Frontal and Temporal Dysfunction of Auditory Stimulus Processing in Schizophrenia

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Attention deficits have been consistently described in schizophrenia. Functional neuroimaging and electro-physiological studies have focused on anterior cingulate cortex (ACC) dysfunction as a possible mediator. However, recent basic research has suggested that the effect of attention is also observed as a relative amplification of activity in modality-associated cortical areas. In the present study, the question was addressed whether an amplification deficit is seen in the auditory cortex of schizophrenic patients during an attention-requiring choice reaction task. Twenty-one drug-free schizophrenic patients and 21 age- and sex-matched healthy controls were studied (32-channel EEG). The underlying generators of the event-related N1 component were separated in neuroanatomic space using a minimum-norm (LORETA) and a multiple dipole (BESA) approach. Both methods revealed activation in the primary auditory cortex (peak latency ≈ 100 ms) and in the area of the ACC (peak latency ≈ 130 ms). In addition, the adapted multiple dipole model also showed a temporal-radial source activation in nonprimary auditory areas (peak latency ≈ 140 ms). In schizophrenic patients, significant activation deficits were found in the ACC as well as in the left nonprimary auditory areas that differentially correlated with negative and positive symptoms. The results suggest that (1) the source in the nonprimary auditory cortex is detected only with a multiple dipole approach and (2) that the N1 generators in the ACC and in the nonprimary auditory cortex are dysfunctional in schizophrenia. This would be in line with the notion that attention deficits in schizophrenia involve an extended cortical network.   © 2002 Elsevier Science (USA)

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INTRODUCTION

Neuropsychological studies have consistently described attention deficits to be among the most prominent cognitive abnormalities in schizophrenic patients and their family members (Strauss, 1993; Nuechterlein *et al.,* 1994; Cornblatt *et al.,* 1997; Nuechterlein *et al.,* 1994; Egan *et al.,* 2000). Several lines of evidence suggest that the anterior cingulate cortex (ACC) plays a key role in attention (Posner and Petersen, 1990; Posner and Dehaene, 1994; Bench *et al.,* 1993) and in attention deficits of schizophrenic patients. For instance, reduced activity of the ACC was reported in schizophrenic patients by neuroimaging studies across a variety of cognitive tasks like tone frequency recognition (Holcomb *et al.,* 2000), Stroop color-word interference task (Carter *et al.,* 1997), and auditory verbal supraspan memory task (Dolan *et al.,* 1995). However, there is evidence that the effect of attention also involves a relative amplification and synchronization of activity within other cortical areas relevant to a given task such as in the visual cortex (Posner and Dehaene, 1994; Fries *et al.,* 2001). Accordingly, one also might expect a reduced activation amplification effect in the sensory cortices of schizophrenic patients. In fact, a reduced activation of the superior temporal lobe during attention-related auditory stimulation was reported in schizophrenic patients (Ganguli *et al.,* 1997). However, others failed to show this deficit (Holcomb *et al.,* 2000; Higashima *et al.,* 2000). One possible reason that may account for these different observations might be the incomplete separation of the amplification effect of attention in the primary and nonprimary (secondary/association) auditory cortices and the resulting difficulty to quantify partial activation in either of these two closely neighboring areas.

The analysis of activation in the time domain can help to improve the separation of spatially closely related areas. Auditory evoked potentials reflect cortical activity in the time range of milliseconds. After auditory stimulation, the N1 component appears as a char-

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acteristic potential distribution on the scalp with a maximum negative amplitude at the vertex around 100 ms poststimulus. The major source contributors of the N1 component are the primary auditory cortex (Celesia, 1976; Hari *et al.,* 1980; Elberling *et al.,* 1982) and nonprimary auditory areas (Celesia, 1976; Knight *et al.,* 1988). The peak latency of the nonprimary auditory cortex is 30–40 ms later than that of the primary auditory cortex, indicating a sequential activation (Celesia, 1976; Scherg and von Cramon, 1985; Gallinat and Hegerl, 1994). Furthermore, evidence for a frontal generator in the time range of the N1 has been reported (Giard *et al.,* 1994; Winterer *et al.,* 1999; Mulert *et al.,* 2001) and intracerebral recordings in humans have found an amplitude negativity in the orbital, dorsolateral prefrontal, and cingulate areas (Walter, 1964; McCallum and Curry, 1980; Baudena *et al.,* 1995). Of note, a pronounced augmenting effect of selective attention on the scalp measured N1 amplitude has been described (Hillyard *et al.,* 1973). Intracortical recordings in humans suggest that an attention-dependent increase of frontal activity may be responsible for this N1-augmenting effect (Baudena *et al.,* 1995). Moreover, electrophysiological animal data provide evidence that the primary and nonprimary auditory cortex are differentially modulated by attention (Hocherman *et al.,* 1976; Grady *et al.,* 1997). Therefore, it seems likely that the N1 component in humans is also modulated by attention effects on the primary and/or nonprimary auditory cortex.

Employing an attention-requiring auditory choice reaction task, our group has described a decrease of frontal midline activation during the N1 time window in the ACC in schizophrenic patients with source localization (low-resolution electromagnetic tomography; LORETA) (Winterer, 2000; Mulert *et al.,* 2001). In contrast, no activation decrease of schizophrenic patients was observed in the auditory cortex. A possible reason for the negative finding with respect to the auditory cortex might be that no augmentation deficit exists in the auditory cortical processing in schizophrenic patients. Another reason may be that primary and nonprimary auditory cortices are differently modulated by attention in schizophrenic patients, and that the separation of these closely located generators was inaccurate. The separation of these two subsequent sources in the time domain can be improved when the different dipole orientations of the two sources in cortical space are taken into account: The primary auditory cortex occupies most of Heschl's gyrus on the superior temporal plane with a fronto-central orientation of the neurons (Morosan *et al.,* 2001; Pandya, 1995; Hari *et al.,* 1980; Elberling *et al.,* 1981), while nonprimary auditory areas (auditory association areas/secondary auditory cortex) reach over the lateral cunt of the temporal lobe (Pandya and Sanides, 1973; Woolsey and Walzl, 1982) with an orientation of the neurons toward the temples. The orientation of the columnally organized neurons determines the topographical distribution of their electrical activity on the scalp. Source analysis methods using fixed dipole sources of a distinct orientation deploy this information and may separate the activity despite their close localization (Gallinat and Hegerl, 1994) (Fig. 1). Therefore, a multiple dipole source analysis (brain electric source analysis; BESA; Scherg and von Cramon, 1985) was employed in the present study in addition to the minimum-norm approach.

A further intention of the present study was to investigate the relationship between the cortical N1 generators and schizophrenic psychopathology. With respect to the electromagnetic source in the area of the ACC, clinical observations of patients with ACC brain lesions (Damasio and Van Hoesen, 1983; Cohen *et al.,* 1999) have suggested a direct relation between reduced ACC function and apathy, lack of spontaneity, and emotionally induced loss of muscular tonus (cataplexy). From these observations one might deduce that schizophrenic patients with reduced ACC activation may show similar symptoms. However, in schizophrenia no exclusive relationship exists between attention deficits and the expression of clinical symptomatology such as apathy or more generally "negative symptoms" (Strauss, 1993; Cornblatt *et al.,* 1997; Nelson *et al.,* 1998). In contrast, several authors have suggested an important role of attention deficits in the genesis of "positive symptoms" such as hallucinations (Addington and Addington, 1997; Berman *et al.,* 1997; Nelson *et al.,* 1998). Such a relation, however, rather would suggest an involvement of the temporal lobe (Silbersweig *et al.,* 1995; Dierks *et al.,* 1999).

The aim of the study was to investigate whether an electrical cerebral activation deficit (N1 component) in schizophrenia is present in the temporal lobe/auditory cortex when an attention-requiring task is performed. As in our previously performed studies, we recorded brain electric activity during an auditory choice reaction task. However, in the present study the number of electrodes was increased to 32 channels and a new sample of 21 drug-free schizophrenic patients and 21 age-matched normal subjects was investigated. For an optimal spatio-temporal analysis of the cerebral activity two source localization methods were combined: The number and localization of N1 generators is determined using the minimum-norm approach. This information is used to constitute an initial multiple dipole model. In a second step, the localization and orientation of these dipoles is adapted to reach an optimal explanation of the cerebral activity. With this final dipole configuration, fine graded time course and activity analyses of N1 generators are performed.

Specifically, the following questions were addressed:
— Is there a deficit of the overall activity in the auditory cortex reflected by the minimum-norm solu-
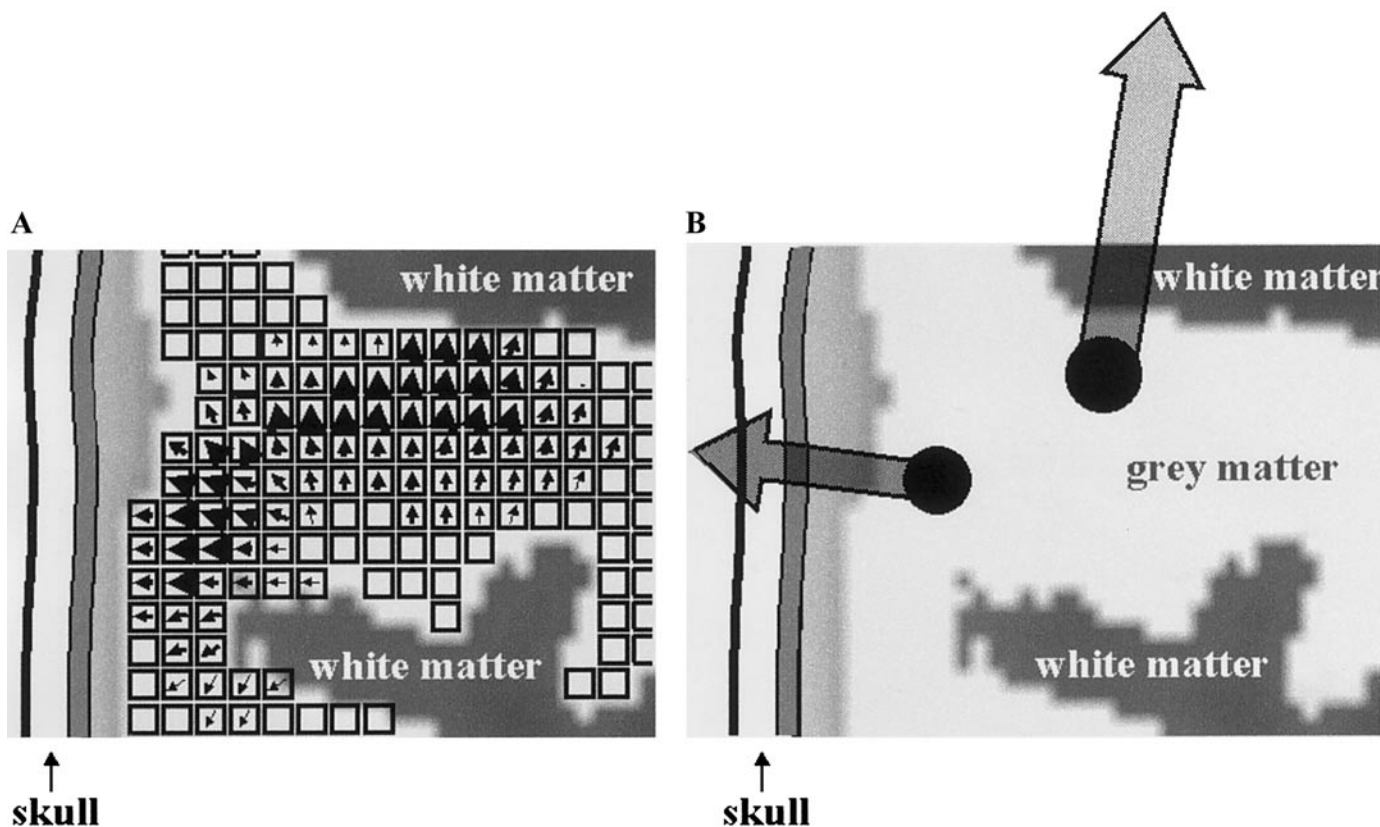
FIG. 1. Presentation of a head model (the 2-dimensional detail of the 3-dimensional space shows a coronal slice of the left temporal lobe with the supratemporal plane) to illustrate the principles of the minimum-norm (represented by LORETA, part A) and multiple dipole approach (represented by BESA, part B). (A) A schematic dens grid of voxels used by LORETA on which the electrical activity is projected as amplitude of the current source density (μAm/mm^2) computed for a single time point or epoch. The voxel grid (solution space for the inverse solution) is restricted to the gray matter and hippocampus according to the Talairach atlas. The thickness of the arrows within the voxels illustrates the strength of the current density for a hypothetical activity of the given brain area. The orientation of the arrows indicates the orientation of the electrical activity which is used to compute the inverse solution but which is not visualized in the resulting images (compare to Fig. 3). This approach does not require assumptions on the part of the user. (B) The same detail of a head model. The hypothetical distributed electrical activity can be modeled by a small number of equivalent dipoles with stationary location and orientation closely related to the spatial organization of the neural subset. The generator activity is expressed as a dipole source curve (dipole magnitude) varying over time (see Fig. 8). The number of dipoles is user defined and their best configuration is obtained by an iterative fit procedure. Based on the orientation and activity course of the dipoles, cortical areas may be separated even when they are located close together.

tion using a higher electrode density as in our previous study?

— Is this deficit due to a decreased activity of the primary or nonprimary auditory cortex as reflected by different dipole sources?

— Can the previously reported ACC hypoactivation of the late N1 peak be replicated with the minimum-norm solution as well as with the multiple dipole analysis?

— Is the activity of the frontal and temporal sources related to schizophrenic psychopathology, i.e., negative and positive symptoms?

MATERIALS AND METHODS

Subjects

The study was approved by the Ethics Committee of the Benjamin-Franklin-University Hospital of the Free University of Berlin. All subjects gave written informed consent after the procedure was fully explained to them.

Schizophrenic Patients

Twenty-four inpatients from the psychiatric hospital of the Department of Psychiatry, Benjamin-Franklin-University Hospital, Berlin, who met DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994) were enrolled in the ERP investigation. The diagnosis of schizophrenia was determined by a structured interview (SCID-I) (First *et al.*, 1996) and the consensus of the attending physician and a senior house officer. The diagnosis schizophrenia could be verified in all first episode patients ($n = 14$) in the further course of the disease. Exclusion criteria for patients were significant cardiovascular, hepatic, renal, gastrointestinal, metabolic, or other systemic dis-

TABLE 1

Characteristics of Healthy Subjects and Schizophrenic Patients (Mean ± Standard Deviation)

	Healthy controls	Schizophrenic patients
N (m/f)	21 (14/7)	21 (14/7)
Age (y)	30.0 ± 8.6	30.0 ± 9.8
Handedness (r/l)	19/2	19/2
Duration of illness (y)	—	3.3 ± 5.8
Age of onset (y)	—	26.7 ± 9.4
Number of episodes	—	2.1 ± 2.6
Number of hospitalizations	—	1.5 ± 2.7
PANSS-positive score		21.7 ± 5.0
PANSS-negative score	—	22.3 ± 7.3

ease, concurrent psychiatric or neurological illness, organic mental disorder, seizure disorder, mental retardation, significant alcohol or substance abuse within the previous 12 months, Parkinson's disease, toxic central nervous system depression or any clinically relevant abnormalities in blood chemistry, or other laboratory tests.

The EEG recording was obtained shortly after admission and before the initiation of any treatment. No patient was chronically hospitalized. After the EEG recording one patient was excluded because of a suspected organic psychosis. The psychopathology matched completely a schizophrenic episode but due to a general EEG slowing, further diagnostic was undertaken. Lumbar puncture, MRI, and visual-evoked potentials showed pathological results compatible with a diagnosis of an encephalitis or multiple sclerosis. Two Patients did not reach a minimum number of artifact free sweeps during the EEG recording. The remaining 21 patients (295.3, $n = 13$; 295.1, $n = 2$; 295.9, $n = 6$) were included in the analysis. The sample consisted of 14 males (average age 29.0 ± 10.5 years) and 7 females (average age 31.9 ± 8.7 years). Thirteen patients were drug-naive (all of them experienced the first psychotic episode), 3 patients were drug-free for more than 3 month, and 5 patients were unmedicated for at least 3 days. For further details, see Table 1. Clinical ratings were performed within 24 h of the recording session. Patients were rated on the 30-item Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Symptoms are rated from 1 (absent) to 7 (extreme). The classical 7-item PANSS-positive and 7-item PANSS-negative scores were computed.

Healthy Controls

Healthy controls were recruited by newspaper advertisements and paid for their participation. All together 243 healthy controls were investigated. For the present study, a sample of 21 subjects, matched with respect to age, sex, and handedness, was drawn from the whole sample. Health status was screened in a

two-step procedure. (1) Subjects were questioned in a telephone interview performed by 8 students of medicine or psychology using a structured questionnaire, which was specifically designed for this purpose. All students were trained in performing the interview. This questionnaire including items about current or previous psychiatric disorders, psychotropic drug intake, alcohol use, neurological diseases, hearing disorder, and psychiatric diseases in first-degree relatives. Nine hundred fifty subjects responding to the newspaper advertisement were screened. Of these subjects 276 were invited for the further procedure. The remaining volunteers were not considered for further participation in the study. (2) In the second step, subjects who met the applied criteria of the telephone interview were explored by a psychiatrist in the Department of Psychiatry, Free University Berlin. A structured interview was performed (mini-SCID) (Sheehan et al., 1998). Subjects were excluded when fulfilling the criterion of an axis I diagnosis or were likely to have an axis II diagnosis (Cluster A, B, or C) according to DSM-IV criteria. Further reasons for exclusion were severe internal or neurological diseases (e.g., parkinson, ischemic brain insults, noncompensated hypothyroidism, or diabetes mellitus), hearing disorder, or intake of psychotropic medication. Medication for internal diseases like beta receptor blockers, thyroxin, or oral antidiabetic medication was allowed. In addition subjects were screened with respect to psychiatric diagnoses in the family. Axis I diagnosis in first-degree relatives was an exclusion criterion. An axis II disorder in first-degree relatives and/or an axis I and II disorders in second- or higher degree relatives were documented. Of the 276 subjects 26 were excluded in step 2. The reasons were mainly past or current drug use ($n = 10$), alcohol abuse ($n = 6$), affective disorder ($n = 5$), or other psychiatric diseases ($n = 7$). Five subjects were excluded because of an insufficient quality of the recording (mainly due to a small number of artifact free sweeps, see below).

Task

As previously described in more detail (Winterer et al., 1999), 2×30 tones of different pitches (1000 and 2000 Hz) were presented by audiometric headphones at 85 dB SPL with pseudorandomized sequence and interstimulus intervals (ISI: 2.5–7.5 s). The whole task takes 5 min. Tones were generated by a PC stimulator with Creative Labs Soundblaster 16. Based on the known and stable transducer sensitivity of the headphones, calibration was performed by electrical AC voltage measurement at the headphones' terminals before the beginning of the study. Continuous sinewave tones of 1000 and 2000 Hz have been used in the process. Stimulus levels are the absolute sound pressure levels of a continuous sinewave with a peak-to-

peak amplitude equaling that of the referring stimulus. During the experiment subjects had to switch off the tones as soon as possible by pressing one of two buttons. The two buttons were assigned in advance to the high and low tone, respectively. The low tone had to be switched off with the left hand and the high tone with the right hand. Thus, this task requires attention to two different targets, presented in an unpredictable sequence and interstimulus interval, decision-making, whether the left or right button has to be pressed, and a motor response (action) of button pressing. Before the beginning of the recording one test run was carried out. During the task, a computer registered the reaction times and mistakes. Reaction times were calculated from the onset of the stimulus to the button press.

ERP Recording

Recording took place in a sound-attenuated and electrically shielded room adjacent to the recording apparatus (Neuroscan Synamps). Subjects were seated with closed eyes in a slightly reclined chair with a head rest. Evoked responses due to the choice reaction task were recorded with 32 tin electrodes referred to Cz, using an electrode cap. The electrodes were positioned according to the International 10/20 system with the additional electrodes FC1, FC2, FC5, FC6, T1, T2, CP5, CP6, PO9, and PO10. Fpz served as ground. Eye movements were recorded across an electrode 1 cm lateral to the left eye (Lo1). Electrode impedance was less than 10 kohm. Data were collected with a sampling rate of 250 Hz and an analogous bandpass filter (0.16–50 Hz) and 350-ms prestimulus and 800-ms poststimulus periods were evaluated for every sweep. For artifact suppression, all sweeps were automatically excluded from averaging when the voltage exceeded 100 μV in any one of the 32 channels at any point during the averaging period. For each subject, the remaining sweeps were averaged. Targets with a button press response later than 1800 ms were not average. Only waveshapes, based on at least 30 averages, were accepted.

Source Analysis

Minimum-norm approach. We performed a current density analysis in 3-D Tailarach space of the event-related EEG using the LORETA software package (Pascual-Marqui *et al.,* 1994). LORETA images represent the electrical activity at each voxel in neuroanatomic Talairach space as amplitude of the computed current source density (μA/mm^2; Fig. 1a). The characteristic feature of the resulting solution is its relatively low spatial resolution, which is a direct consequence of the smoothness constraint. Specifically, the solution produces a "blurred-localized" image of a point source, conserving the location of maximal activity, but with a certain degree of dispersion. It should be emphasized that this solution will also produce a blurred-localized

image of any arbitrary distribution due to the principle of superposition. The version of LORETA used in the present study used the digitized Talairach atlas (Talairach and Tournoux, 1988), available as digitized MRI from the Brain Imaging Centre, Montreal Neurologic Institute, estimating the current source density distribution for either single time points or epochs of brain electric activity on a dense grid of 2394 voxels at 7-mm spatial resolution (Pascual-Marqui *et al.,* 1999). The solution space (the three-dimensional space where the inverse EEG problem is solved) was restricted to the gray matter and hippocampus in the Talairach atlas. Registration between spherical and realistic head geometry used EEG electrode coordinates reported by Towle *et al.* (1993). A voxel was labeled as gray matter if it met the following three conditions: its probability of being gray matter was higher than that of being white matter, its probability of being gray matter was higher than that of being cerebrospinal fluid, and its probability of being gray matter was higher than 33% (Pascual-Marqui, 1999).

Dipole source approach. Dipole source analysis was performed with brain electrical source analysis (Scherg and von Cramon, 1985) to decompose the scalp measured N1 into dipole sources. The development of the new dipole model was performed with a grand average data set of 112 healthy subjects. The large number of recordings was chosen to obtain a high signal-to-noise ratio. The final solution was obtained in the subsequent way:

(1) To model the activity of the temporal lobe, a dipole configuration of 4 dipoles (2 dipoles per hemisphere), which was developed before for the multichannel recorded N1 component (Gallinat and Hegerl, 1994), was set into the 3-shell head model. This initial configuration contains a tangentially oriented dipole and a radially oriented dipole in each temporal lobe.

(2) With respect to the frontal-midline activity shown by LORETA in the current (Fig. 4) and previous data sets (Mulert *et al.,* 2001), a fifth dipole was placed to the corresponding localization within the 3-shell head model.

(3) For the following iterative fit procedure the radial and tangential dipoles in each hemisphere were bound together and mirror constraints were set for localization and orientation between hemispheres. The frontal-midline source was free in all degrees. The fit procedure was performed within the time frame of negative dipole activity (72–176 ms). The result of this fitting procedure is presented as final dipole configuration in Figs. 6 and 8. The further introduction of a second frontal dipole source did not lead to a stable localization (replicable over several fitting procedures) or a substantial improvement of the explained variance.

This final dipole configuration was used for the 21
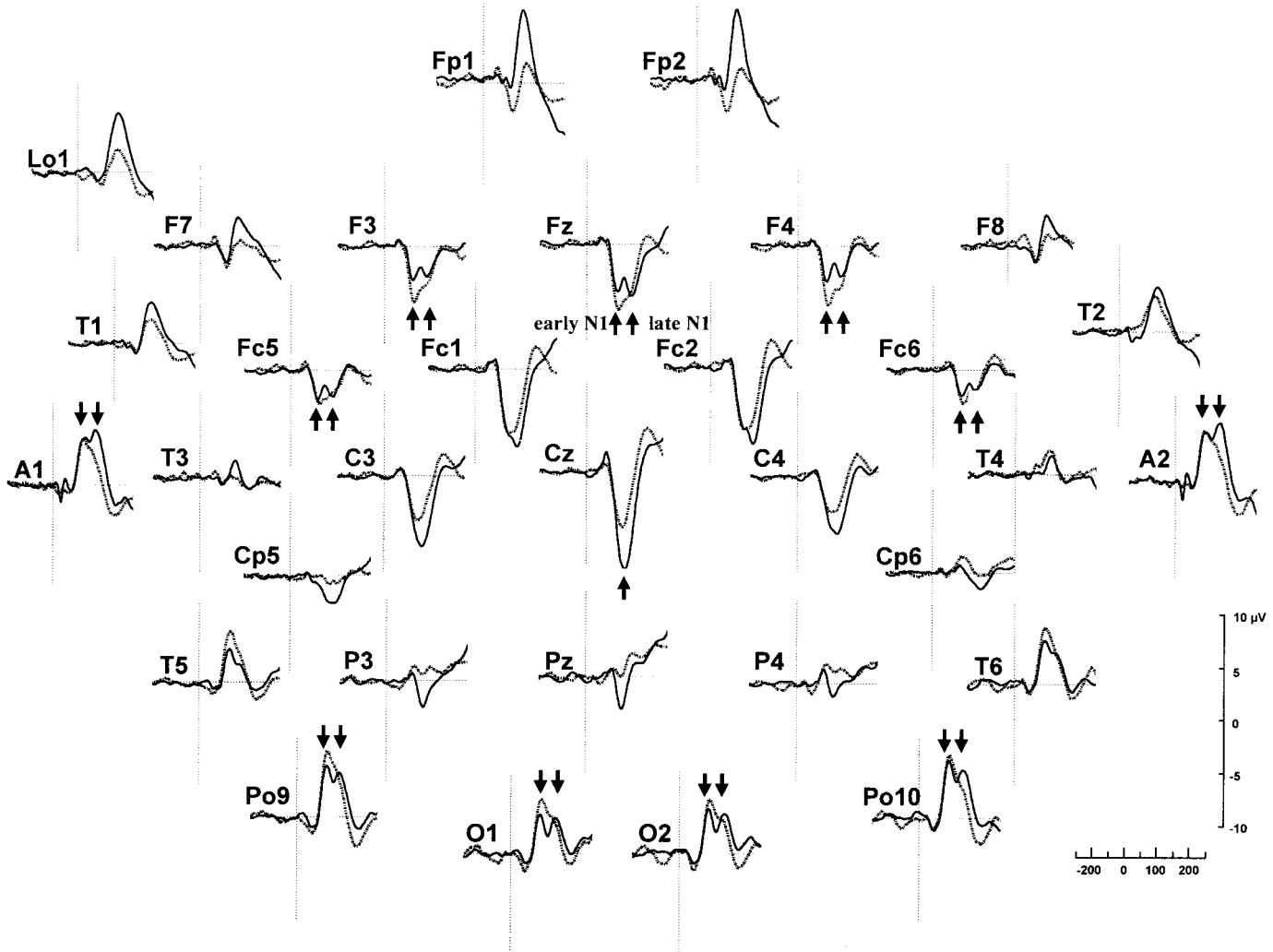
FIG. 2. Grand average curves (average reference) of 21 healthy controls (—) and 21 schizophrenic patients (– – –). The N1 component is indicated by arrows.

schizophrenic patients and the 21 matched controls. The unexplained variance of the model for the whole time range of the N1 activity (72–176 ms) was 4.3% for schizophrenic patients and 4.7% for the 21 healthy controls. The final dipole configuration was used for parametrization of the dipole source strength in every single subject (schizophrenic patients and healthy controls) without further adjusting the dipole localization or orientation.

Parametrization

Peaks and latencies at scalp electrodes. Latencies and amplitudes of the N1 scalp waves were determined at Cz and Fz based on an automatic peak detection (Brain Vision Analyzer Version 1.1) in combination with a visual control. The N1 was identified as the largest negative deflection occurring between 60 and 190 ms.

Peaks and latencies of dipole activity curves. In ev-

ery single subject the N1 dipole amplitudes and latencies were defined as the most negative points of the dipole activity (two temporal-tangential and two temporal-radial dipoles as well as one frontal dipole) in the N1 interval (60–190 ms). The amplitude of each dipole activity was measured in units of nano-ampere-meters (nAm). This unit is used for current * distance (Am) with respect to the dipole localization in the head model (Scherg and von Cramon, 1990). All determinations of N1 dipole source analysis, latency, and amplitude were performed in a blind manner with respect to diagnosis. All peak determinations were reviewed by an additional investigator and in the case of divergent peak determination a consensus was obtained.

Statistics

Statistical group comparisons of the N1 amplitude and latency were performed with Mann-Whitney U

TABLE 2

Peak Amplitudes of Dipole Source Curves (nAm ± Standard Deviation) and Scalp Potentials
(μV ± Standard Deviation) in Schizophrenic Patients and Controls

	Healthy controls	Schizophrenic patients	Mann-Whitney		
			z	df	P
Fz (μV)	−13.1 ± 4.8	−11.4 ± 6.7	−0.818	21	0.414
Cz (μV)	−16.1 ± 5.8	−10.3 ± 6.7	−2.679	21	**0.007**
1a Temp.-tangential left	−50.4 ± 26.7	−66.0 ± 38.0	−1.396	21	0.163
1b Temp.-tangential right	−54.3 ± 23.8	−71.0 ± 42.5	−1.220	21	0.222
2 Frontal-midline	−138.6 ± 56.1	−56.0 ± 56.2	−3.836	21	**0.00012**
3a Temp.-radial left	−40.2 ± 25.3	−25.5 ± 22.4	−2.277	21	**0.023**
3b Temp.-radial right	−34.1 ± 21.7	−22.7 ± 17.8	−1.597	21	0.110

Note. Significant *P* values are in bold.

tests. The relationship between dipole N1 amplitudes and psychopathology was analyzed by means of Spearman's rank correlation coefficient. All tests were performed with a 2-sided $P < 0.05$.

Current density analysis with LORETA was performed in the subsequent way: Following the recommendations of Picton *et al.* (1999), we used a statistical procedure in order to get information about the significance of sources. Therefore, we first performed a comparison of the event-related current density values with baseline values as voxel-by-voxel *t* tests (Holmes *et al.,* 1996). This "maximum *t* statistic" is a nonparametric analysis that offers after a procedure of randomizations (e.g., 5000 randomly created groups across conditions) a randomization distribution of the maximal statistic and will produce threshold values for single voxel *P*s. The consideration of a maximal statistic deals with the multiple-comparison problem. Let T_{max} be the maximum of the observed statistic image *T,* searched over the intracerebral voxels. If the omnibus null hypothesis H_Ω (no activation anywhere in the brain) is true, T_{max} is as likely as any of the randomization values. The probability (under H_Ω) of observing a statistic image with maximum intracerebral value as or more extreme than the observed value T_{max} is simply the proportion of randomization values greater than or equal to it. This gives a *P* value for the omnibus null hypothesis. This *P* value will be <0.05 if T_{max} is in the largest 5% of the randomization values, which *is the case* if and only if it is greater than the 95th percentile of the randomization values (Holmes *et al.,* 1996). We compared the electrical activity during the baseline (averaged 270 ms prestimulus) against the activated time frames, based on the log-transformed power of the estimated electric current density. We also measured the absolute current density values from the grand average as done by others (Pascual-Marqui, 1999). The time frames of interest were preselected on the basis of the expectations from the prior conventional ERP analysis.

Secondly, between-group comparisons (21 schizophrenic patients versus 21 controls) of the LORETA current density distribution were performed again using the same nonparametric statistical analysis based on voxel-by-voxel *t* tests. These calculations were based on the average waves of each subject (i.e., current source density).

RESULTS

Task Performance and Event-Related Activity

Mean reaction time differed significantly between normal controls (505 ± 161 ms) and schizophrenic patients (728 ± 301 ms; $z = -2.403$; $df = 21$; $P = 0.016$). In Fig. 2 the grand average curves (32 channels) of 21 normal subjects and 21 schizophrenic patients are presented. The N1 amplitude at Cz is significantly reduced in schizophrenics as compared to controls, while no group difference is observed at Fz (Table 2). At frontal (Fz, F3, F4, Fc1, Fc2) and basal electrodes (A1, A2, Po9, Po10, O1, O2) a characteristic double peak in both groups was observed. In schizophrenic patients the first N1 peak is equal to or even higher than the corresponding peak in healthy controls. The second peak, however, is reduced in patients as compared to controls. The early and late N1 peaks at the Fz electrode were chosen as landmarks for the time frames of the minimum-norm analyses. Note the reduced amplitudes of schizophrenic patients in the time range of the N1 at temporal electrodes, mainly on the left side.

Minimum-Norm Source Localization in Healthy Controls

The minimum-norm source localization was performed as a *t* test comparison of the prestimulus condition (the time frame from 270 to 250 ms before stimulus onset was chosen as baseline activity) to the time frame of the N1 peak (early N1; 90–110 ms, as well as

the late N1; 122–146 ms). For the early N1 peak the highest t values were located in the inferior parietal and superior temporal lobe on both sides (Fig. 3). In contrast, the analysis of the generator structure in the time frame of the late N1 component revealed a significant activity in the anterior gyrus cinguli as well as in the precentral cortex (left and right supplementary motor area; Brodmann area 6, Fig. 4). Significant activity was also observed in and near the auditory cortex on both sides (lower box Fig. 4).

Minimum-Norm Source Activity: Schizophrenic Patients versus Controls

A t map comparing healthy controls and schizophrenic patients was calculated for the early N1 (90–110 ms) and the late N1 (122–170 ms). For the time window 90–110 ms (early N1) after the tone no group differences were observed (highest t value in the interval 90–110 ms, −2.31; 1% P value threshold $t = -4.06$). In the second time window containing the late N1 peak, schizophrenic patients showed a pronounced activation deficit in the ACC as compared to controls (Fig. 5). No statistically significant group difference of absolute current density values in or near the auditory cortex was observed in the late N1 time frame (highest t value, −0.62; 1% P value threshold $t = -4.13$).

Spatio-Temporal Multiple Dipole Source Localization in Healthy Controls

The best fitting dipole solution in BESA was obtained using a previous developed dipole model of the N1 component elicited with an attention-free paradigm (Gallinat and Hegerl, 1994) together with an additional frontal dipole, which was introduced due to the results of the minimum-norm analysis in the present attention-related paradigm (see also Materials and Methods). Adjusting the dipole localization and orientation with an iterative fitting procedure led to the final solution (Fig. 6). The two temporal-tangential dipoles (1a and 1b) are located in the supratemporal plane of both hemispheres and are oriented toward the Fz electrode. The frontal dipole (2) is located in the anterior cingulate gyrus with an orientation toward the central/parietal midline area. The two temporal-radial dipoles of both hemispheres (3a and 3b) are located in the lateral temporal lobe and show a radial orientation toward the temples. The explained variance with the obtained solution in the time range of the N1 component was 95.3% for the 21 healthy subjects and 95.7% for the 21 schizophrenic patients (see also Materials and Methods).

Temporal Course of Dipole Source Activity in Healthy Subjects

The peak latencies of the scalp electrodes (Fz, Cz) as well as the dipole source activity are presented in Table 3. Comparing the time course of the 3 dipole sources, a characteristic sequence of three negative peaks was observed (Fig. 7; compare with mean latencies in Table 3). The first negative peak occurs at the temporal-tangential source (dipole 1a and 1b; Fig. 8) at 92 ms. About 30 ms later, the frontal source shows a prominent negative peak activity (dipole 2). The last negative peak can be observed another 20 ms later at the temporal-radial sources (3a and 3b) at about 140 ms. The dipole-latencies showed a statistical significant difference (Friedman test for mean latencies of left and right hemisphere in healthy controls, $\chi^2 = 13.238$; $df = 2$; $P < 0.001$; Wilcoxon test, tangential vs frontal-midline dipole $Z = -1.999$; $P = 0.046$; tangential vs radial dipoles $F = -3.250$; $P < 0.001$; frontal-midline vs radial dipoles $Z = -2.937$; $P = 0.003$). Note the similarity between the dipole peak latencies and the component latencies at the scalp electrodes (Fig. 7).

Dipole Source Activity in Schizophrenics and Controls

Comparing the dipole source activity, a pronounced and statistically significant deficit was observed in the peak amplitude of the frontal dipole source in schizophrenic patients as compared to healthy controls (Fig. 8; Table 2). With respect to the temporal-tangential dipole source, a slightly higher but not statistically significant peak activity can be seen in schizophrenic patients. The comparison of the temporal-radial peak activity at about 140 ms revealed a significant deficit in schizophrenic patients on the left side.

Dipole Source Activity and Psychopathology

Correlation analysis (Spearman rank correlation analysis) between the 5 dipole peak amplitudes and the PANSS-positive and -negative syndrome score revealed a significant negative correlation between the left-radial source and positive symptomatology (Table 4). Furthermore, the number of episodes correlated positively with the left radial ($r = 0.425$, $df = 21$, $P = 0.049$) and with the right tangential dipole activity ($r = 0.489$, $df = 21$, $P = 0.025$). No correlation between any dipole amplitude and the age of onset or duration of illness was observed.

DISCUSSION

A sample of 21 unmedicated and mainly first-episode schizophrenic patients was studied with an attention-requiring auditory choice reaction paradigm to investigate cortical signal processing with high temporal resolution. Two principally different source analysis methods revealed consistently a pronounced deficit of the anterior cingulate cortex in schizophrenic patients as compared to healthy controls. The analysis of the temporal lobe activity showed a significant deficit of the left-sided and radially oriented source activity in
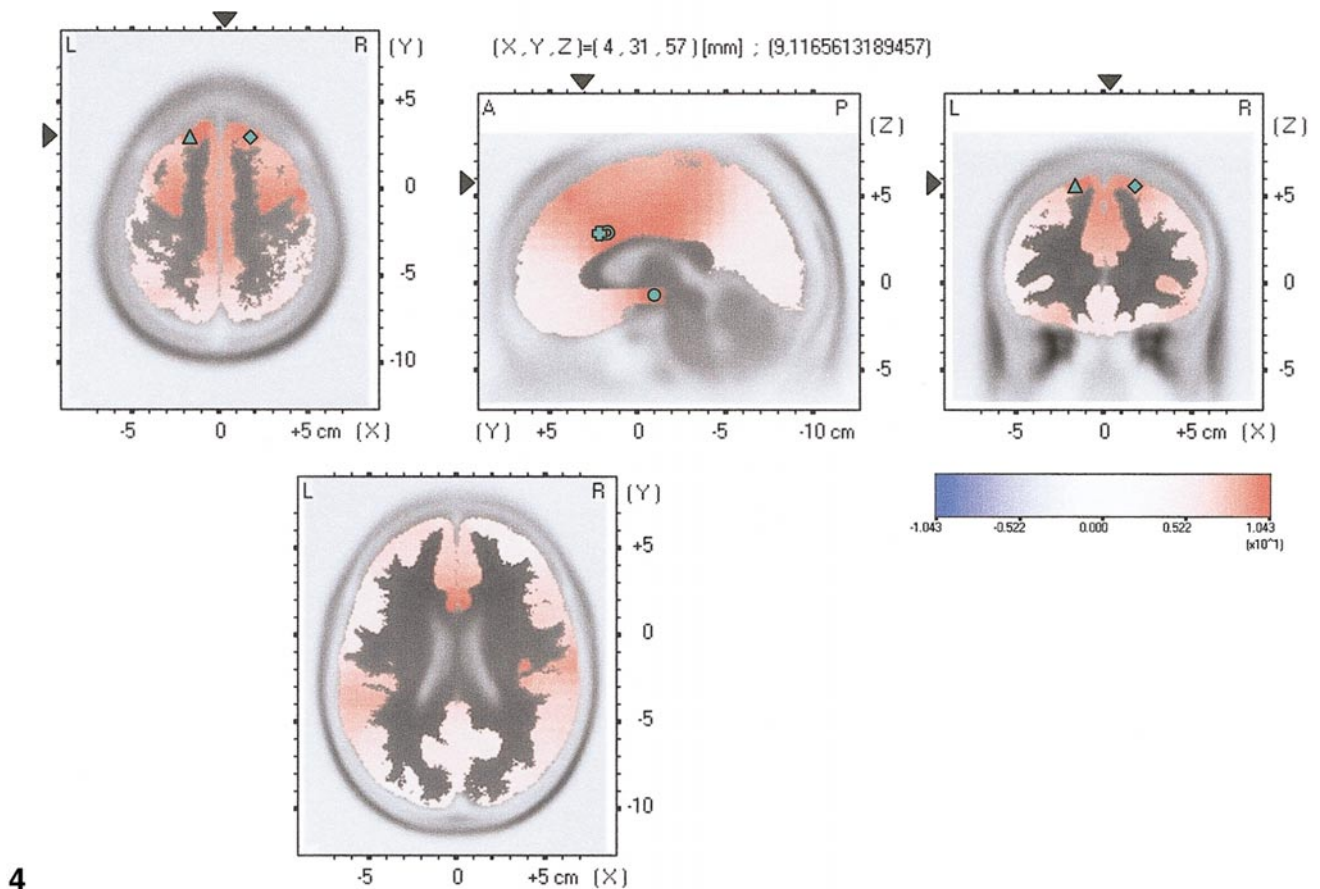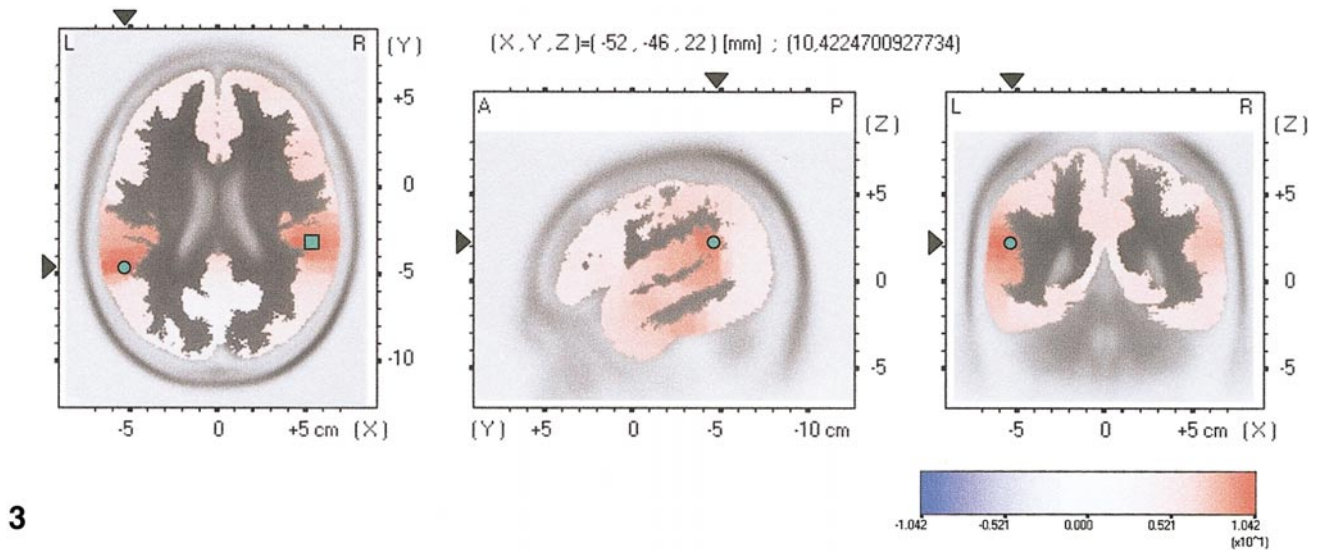
FIG. 3. Absolute current density maxima of normal controls ($n = 21$) at 90–110 ms poststimulus compared to prestimulus baseline activity (270–250 ms prestimulus). Red color indicates statistically significant more activity poststimulus. The maximum t values and their Talairach coordinates (x, y, z) are as follows: = 10.42 (−52, −46, 22; BA 40; inferior parietal lobe, green circle); = 10.17 (53, −32, 22; BA 13; insula, parietal lobe, green square); = 9.03 (−31, −25, 15; BA 13; insula, sublobar, not indicated); = 8.86 (39, −4, 1; BA 13; insula, sublobar, not indicated); = 8.86 (46, 3, 50; BA 6; middle frontal gyrus right, not indicated); 1% P value threshold: $t = 3.76$; exact P for maximum = 0.0002. t values below 5 are not indicated.

FIG. 4. Absolute current density maxima of normal controls ($n = 21$) at 122–146 ms poststimulus compared to prestimulus baseline activity. Red color indicates statistically significant more activity poststimulus. The maximum t values and their Talairach coordinates (x, y, z) are as follows: = 10.43 (−3, −11, −6; BA 25; anterior cingulum, green circle); = 10.18 (39, −18, 8; BA 13; BA 13, insula, temporal Lobe, not shown); = 10.02 (−17, 31, 57; BA 6; superior frontal gyrus, green triangle); = 10.02 (4, 17, 29; BA 24; cingulate gyrus, green cross); = 10.02 (−3, 17, 29; BA 24; cingulate gyrus, green ring); = 9.86 (18, 31, 57; BA 6; superior frontal gyrus, green rhomb); Additionally, the temporal cortex slice is presented in the lower box with significant t values in the area of the auditory cortex on both sides. A 1% P value threshold: $t = 3.73$; exact P for maximum = 0.0002. t values below 5 are not indicated.
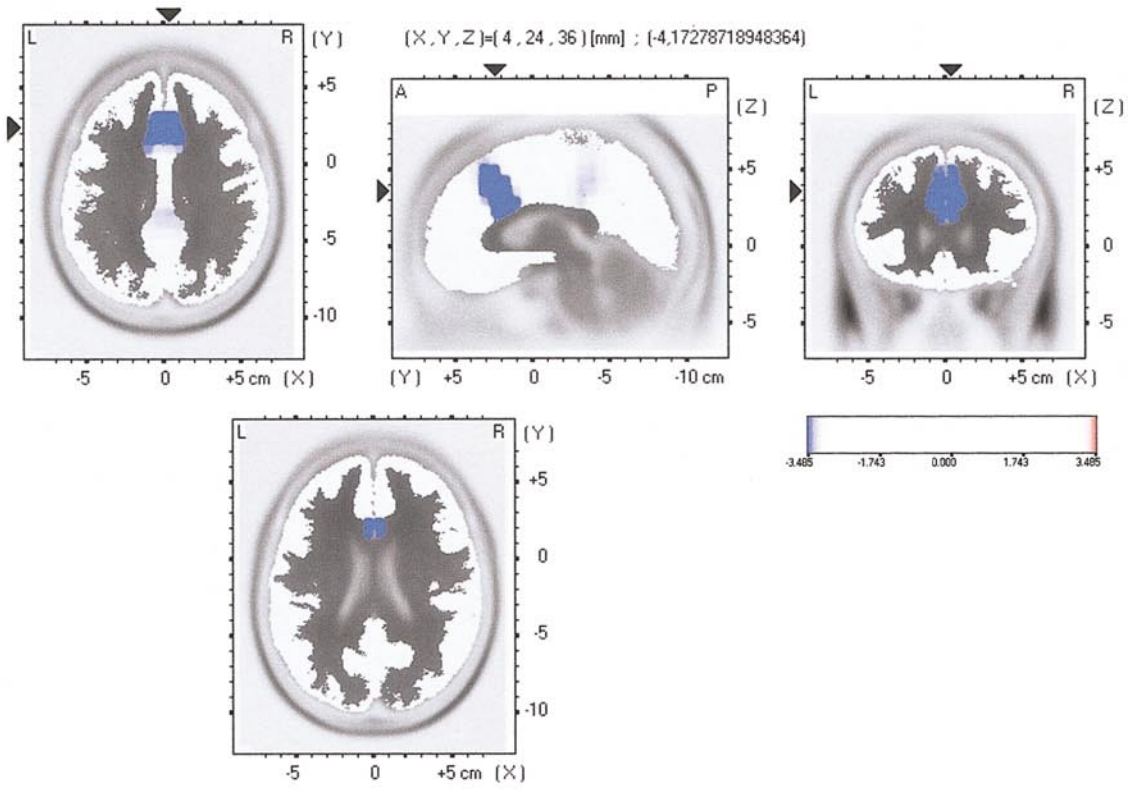
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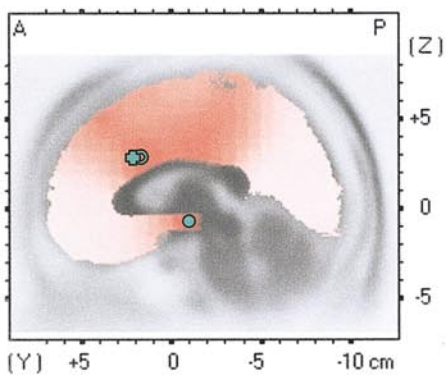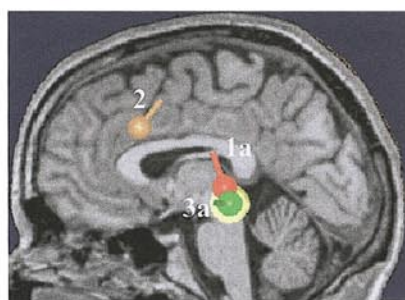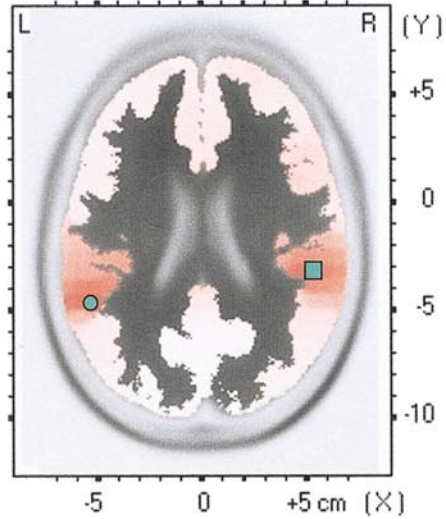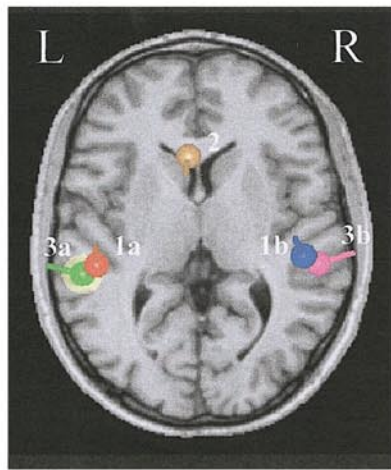
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TABLE 3

Peak Latencies of Dipole Source Curves and Scalp Potentials in Schizophrenic Patients
and Controls (ms ± Standard Deviation)

	Healthy controls	Schizophrenic patients	Mann-Whitney		
			z	df	P
Fz (μV)	122.5 ± 24.1	102.5 ± 13.4	−2.590	21	**0.010**
Cz (μV)	127.4 ± 13.6	108.0 ± 13.0	−3.842	21	**0.0001**
1a Temp.-tangential left	112.2 ± 24.5	101.8 ± 11.0	−0.667	21	0.505
1b Temp.-tangential right	115.5 ± 24.8	102.1 ± 15.1	−1.648	21	0.099
2 Frontal-midline	127.5 ± 11.3	130.9 ± 26.2	−0.516	21	0.606
3a Temp.-radial left	143.2 ± 19.8	136.3 ± 31.3	−0.314	21	0.753
3b Temp.-radial right	146.6 ± 24.0	143.7 ± 21.3	−0.340	21	0.734

Note. Significant *P* values are in bold.

schizophrenic patients, which was not observed in the minimum-norm solution. This source showed the latest poststimulus activity of all generators and is supposed to reflect stimulus processing of nonprimary auditory areas. Its activity was correlated to the positive symptomatology of schizophrenic psychopathology on the left side.

Primary Auditory Cortex

The minimum-norm source analysis located the early N1 component close to the superior temporal gyrus with the auditory cortex on both sides (Fig. 3). A very similar localization was revealed by the dipole analysis expressed as temporal-tangential-oriented dipole sources (dipoles 1a and 1b). The overall localization of the N1 activity is consistent with previous dipole source analyses (Gallinat and Hegerl, 1994; Gallinat *et al.,* 2000) intracerebral recordings (Halgren *et al.,* 1995; Celesia, 1976), and lesion studies (Woods *et al.,* 1987) which described the superior temporal and the inferior parietal lobe as main generators of the N1 component recorded at midline electrodes.

More specifically, the dipole sources provide information about the orientation as well as the time course of the active generators. The orientation of the temporal-tangential dipoles is in line with results from magnetencephalographic (MEG) investigations describing the activity of cortical areas to be almost perpendicular oriented to the sylvian fissure (Hari *et al.,* 1980; Elberling *et al.,* 1981; Nishitani *et al.,* 1998). This orientation is compatible with the anatomy of the primary auditory cortex covering most of Heschl's gyrus on the superior temporal plane projecting toward the frontocentral scalp (Morosan *et al.,* 2001; Pandya, 1995). Furthermore, the peak latency of the temporal-tangential dipole is in line with the peak latency described in the MEG investigations (between 90 and 100 ms) (Hari *et al.,* 1980; Elberling *et al.,* 1981) as well as intracerebral recordings in the primary auditory cortex (Halgren *et al.,* 1995). Therefore the temporal-tangential dipole is supposed to reflect activity of the primary auditory cortex representing the first negative activity in a sequence of further generators of the N1 component (see below). Interestingly, schizophrenic patients did not show a reduced amplitude of the temporal-tangential dipole sources as compared to controls. Their activity was found to be even higher but this was statistically not significant (Fig. 8). Therefore, the reduced amplitude of the N1 component at the Cz electrode is unlikely to be a consequence of impaired activity of the primary auditory cortex. Furthermore, the preserved activity of the tangential source in schizophrenic patients indicates that the hypothesized deficit of the amplification effect of attention on sensory cortical areas does not influence the primary auditory cortex.

Anterior Cingulate and Precentral Cortex

In the time range of the late N1 component, a completely different activation pattern was found with

FIG. 5. Group comparison of absolute current density values between schizophrenic patients and healthy controls in the time range 122–170 ms: Blue color indicates less activity in the schizophrenic group. The maximum *t* values and their Talairach coordinates (*x, y, z*) are −4.17 (11, 24, 36) and −4.17 (4, 24, 36), both BA 32, cingulate gyrus, frontal lobe. Additionally, the temporal cortex slice is presented in the lower box. No significant *t* values in the area of the auditory cortex were observed. The 1% P value threshold is *t* = −4.13; exact *P* for minimum = 0.009.

FIG. 6. Final dipole configuration of the N1 component projected on a standard MRI head. The minimum-norm solutions for the early (right top) and late (right bottom) N1 component are presented for comparison. The frontal-midline dipole shows a similar location as compared to the minimum-norm solution. The temporal dipoles (tangential 1a/b and radial 3a/b) show a slightly more caudal localization as compared to the LORETA solution. The Talairach coordinates of the dipole locations are not applicable.
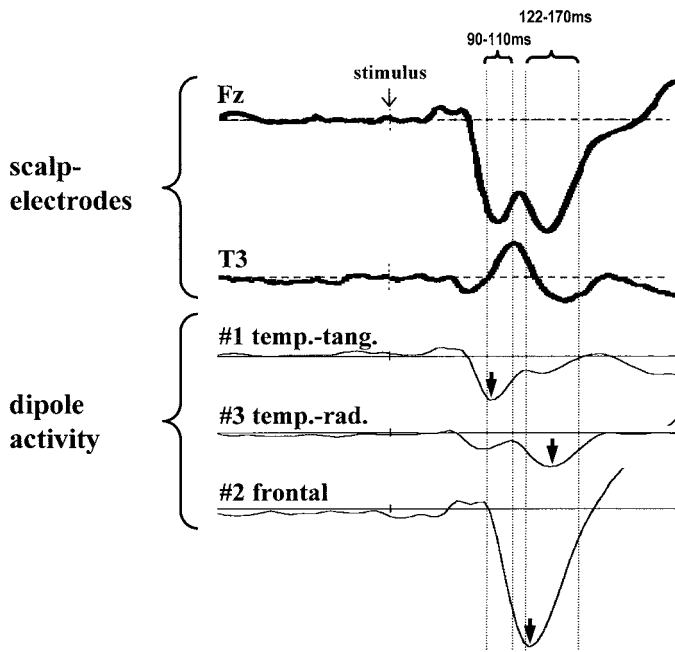
FIG. 7. Comparison of the scalp measured grand average data (midline located Fz and temporal located T3 electrode) and dipole source activity in 21 healthy controls. Note the similar latency of the early N1 component at Fz and the temporal-tangential dipole source activity. Furthermore, the peak latency of the late N1 component is similar to the peak latency of the frontal dipole activity. The negative peak at the temporal T3 electrode (at about 156 ms) is similar to the negative deflection at the temporal-radial dipole. The radial dipole activity cannot contribute to midline electrodes (e.g., Fz) because of the lateral orientation toward the temples. Arrows indicate the peak activity of each dipole source in the grand average.

both localization methods as compared to the early N1 component. The minimum-norm solution showed a significant activation (as compared to the prestimulus time) in the anterior cingulate cortex (BA 25 and 24) in healthy subjects (Fig. 4). Consistent with this result, the dipole source analysis for the whole N1 time frame revealed a frontal-midline source with a location just above the corpus callosum in the anterior cingulate gyrus (see Fig. 6). The location of the dipole seems to reflect the center of gravity of the blurred activity shown in the minimum-norm solution. The frontal-midline source showed the most pronounced activity of all dipoles with a peak latency later than the temporal-tangential dipole sources. The localization of this source fits well with recent microelectrode recordings in the human ACC showing direct evidence for a modulation of single neuron firing during attention-demanding tasks (Davis et al., 2000). Furthermore, the localization is in line with the activity observed in imaging studies employing attention-requiring tasks in the auditory (Tzourio et al., 1997; Ohyama et al., 1993) as well as visual modality (Pardo et al., 1990; Bench et al., 1993). In the present investigation the activity of the ACC was found to be reduced in schizo-

phrenic patients as compared to healthy controls. This was observed in the minimum-norm solution as well as with dipole source analysis and is in good agreement with the results of our previous investigation (Mulert et al., 2001) employing only the minimum-norm solution. The present dipole source analysis showed that the main activity of the ACC is oriented toward the vertex and parietal regions. This suggests that the reduced N1 amplitude in schizophrenic patients measured at the Cz electrode and reported by others (Ward et al., 1991; Michie et al., 1990) is a consequence of an impaired activity of the ACC.

A further generator of the late N1 component was revealed by the minimum-norm solution, namely in the precentral cortex and BA 6 bilaterally (Fig. 4). This was not observed in our previous investigation employing the same choice reaction paradigm, which may be due to the lower density of electrodes. Neuroimaging studies described an activation of BA 6 including the supplementary motor area (SMA) in simple reaction tasks with the requirement to press a button as in our paradigm (Naito et al., 2000) but also during auditory listening tasks without any motor reaction (Tzourio et al., 1997) and a visual choice reaction task (Winterer et al., 2001). Therefore, it was suggested that this regional activation is part of the anterior attentional network and a correlate of a precentral generator of the N1 component (Tzourio et al., 1997). Evidence for a generation of the N1 in the motor and premotor cortex was found in intracranial recordings in monkeys (Arezzo et al., 1975; Steinschneider et al., 1980). Our attempt to model this activity by an equivalent dipole did not result in an unequivocal localization or delimiting activity pattern as also described by others (Picton et al., 1999). This may be due to a multiorientation of this generator, which would be difficult to model by an equivalent dipole. However, the present results suggest that a more comprehensive modeling of such activity seems to be possible with the minimum-norm principle. With respect to schizophrenic patients, no evidence for a deficit activation of the precentral generator was found, which is in conflict to a recent PET study (Holcomb et al., 2000). Since a more difficult task was employed in the PET investigation as compared to ours, the different results may be explained by this methodological aspect.

Nonprimary Auditory Cortex

The most characteristic feature of the temporal-radial dipole—a third dipole generator in the N1 time range—is a late peak latency as compared to the temporal-tangential and the frontal-midline source (Fig. 8). Its peak latency of about 140 ms corresponds to a negative component which has been frequently reported to occur at temporal electrodes after auditory stimulation (Wolpaw and Penry, 1975; Giard et al.,
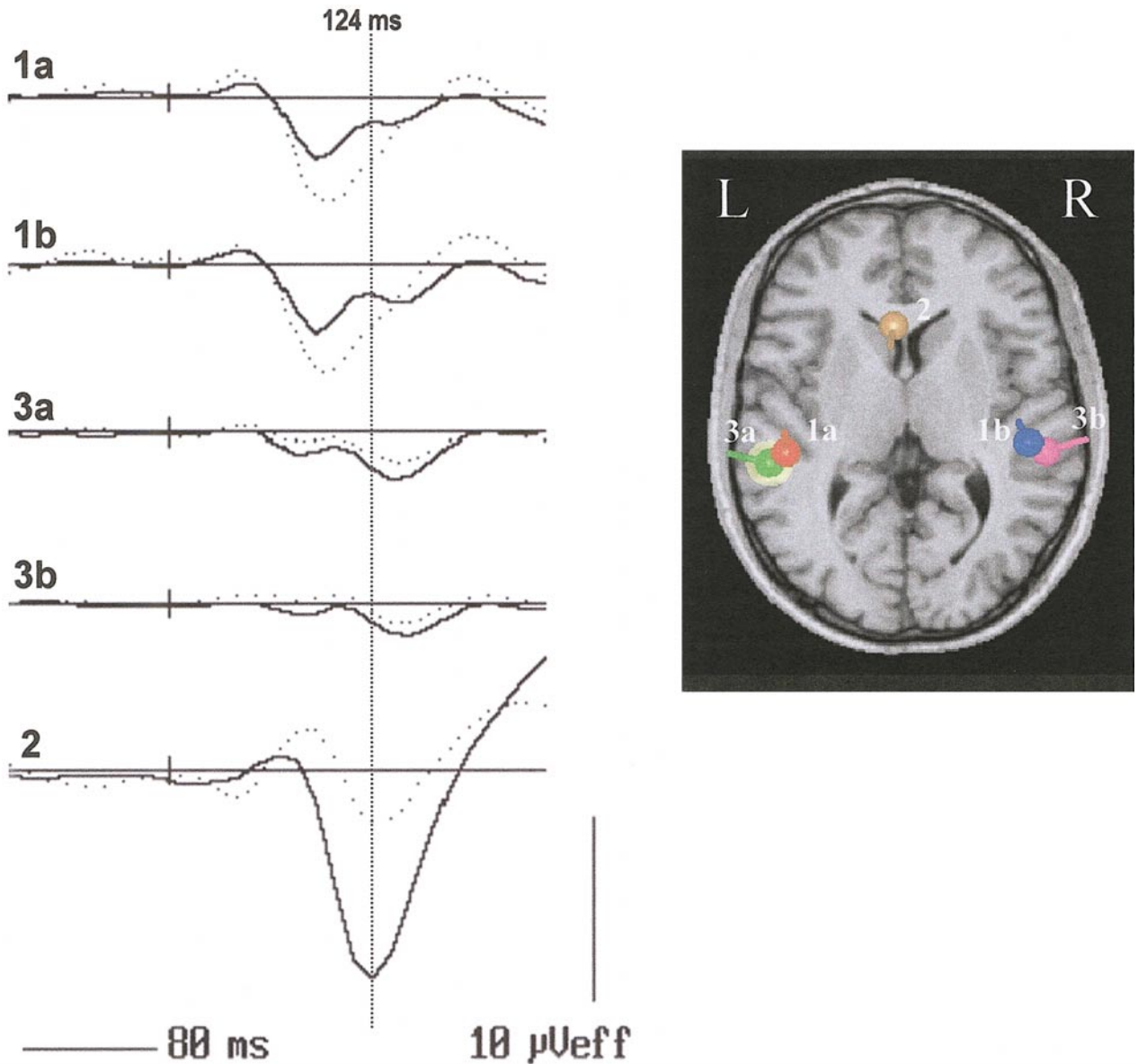
FIG. 8. Dipole source activity of healthy controls (—) and schizophrenic patients (– – –) in the N1 time frame. Significant reduced peak amplitudes in schizophrenic patients were found for the frontal-midline source and the left temporal-radial source.

1994; Picton *et al.,* 1999). Furthermore, the radial orientation of the dipole indicates cortical activity of areas lateral of the primary auditory cortex reaching over the lateral cunt of the superior temporal gyrus (Pandya and Sanides, 1973; Woolsey and Walzl, 1982) (compare Fig. 1). In recent years, several studies have shed light on the auditory cortex covering the superior temporal plane: The medial part of the transverse temporal gyrus of Heschl (HG) is commonly considered the anatomical locus of primary auditory cortex (Liegeois-Chauvel *et al.,* 1991; Penhune *et al.,* 1996). HG separates the supratemporal plane into a rostral (planum polare) and caudal part (planum temporale) (Morosan *et al.,* 2001). A recent quantitative observer-

independent cytoarchitectonic analysis in humans identified three koniocortical areas (Te1.1, Te1.0, and Te1.2) along the mediolateral axis of the Heschl gyrus, representing the (functionally defined) primary auditory cortex, similar to Brodmann's area 41 (Brodmann, 1909) and von Economo's and Koskina's areas TC and TD (Economo and Koskinas, 1925). This koniocortical core field (Te1) is surrounded by belt areas of prokoniocortex on the superior temporal plane and superior temporal gyrus including the planum temporale and planum polare (Galaburda and Sanides, 1980; Rademacher *et al.,* 2001). Classical architectonic studies of the STG have effectively treated this region as a single cortical entity, notably area 22 (Brodman,

TABLE 4

Spearman Rank Correlation between Peak Activity of Dipole Source Curves (nAm)
and the PANSS Scores in Schizophrenic Patients

	PANSS positive			PANSS negative		
	r	df	p	r	df	p
1a Temp.-tangential left	−0.337	21	0.135	−0.286	21	0.208
1b Temp.-tangential right	−0.209	21	0.362	−0.199	21	0.388
2 Frontal-midline	0.034	21	0.884	0.366	21	0.103
3a Temp.-radial left	−0.450	21	**0.041**	−0.180	21	0.434
3b Temp.-radial right	−0.374	21	0.095	0.053	21	0.820

Note. Significant *P* values are in bold.

1909), but several architectonic subregions have been identified (Pandya and Sanides, 1973; Galaburda and Pandya, 1983; Pandya, 1995). These regions are considered as auditory association cortex (Knight *et al.,* 1988; Hocherman *et al.,* 1976; Ohyama *et al.,* 1993) or secondary auditory cortex (Liegeois-Chauvel *et al.,* 1994; Belin *et al.,* 1999). Because no consensus exists with respect to the nomenclature and physiology of these regions we prefer the more neutral term nonprimary auditory cortex which has been proposed previously (Morosan *et al.,* 2001).

There is good evidence from intracerebral recordings in monkeys (Arezzo *et al.,* 1975) and humans (Liegeois-Chauvel *et al.,* 1994, 2001; Celesia, 1976) that the nonprimary auditory areas surrounding the primary auditory cortex generate an AEP component with a prolonged latency (about 140 ms) and a more lateral topography as compared to the primary auditory cortex response. We therefore treat the activity of the temporal-radial dipole in the latency range of 140 ms as response of nonprimary auditory areas.

On the left side, a significantly reduced peak amplitude of the temporal-radial source was observed in schizophrenic patients as compared to controls, suggesting an impaired activity of the left nonprimary auditory cortex during auditory signal processing. A left-sided amplitude reduction of the N1 component in schizophrenic patients compared to controls was shown in an AEP investigation requiring attention (Saitoh *et al.,* 1983). This is in line with the assumption of an impaired amplification or synchronization effect in this particular sensory area due to disturbed attention. It is noticeable that the activity of the primary auditory cortex, represented by the temporal-tangential dipole, is not impaired in schizophrenia. This may suggest that the primary and nonprimary auditory cortex underlay a differently modulation by attention. Compatible with this, it was reported in monkeys that attention to an auditory stimulus increased the firing rates of more neurons in the auditory association cortex than in the primary auditory cortex (Hocherman *et al.,* 1976) and other evidence from studies in rats suggests that the activity of both areas might be independent from each other due to parallel thalamo-cortical activation (Barth *et al.,* 1993; Di and Barth, 1992). Imaging studies reported a greater activation of the bilateral associate auditory cortex as compared to the primary auditory cortex when attention is directed to the stimuli (Ohyama *et al.,* 1993; Grady *et al.,* 1997). Moreover, other imaging studies of auditory signal processing suggest a lateralization of that attention-related temporal cortex activation (Jancke *et al.,* 1999; Tzourio *et al.,* 1997; Higashima *et al.,* 2000) which may explain the predominant left-sided deficit of the schizophrenic patients.

However, a PET study of schizophrenic patients failed to find an activation deficit in the auditory cortex activity as compared to controls employing a tone discrimination task similar to ours (Holcomb *et al.,* 2000). One explanation for the discrepant results of electrophysiological and imaging techniques may be a different representation of neuronal activity. For instance, attention to a stimulus was found to enhance neuronal synchronization rather than neuronal firing rate in sensory areas that are involved in stimulus-processing (Steinmetz *et al.,* 2000; Fries *et al.,* 2001; Moran and Desimone, 1985). It is possible that a change in synchronization affect evoked potential amplitudes more than parameters obtained with neuroimaging techniques (Chawla *et al.,* 1999; Logothetis *et al.,* 2001). In fact, from a prior electrophysiological study of schizophrenic patients (Winterer *et al.,* 2000), we have obtained evidence that schizophrenic patients are unable to increase neuronal synchronization in the temporal lobe area during an attention-requiring auditory choice reaction task, which is compatible with a reduced evoked activity in the present data.

Generator Activity and Schizophrenic Psychopathology

A significant negative correlation between the left radial source activity and the PANSS-positive score was seen, while none of the other dipole amplitudes showed a significant correlation with psychopathology.

The results support the view that schizophrenic-positive symptomatology is associated with a temporal lobe dysfunction and more specifically, with an impaired function of the nonprimary auditory cortex. Because positive symptomatology and behavioral disorganization were shown to be related to attentional deficits in schizophrenia (Liddle *et al.,* 1992; Liddle and Morris, 1991; Green and Walker, 1986), the present results do support the view that the nonprimary auditory cortex is modulated by attention. However, the negative correlation indicates a higher amplitude (more negative) in patients with pronounced positive symptoms and vice versa. Assuming a disturbed cortical synchronization, which per se is associated with reduced AEP amplitudes (Winterer *et al.,* 2000), the correlation can be explained by a higher overall activity of the nonprimary auditory areas when positive symptoms are present. This assumption is supported by neuroimaging studies in schizophrenic patients indicating a higher activity in the auditory cortex, predominantly on the left side, when patients experience hallucinations (Shergill *et al.,* 2001; Lennox *et al.,* 2000; Dierks *et al.,* 1999; David *et al.,* 1996; Suzuki *et al.,* 1993). This increased activity during hallucinations and presumably other positive symptoms may lead to a relative enhancement of the temporal-radial dipole activity as compared to patients with only mild positive symptoms, but due to a disturbed synchronization the dipole activity may be reduced as compared to healthy controls.

One might speculate that attention may represent the synchronization effect of frontal brain areas on the temporal cortex. However, in this case a correlation between the activity of the ACC and positive symptomatology would be expected, which was not observed in the present data. The frontal dipole activity showed a correlation with the negative syndrome score, which, however, did not reach significance ($r = 0.366$, $P = 0.103$). These results may indicate a more complex relationship between schizophrenic psychopathology and generator activity during an attention-requiring paradigm. Such a complexity was stressed previously and some evidence indicates the existence of at least two attention networks involved in auditory stimulus processing, namely a frontal network including the ACC and a local network involving the temporal cortex (Tzourio *et al.,* 1997).

Methodological Considerations and Conclusion

The source analysis of the N1 component evoked in an attention-requiring listening paradigm provides evidence for a characteristic sequence of generator activity in the order (1) primary auditory cortex, (2) anterior cingulate cortex, and (3) nonprimary auditory cortex. This time pattern of activation is in line with intracranial recordings showing a sequential activation of the auditory and cingulate cortex (Baudena *et al.,* 1995). Both source analysis methods showed a similar localization of these major generators of the scalp measured N1 component and provided evidence for a dysfunction of the anterior cingulate cortex in schizophrenia. Therefore, the present study replicates and extends the results of our previous investigation and suggests the ACC deficit in schizophrenia to be a robust electrophysiological finding which is in line with several imaging studies in schizophrenia (see the introduction). The dipole source analysis also provided evidence for a dysfunction of the left nonprimary auditory cortex, which is compatible with the notion that impaired cortical activation in schizophrenia in the context of attention deficits involves an extended network that encompasses the ACC and sensory association cortices. However, the temporal lobe deficit was not observed with the minimum-norm approach. The different results are supposedly based on the principal difference of both source localization approaches: The dipole analysis more strongly utilizes information about the orientation of generator activity which allow—in the case of orthogonally oriented generators—a separation of activity. Furthermore, the differentiation of closely located generators in the minimum-norm approach may be impaired by the smoothness constraint which ensures that currents change little between adjacent regions of the brain (Pascual-Marqui *et al.,* 1994). On the other hand, the strength of the minimum-norm approach is the better representation of widely distributed or multiple-oriented activity, which is difficult to model with single dipoles. Therefore, combining both methods improves the knowledge about the number and orientation as well as activity course of cerebral generators.

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