9	2,320 ± 848	37 ± 13.7
Controls total (n = 8)	1,430 ± 234	27 ± 4.0	1,430 ± 369	33 ± 6.9	2,400 ± 480	35 ± 7.2	2,310 ± 472	33 ± 10.6
Dipole localization	NDC		NDC		NDC		NDC	
p value	<0.001	<0.001	<0.001	0.015	0.082	0.003	0.960	0.952

D_{max} = Dipole density maximum; STG = superior temporal gyrus; DPC = dorsolateral prefrontal cortex; NDC = no dipole concentration. Mean values ± standard deviations are given. Significant p values are italicized.

Dipole Localization

In the group of patients with and without hallucinations dipoles in the slow frequency range were mainly localized over the superior temporal gyri in both hemispheres. In the fast frequency range dipoles were also localized equally over the temporal lobe of the right hemisphere. On the left hemisphere we found a concentration of dipoles on the superior temporal gyrus and parts of the dorsolateral prefrontal cortex in patients with auditory hallucinations. Patients with imperative voices showed a combined and confluent localization of dipole maxima in the left superior temporal gyrus and parts of the left dorsolateral prefrontal cortex (fig. 2), while patients with acoasms (unspecific noise) showed only a concentration of dipoles on the left superior temporal gyrus. In healthy controls no dipole concentration over either hemisphere could be found in the slow or fast frequency range.

The small sample size of patients with dipole localization considerably limits the conclusions that can be drawn from them.

Discussion

Firstly, within the context of the present MEG spontaneous measurements on schizophrenic patients with and without auditory hallucinations, the increases in slow dipole activity in the temporal lobes of both hemispheres already known from previous investigations comparing schizophrenic patients with healthy controls [1, 4] were confirmed. Furthermore, we tested the hypothesis that qualitatively different specific auditory hallucinations in

Fig. 2. Thirty-five-year-old female patient with imperative voices. Isosonor (black) lines, representing magnetic activity in the fast frequency range 12.5–30 Hz, are projected onto respective cranial MRT slices of the patient. Focal magnetic maxima were located in the left superior temporal gyrus and parts of the left dorsolateral frontal cortex.

schizophrenia may have different neuronal correlates. Recent results of spontaneous MEG activity in hallucinating patients with schizophrenia have shown different dipole clusters in the slow and fast activity ranges mainly in the superior temporal and dorsolateral frontal region [3–5, 9, 20, 21]. Although increasing agreement with regard to dipole localization has crystallized out of the MEG investigations conducted to date, the increase in

activity in the slow [1, 5] and fast frequency range [10] in auditory hallucinations has still to be considered controversial. In the present study, within the overall group of schizophrenic patients, there was an increase in slow dipole activity over both temporal lobe regions, which did not show any specific weighting in a subregion in this frequency range. Under specific consideration of a partial aspect of the disease in the form of a selective determination of MEG spontaneous activity during auditory hallucinations, the left superior temporal lobe and the left dorsolateral prefrontal cortex turned out to be two regions that, in the sense of an epiphenomenon of the underlying disease, stood out with a specific neuronal correlate in the form of a dipole elevation in the fast frequency range. A remarkable finding within this population was a further specification in the form of a 'border zone transgressing' fast dipole localization from the left superior temporal cortex to adjacent parts of the left dorsolateral prefrontal cortex only in patients with specific hallucinations, while unspecific hallucinations in the form of acoasms showed a focus on the left superior temporal lobe.

We therefore assume that different cortical regions are involved in different forms of auditory hallucinations. Distinct symptoms of schizophrenia may be related to different types of brain dysfunction. It is possible to investigate the patterns of brain activity underlying schizophrenic symptoms by mapping regional metabolism or regional cerebral blood flow in vivo with positron emission tomography and SPECT. Using this technique, some authors have related subsyndromes of symptoms to distinct regional cerebral blood flow patterns [22], whereas others have focused on the metabolic changes associated with more specific phenomena, most frequently auditory hallucinations [18, 23]. In MEG case reports [10, 24], a temporal dysfunction has been discussed. In a recently published MEG study by Kawaguchi et al. [2], a dysfunction in the left dorsolateral prefrontal cortex was related to auditory hallucinations. Hypofrontality, particularly in the dorsolateral prefrontal cortex, has been commonly found in schizophrenia with different neuroimaging techniques [25–27]. Superior temporal gyrus abnormalities have been associated with auditory hallucinations [28].

Alterations in connectivity between frontal and parietotemporal speech-related areas might contribute to the pathogenesis of auditory hallucinations [6, 7, 29, 30]. The failure of a corollary discharge has been confirmed using event-related brain potentials (ERP N1) in the N1 component in auditory hallucinations [31].

There is some evidence that the activity in the temporal cortex in hallucinations depends on its specific form. Less activity is assumed in the temporal cortex if the subject hears his own voice. It was assumed that the reduction of activity is the consequence of inhibitory signals arising from vocalization areas (e.g. in the Broca area, the anterior cingulate cortex, and the frontal cortex). The functional anatomy of verbal fluency has been well characterized in normal subjects using positron emission tomography. Generating words beginning with a given letter activates the left dorsolateral prefrontal cortex and deactivates the bilateral superior temporal gyrus. In schizophrenia, investigators have reported a failure of deactivation of the superior temporal gyrus, mainly in the left hemisphere. In our patients we found a significantly elevated dipole concentration in the temporal and combined frontal and temporal region over both hemispheres in the fast frequency ranges with respect to the specificity of hallucinations. These results confirm findings reported by Dierks et al. [15], who described an activation of Heschl's gyrus during auditory hallucinations using functional MRI. The activation of the frontal lobe in patients with specific hallucinations as found in our present study supports the hypothesis that there is a failure of corollary discharge in auditory hallucinations [6–8, 31]. It still remains unclear whether different cortical centers are responsible for different kinds of internal and external voices in auditory hallucinations. The concentration of dipoles in the temporal lobe in unspecific hallucinations (e.g. noise, music) without any participation of the frontal lobe could be interpreted as a sign of a diminished cortical involvement compared to complex mechanisms that are involved in externally generated stimulators like voices. These questions remain open. But according to the present MEG findings we will have to strictly separate different qualities of internal and external hallucinations in future investigations.

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