Spontaneous, slow and fast magnetoencephalographic activity in patients with schizophrenia

W. Sperling a,*, P. Martus b, H. Kober c, S. Bleich a, J. Kornhuber a

a Department of Psychiatry and Psychotherapy of Friedrich Alexander University of Erlangen–Nuremberg, Schwabachanlage 6-10, 91054 Erlangen, Germany
b Department of Medical Statistics of Free University of Berlin, Berlin, Germany
c Department of Neurosurgery of the University of Erlangen–Nuremberg, Germany

Received 22 October 2001; accepted 8 February 2002

Abstract

A 2*37 channel biomagnetic system (Magnes II) was used to record spontaneous magnetic activity for the frequency ranges 2–6 Hz and 12.5–30 Hz in 30 patients with schizophrenia (23 men and 17 women) and 30 healthy volunteers in both hemispheres during a resting condition. The dipole localization was calculated by the dipole density plot (DDP) method, which is a spatial averaging in order to decrease the influence of the nonfocal activity. The quantified DDP results were superimposed to T2-weighted MR-images of each patient’s head as isocontour lines. To superimpose the MEG results to 3-D MRI data, the scanned head data set was fitted to the reconstructed MRI head shape using a surface fit programme developed by our department. The absolute dipole values were correlated with the psychopathological findings and the cumulative neuroleptic dosage for each patient. The group of patients with schizophrenia differed overall from the healthy subjects in the elevation of absolute dipole values measured in both hemispheres. For the region of slow dipole activity (2–6 Hz), a high correlation was found between the intensity of dipole concentration and productive psychotic symptoms (PANSS, P1–P7). Dipole localization (for both frequency ranges) showed a concentration effect (DCE) in the temporoparietal region in patients with schizophrenia. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Magnetoencephalography; Schizophrenia; Dipole density plot; Dipole concentration effect

1. Introduction

A growing body of research suggests that schizophrenia is associated with structural and metabolic brain abnormalities. Increased delta wave activity in patients with schizophrenia was reported in EEG measurements before neuroleptics became available (Hoagland et al., 1937; Gibbs et al., 1938). These findings were consistent with topographic EEG measurements in unmedicated or drug naive patients with schizophrenia. Analyses of correlation between delta activity and the neuroleptic dosage were negative (Takeuchi et al., 1994). All these findings suggest that increased delta activity in schizophrenia may reflect underlying pathogenetic factors. Several researchers have reported that dysfunction in the diencephalic structures, including the thalamus and hypothalamus, produced diffuse polymorphic delta...
wave activity on the scalp (Gloor et al., 1977; Hirose et al., 1981).

In addition, a positive correlation between the area of the third ventricle (enlargement) and the EEG power ratio of the delta frequency bands was interpreted as a possible dysfunction of diencephalic structures associated with morphological abnormalities in schizophrenia (Takeuchi et al., 1994). However, the association of EEG activity with underlying anatomical structures is hypothetical, because it has not yet been elucidated how many dipoles contribute to electrical fields measured on the skull.

Diffuse Delta EEG (DDA) in patients with schizophrenia was also investigated from the perspective of a subtype specific analysis. Matsuura and Yoshino (1994) found that the disorganized type was frequent in the DDA group, while the residual type showed no differences to healthy controls. In topographic EEG studies patients with schizophrenia showed more delta wave activity in the right parietooccipital region than normal controls. Alpha-2 wave activity was reduced in the entire region in patients with schizophrenia (Takeuchi et al., 1994). In the context of cerebral mapping technologies, the EEG continues to provide unique information techniques on understanding brain dysfunction in schizophrenia.

Recent EEG studies also indicated that gamma-range (30–50 Hz) may be a key mechanism of information processing in neural networks and indexes cognitive activation in a complex way (Tallon-Baudry et al., 1995; Gruber et al., 1999). For example, gamma synchronization may be involved in the perception of a complex object, which requires integration of many features (e.g. luminance, color, texture, contours), which are analysed by discrete neurons or neural systems in the brain. The synchronization of the EEG with different rates of auditory stimulation (i.e. clicks at 20, 30 and 40 Hz) revealed at 20 and 30 Hz similar waveforms in patients with schizophrenia and controls (Kwon et al., 1999). At 40 Hz, however, the groups differed in the predicted manner. Controls continued to show a synchronized EEG waveform with most of the power at 40 Hz. In contrast, the EEGs of the patients were less synchronized and the power spectra revealed almost equal power at 20 and 40 Hz. Scalp-EEG and the new method of magnetoencephalography (MEG) yield both complementary and confirmatory information and both have a high resolution, which cannot be reached by other techniques.

While scalp-EEG detects both tangential and radial sources, i.e. activity in the sulci and gyri, MEG selectively measures tangential sources, i.e. activity in the sulci. Scalp-EEG measures extracellular volume currents and MEG primarily intracellular currents. Finally, the spatial resolution of MEG is about 1/3 better than that of scalp-EEG. Furthermore, the magnetic fields are not distorted by the different conductivities of the scalp as in the case with EEG. With multichannel SQUID magnetometers, field patterns can be obtained and source localizations determined even with a “single shot” measurement without repositioning the instrument, thus opening up new possibilities for clinical psychiatric applications as well as for studies of the neural basis of cognitive functions.

MEG studies in patients with schizophrenia were mainly based on acoustically evoked fields. They showed dipole abnormalities and significant differences in dipole orientations in the left hemisphere, specifically in male patients (Sauer et al., 1998). Spontaneous MEG activity without external stimulation has also been investigated in patients with schizophrenia. Canive et al. (1996) described lower MEG alpha power and peak frequencies in schizophrenia than in controls. Sperling et al. (1997) found a significant increase in the spontaneous beta-wave activity in the temporoparietal region over both hemispheres in patients with acoustic hallucinations. MEG gamma band activity was also investigated in patients with schizophrenia and healthy controls in mental arithmetic tasks (Kissler et al., 2000). Healthy subjects showed a left frontal and left frontotemporal increase of the gamma power. Patients with schizophrenia failed to display such a task effect or had reversed lateralization. The influence of neuroleptics on spontaneous magnetic activity has also been investigated. The increases in MEG-beta activity (12.5–30 Hz), which was found in patients treated with the atypical neuroleptic clozapine, could not be detected either in healthy subjects nor in haloperidol-treated patients with schizophrenia (Sperling et al., 1999). The possibility that these beta peaks resulted from the specific medication with the atypical neuroleptic cannot be ruled out. So far, the spontaneous magnetoencephalogram (MEG) has not been investigated in depth in
either normal subjects or psychiatric patients (i.e. schizophrenics), specifically in the frequency range 0–6 Hz.

In this context, we used the new development of the simultaneous recording technique of multi-channel MEG/EEG fused with 2-D MRI slices to investigate patients with schizophrenia in the frequency ranges 0–30 under the specific auspices of a variance analysis with respect to intervening parameters of the disease (e.g. psychopathological findings, medication).

2. Methods

Spontaneous magnetic brain activity was measured in a magnetically shielded room, using a 2*37 channel biomagnetic system (Magnes II, Biomagnetic Technologies, San Diego, CA). This twin sensor system comprises the gradiometer systems for sensor A, which records the spontaneous magnetoencephalographic activity of the left hemisphere and sensor B, which records the spontaneous activity of the right hemisphere. The patient lies on a bed with the head fixed between the two MEG dewars with monitoring of electrocardiogram (ECG). One dewar with 37 channels covered the left hemisphere (sensor A) while the other was on the right hemisphere (sensor B). The distance between sensor A and the left hemisphere was kept below 0.5 cm so as not to produce any attenuation of the signals vis-a-vis sensor B applied to the right hemisphere. The total examination time was about 30 min and included the time for head scanning and the reduction of artefacts by exact adjustment of both sensors to the hemispheres. After acquisition, the data was notchfiltered digitally at 50 Hz and the magnetic noise of the heart beat was removed by subtraction of ECG signals.

The processed data was digitally filtered using a 2–6-Hz bandpass filter with a steep roll-off (slope of 40 dB/Hz and flat form 2–6 Hz) or 12.5–30-Hz bandpass filter with a steep roll-off (slope of 40 dB/Hz and a flat from 12.5 to 30 Hz) for the analysis of slow and fast wave activities, respectively. After the single equivalent current dipole estimation, the only dipoles having a signal-to-noise ratio higher than 2 and a minimum correlation value of 0.8 were accepted. The spatial distribution of dipoles was determined by a 3-D convolution with a Gaussian envelope. The variance considered the localization uncertainty of the dipole density plotting (DDP) method (Kober and Vieth, 1992) The DDP method uses consecutively estimated dipoles across an artefact-free period of 10 s and delivers quantified dipole concentrations in three dimensions, which can be adjusted exactly to individual slices of the imaging techniques. In order to minimize the influence of simultaneous active multiple sources, we applied two different procedures.

(1) Before using the time consuming consecutive dipole estimation, only those signals will be automatically selected for the analysis, where the strongest component dominates the measured signal, i.e. where predominantly one source is active (Kober and Vieth), 1992. This selection will be done by using the principal component analysis (PCA). The customized programme of PCA automatically identifies the number of components and the contribution of each component to the signal for each time section and creates a file of total selection time ($T_{\text{total}}$), where only one component of interest was predominantly active (typically more than 90%). Data matrices of overlapping time sections were analysed with the PCA. The length of the time sections was adjusted to the frequency range of interest: 150 and 30 ms for slow and beta waves, respectively. Only time sections with one predominant component were analysed using the single equivalent current dipole model (ECD). As a measure of dominance, we used the percentage of variance of the MEG signal, explained by the strongest singular value. This percentage threshold was individually chosen to extract a minimum of 10 s for dipole

---

1 The advantage of a whole head magnetometer is the possibility of simultaneous recording of both hemispheres with a unique gradiometer system. This system will be available in Erlangen in the year 2002.
localization yielding typical values of between 94% and 98%.

(2) We used the correlation value to access the quality of the dipole fit, which is calculated as the correlation coefficient between measured and theoretical (dipole) magnetic field distribution. Another measure for the dipole fit quality would be the goodness of fit (GoF) value. Although there is no exact relationship between the two measures, in general the goodness of fit values are slightly higher than the correlation values of corresponding dipole fits. A minimal correlation value of $r > 0.8$ between the ECD model and the measured field would correspond to a goodness of fit value of approximately $>0.9$. The spatial distribution of dipoles was determined by a 3-D convolution with a Gaussian envelope. The variance took into account the localization uncertainty of the dipole density plotting (DDP) method. The quantified DDP result was superimposed to T2-weighted MR-images of each patient’s head as isocontour lines. Before each MEG measurement, the accessible surfaces of the subject’s head were scanned by an electromagnetic digitizer (Isotrak 3-D digitizer, Polhemus Navigation Sciences, Colchester, VT) that was directly connected to the dewar containing the MEG sensors. 3-D MRI of the whole head was reconstructed, using a simple edge-detection algorithm. To superimpose the MEG results to 3-D MRI data, the scanned head surface data set was fitted to the reconstructed MRI head shape using a surface fit program developed by our department. For the fitting process, we optimized six transformation parameters (three translation coordinates and three rotation angles); the scaling factors (pixel size and slice distance) were read from the image header information. The sum of the squares of the distances between the points of the scanned head surface and the reconstructed MRI head shape was minimized using the Powell algorithm. The accuracy of this transformation was verified as being 2 mm. Within the framework of the dipole analysis, the following parameters were established:

1. The total length in time of the segments which were determined from the MEG
2. The number of dipoles for slow and fast frequencies picked up by sensor A and sensor B: $D_{\text{total}}$
3. The maximum dipole density: $D_{\text{max}}$
4. The absolute dipole density as a quotient obtained from $D_{\text{max}}$ and $T_{\text{total}}$
5. The relative dipole density as a quotient obtained from $D_{\text{max}}$ and $D_{\text{total}}$
6. The dipole localization for slow (2–6 Hz) and fast activity frequencies (12.5–30 Hz).

Two control EEGs were performed on each patient and control subject before the first and second MEG measurements. The EEGs, recorded using the 10–20 system, were interpreted blind to subject, group assignment, and time in study by a board-certified clinical electroencephalographer. Frequency, amplitude, symmetry and regularity of background activity were listed. Disturbances were registered with regard to their phenotype, their localization and their frequency. The visual blocking reaction of the background activity and changes after activation in the form of hyperventilation were also rated. We used the classical criteria for abnormality detailed in Kugler et al. (1981), in which grades of diffuse slowing “slight” (some $\theta$-waves of 6–7 cps predominantly anterior = “irregular alpha”), “moderate” ($\theta$-waves of 4–7 dominating both in amplitude and occurrence the $\alpha$-rhythm, which is slowed down to 7–8 cps), “severe” (dominating—$\delta$-activity of 1–4 cps in all electrodes, no or almost no $\alpha$-rhythms preserved) are distinguished. Other specific alterations such as nonparoxysmal and paroxysmal changes or sharp waves were also evaluated.

3. Patients and control group

A total of 40 patients with schizophrenia (23 men, 17 women) and 30 control subjects (15 men, 15 women) were investigated. Table 1 shows sociodemographic data on the patients, including information on disease duration, cumulative neuroleptic dosage and of duration in hospital treatment.

In order to achieve a subtype specific homogenization within the group of patients with schizophrenia, only patients of the subtype of paranoid hallucinatory schizophrenia (ICD-10-Systematik, 1995, F.20.0) were admitted to the investigation. The psychopathological diagnoses were undertaken separately by two independent specialists for psychiatric diseases. At the time of examination, patients had been hospitalized...
for at least 6 weeks, and had been treated with haloperidole for a minimum of 4 weeks. The measurements of spontaneous magnetoencephalographic activity we carried out were repeated at intervals of 3 weeks to check the course of the illness and to retest variability. For experimental/technical reasons, the doses of haloperidol (8.5 ± 3.6 mg) remained constant during the interval of the first and the second measurements.

For the evaluation of the psychopathological status, the PANSS and BPRS rating scales were applied at the first and the second measurements by two independent specialists. In order also to ensure maximum psychopathological homogeneity, patients evidencing large standard deviations were excluded from the investigation. The control group was investigated psychopathologically using the BPRS and any control subject achieving a score >10 points was excluded. Exclusion criteria for schizophrenics and controls were organic psychoses, drug-induced psychoses, schizophrenia-like psychoses, addictive diseases, any electroconvulsive or repetitive transcranial magnetic stimulation treatment in the past, metal implants.

4. Statistical analysis

The target parameters for the statistical evaluation were absolute dipole values and the dipole localizations. For the absolute dipole values, the normal distribution assumption was checked. Since no significant deviations were detectable with the aid of the Kolmgorov–Smyrnov test, the data were, without any further transformation, submitted to variance and covariance analyses. In addition to the feature of interest “group” (patients, controls), the factor’s gender (male, female) and sensor (sensor A, sensor B) were also considered as relevant influencing variables. The duration of the illness and the cumulative neuroleptic dosage were investigated as continuous parameters. The influence of the factors on the absolute dipole values was investigated as continuous parameters. The interaction of the factors investigated being taken into account in the latter analysis. Influence on localization was tested for the qualitative items using Fisher’s exact test, with only the two most common localizations (central, temporoparietal) being applied. The influence of cumulative neuroleptic dosage and disease duration, together with the relationship between absolute dipole values and localization, was checked using t-tests. The relationship between the rating scores and the absolute dipole values, disease duration, and cumulative neuroleptic dosage was investigated using correlation analysis. For all statistical tests, the error of first type was set to 0.05 and a statistically significant result was assumed at p values of >5% and <10%. P values were adjusted for multiple testing using the Bonferroni correction.

The main focus of the study (which was established prior to the collection of data) was the difference in absolute dipole values between patients and controls. The reproducibility of absolute dipole values was determined with the aid of intraclass correlations.

5. Results

5.1. 2–6 Hz (slow activity)

Table 2 contains the results of the variance analysis of the groups (patients, controls)—gender-specific, and sensor (sensor A, sensor B)—specific absolute dipole values ($T_{\text{total}}$, $D_{\text{total}}$, $D_{\text{max}}$, absolute dipole density, relative dipole density).

The group of schizophrenic patients revealed a statistically significant elevation in $D_{\text{max}}$, relative dipole density and absolute dipole density vis-a-vis the control group. Sensor-specifically, the density maximum for the overall group picked up by sensor A (left hemisphere) was elevated. While the two path interactions variance analysis merely revealed a ten-dential rise in schizophrenic patients for sensor A ($F=3.421, p < 0.067$), the covariance analysis revealed statistically significant elevation for $D_{\text{total}}$ ($p < 0.000, F=21.037$) and $D_{\text{max}}$ ($p < 0.051, F=3.931$) for sensor

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sociodemographic data in patients with schizophrenia and controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male patients</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
</tr>
<tr>
<td>Age</td>
<td>33.5 ± 3.5</td>
</tr>
<tr>
<td>Diagnosis schizophrenia</td>
<td>23</td>
</tr>
<tr>
<td>First onset of manifestation</td>
<td>27.0 ± 4.5</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>8.5 ± 2.5</td>
</tr>
</tbody>
</table>
A in patients with a long disease duration and patients with a high cumulative neuroleptic dose. The psychopathological correlation analysis showed a relationship primarily between dipole density maximum, absolute dipole density, relative dipole density and positive schizophrenic symptoms (see Table 3).

In the determination of dipole localization via sensor A and sensor B in the slow activity range, the central and temporoparietal dipole localization was predominant in 93% of the overall group investigated, so that for the localization analysis, a differentiation was made in accordance with these dominant distributions. Highly significant was a temporoparietal dipole localization for male gender, patients vis-a-vis male controls, male patients vis-a-vis male controls (p < 0.005) (see Fig. 1).

5.2. Fast activity 12.5–30 Hz

The results of the variance analysis for the absolute dipole values (Dtotal, Dmax, absolute and relative dipole densities) can be seen in Table 4.

Significant or tendential deviations were found in the group of schizophrenic patients vis-a-vis controls for Dmax (p < 0.05), the absolute and the relative dipole densities (p < 0.01). For sensor A there was a significant elevation of Dtotal (p < 0.05) and the absolute dipole density (p < 0.05); for sensor B for the relative dipole density (p < 0.05). Women proved to have significantly elevated values for Dtotal (p < 0.05) and Dmax (p < 0.05). The absolute dipole density was very significantly elevated (p < 0.005) within the group of female patients. The covariance analysis showed Dmax (p < 0.001, F = 12.315) and the absolute dipole density (p < 0.01) to be significant for female gender, patients with long disease duration and high cumulative neuroleptic dose. The correlation analysis revealed no significance between absolute dipole values (Dtotal, Dmax, absolute and relative dipole densities) and the rating scales applied (BPRS, PANSS[P1–P7], PANSS[N1–N7]) (see Table 3). With regard to dipole localization for fast activity, the concentration in the temporoparietal and central regions (92%) already described for slow activity was again observed.

### Table 2
Variance analysis 2–6 Hz for absolute dipole values (Dmax, Dtotal/Ttotal), relative dipole density (Dmax/Dtotal), absolute dipole density (Dmax/Ttotal) dependent on sensor (sensor A, sensor B), gender and group (schizophrenics, healthy controls)

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 140)</th>
<th>Sensor A (n = 70)</th>
<th>Sensor B (n = 70)</th>
<th>Male (n = 76)</th>
<th>Female (n = 64)</th>
<th>Patients (n = 80)</th>
<th>Control (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dtotal (n^a) ±</td>
<td>2100 (587)</td>
<td>2296 (587)</td>
<td>1905 (516)</td>
<td>2089 (502)</td>
<td>2114 (673)</td>
<td>2113 (591)</td>
<td>2083 (580)</td>
</tr>
<tr>
<td>Dmax (n^b) ±</td>
<td>51.5 (25.0)</td>
<td>56.9 * (27.4)</td>
<td>46.2 (21.2)</td>
<td>53.7 (24.6)</td>
<td>48.9 (25.4)</td>
<td>56.8 ** (30.3)</td>
<td>44.4 (12.3)</td>
</tr>
<tr>
<td>Dmax/Dtotal (m/n) ±</td>
<td>0.026 (0.01)</td>
<td>0.026 (0.01)</td>
<td>0.026 (0.01)</td>
<td>0.028 * (0.01)</td>
<td>0.023 (0.01)</td>
<td>0.029 ** (0.01)</td>
<td>0.022 (0.01)</td>
</tr>
<tr>
<td>Dmax/Ttotal (m/s) ±</td>
<td>4.47 (2.07)</td>
<td>4.54 (2.11)</td>
<td>4.39 (2.04)</td>
<td>4.61 (1.86)</td>
<td>4.30 (2.31)</td>
<td>4.86 * (2.49)</td>
<td>3.98 (1.16)</td>
</tr>
<tr>
<td>T_total (s^c) ±</td>
<td>11.5 (1.38)</td>
<td>12.53 (1.56)</td>
<td>10.52 (1.34)</td>
<td>11.64 (1.42)</td>
<td>11.37 (1.53)</td>
<td>11.68 (2.12)</td>
<td>11.15 (1.58)</td>
</tr>
</tbody>
</table>

* Number of calculated dipoles.  
** The calculated maximum dipole density.  
* The total length of time from segments, which were determined from the MEG.  
*p < 0.05.  
**p < 0.01.

### Table 3
Correlation analysis between actual psychopathological findings in the BPRS, PANS and SANSs scale and the frequency ranges 0–6 and 12.5–30 Hz

<table>
<thead>
<tr>
<th></th>
<th>Dtotal (2–6 Hz)</th>
<th>Dmax (2–6 Hz)</th>
<th>Dmax/Dtotal (2–6 Hz)</th>
<th>Dmax/Ttotal (2–6 Hz)</th>
<th>Dtotal (12.5–30 Hz)</th>
<th>Dmax (12.5–30 Hz)</th>
<th>Dmax/Dtotal (12.5–30 Hz)</th>
<th>Dmax/Ttotal (12.5–30 Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS</td>
<td>r = -0.69</td>
<td>r = 0.213</td>
<td>r = 0.278</td>
<td>r = 0.267</td>
<td>r = 0.076</td>
<td>r = 0.027</td>
<td>r = 0.122</td>
<td>r = -0.142</td>
</tr>
<tr>
<td>p</td>
<td>0.543</td>
<td>0.057</td>
<td>0.012</td>
<td>0.0137</td>
<td>0.448</td>
<td>0.807</td>
<td>0.309</td>
<td>0.208</td>
</tr>
<tr>
<td>PANSS [P1–P7]</td>
<td>r = 0.117</td>
<td>r = 0.321</td>
<td>r = 0.347</td>
<td>r = 0.020</td>
<td>r = 0.048</td>
<td>r = -0.054</td>
<td>r = -0.039</td>
<td>r = 0.015</td>
</tr>
<tr>
<td>p</td>
<td>0.303</td>
<td>0.004</td>
<td>0.002</td>
<td>0.259</td>
<td>0.6712</td>
<td>0.662</td>
<td>0.727</td>
<td>0.309</td>
</tr>
<tr>
<td>SANSs [S1–S7]</td>
<td>r = -0.234</td>
<td>r = 0.153</td>
<td>r = 0.027</td>
<td>r = 0.125</td>
<td>r = -0.108</td>
<td>r = -0.047</td>
<td>r = -0.07</td>
<td>r = 0.104</td>
</tr>
<tr>
<td>p</td>
<td>0.837</td>
<td>0.176</td>
<td>0.811</td>
<td>0.266</td>
<td>0.337</td>
<td>0.675</td>
<td>0.534</td>
<td>0.357</td>
</tr>
</tbody>
</table>
temporoparietal dipole concentration was very significantly elevated in males vis-a-vis females ($p<0.005$), in schizophrenic patients vis-a-vis controls ($p<0.005$), and in male schizophrenics vis-a-vis male controls ($p<0.005$). No statistically demonstrable effect on localization was seen for cumulative neuroleptic dose, disease duration and current psychopathological findings.

EEG: In both frequency ranges investigated (2–6 Hz, 12.5–30 Hz) we found no differences between

---

**Table 4**

<table>
<thead>
<tr>
<th></th>
<th>Total ($n=140$)</th>
<th>Sensor A ($n=70$)</th>
<th>Sensor B ($n=70$)</th>
<th>Male ($n=76$)</th>
<th>Female ($n=64$)</th>
<th>Patients ($n=80$)</th>
<th>Control ($n=60$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{\text{total}}$ ($n^2$)</td>
<td>2162 (903)</td>
<td>2327* (901)</td>
<td>1998 (873)</td>
<td>1958 (760)</td>
<td>2374* (1014)</td>
<td>2175 (1013)</td>
<td>2146 (739)</td>
</tr>
<tr>
<td>$D_{\text{max}}$ ($m^2$)</td>
<td>47.0 (33.1)</td>
<td>49.0 (28.3)</td>
<td>44.9 (37.3)</td>
<td>36.8 (16.6)</td>
<td>59.1* (42.6)</td>
<td>50.7* (41.0)</td>
<td>41.9 (16.8)</td>
</tr>
<tr>
<td>$D_{\text{max}}/D_{\text{total}}$ ($m/m$)</td>
<td>0.026 (0.02)</td>
<td>0.022 (0.01)</td>
<td>0.029* (0.02)</td>
<td>0.024 (0.022)</td>
<td>0.027 (0.02)</td>
<td>0.028* (0.02)</td>
<td>0.021 (0.02)</td>
</tr>
<tr>
<td>$D_{\text{max}}/T_{\text{total}}$ ($m/s$)</td>
<td>3.81 (2.58)</td>
<td>4.27* (2.56)</td>
<td>3.36 (1.98)</td>
<td>3.19 (2.58)</td>
<td>4.56** (3.32)</td>
<td>4.07** (3.15)</td>
<td>3.47 (1.47)</td>
</tr>
<tr>
<td>$T_{\text{total}}$ (s)</td>
<td>12.33 (1.32)</td>
<td>11.47 (1.89)</td>
<td>13.36 (1.22)</td>
<td>11.53 (2.34)</td>
<td>12.96 (1.32)</td>
<td>12.45 (1.45)</td>
<td>12.07 (1.22)</td>
</tr>
</tbody>
</table>

*a* Number of calculated dipoles.

*b* The maximum dipole density.

*c* The total length of the segments, which were determined from the MEG.

(*$)$ ($p<0.1$).

*($p<0.05$).

**($p<0.005$).
patients with schizophrenia and controls by visual inspection. In both groups a mild to moderate beta frequency range predominated over both hemispheres.

5.3. Retest variability

The retest variability in the low frequency range (2–6 Hz) was within the range >80% for the absolute dipole values [$D_{\text{total}}$ (retest = 91%, $F = 11,372$), $D_{\text{max}}$ (retest = 97%, $F = 34,116$), absolute dipole density (retest = 80%, $F = 4,126$), relative dipole density (retest = 98%, $F = 3,328$)], as in the case for dipole localization (retest = 83%, $F = 5,24$). This was also confirmed for the high frequency range (12.5–30 Hz) for the absolute dipole values [$D_{\text{total}}$ (retest = 93%, $F = 14,001$), $D_{\text{max}}$ (retest = 97%, $F = 35,02$), absolute dipole density (retest = 97%, $F = 35,76$), relative dipole density (retest = 96%, $F = 27,73$)] and dipole localization (retest = 87%, $F = 6,38$). In three cases, we also checked the reliability of the results of sensors A and B by changing the position of the patient (sensor A was now recording the right, sensor B the left hemisphere). The results were not different to the primary measures.

6. Discussion

The following results of the measurement of magnetoencephalographic activities in schizophrenia patients and healthy subjects are worth noting.

(1) Both in the case of slow and fast activity, the absolute dipole values ($D_{\text{total}}$, $D_{\text{max}}$, absolute and relative dipole densities) were significantly or tendentially elevated in the overall group of patients with schizophrenia vis-a-vis controls.

(2) In the low frequency range, the parameters of disease duration and cumulative neuroleptic dose had an effect only on the density maximum and dipole localization. In the fast activity range, the influence of these course determining parameters was clearly shown by all absolute dipole values, but not by dipole localization.

(3) In the case of slow activity, the current psychopathological findings (as determined by BPRS and PANSS) correlated with $D_{\text{max}}$, absolute and relative dipole densities in the case of BPRS and the positive scale in PANSS (P1–P7).

(4) In schizophrenic patients and controls, dipole localization revealed two areas of concentration—temporoparietal and central, for all the frequency ranges measured. A significant difference was seen between the group of schizophrenic males and schizophrenic females, and between male and female controls, namely, the fact that the dipole localization was concentrated in the temporoparietal region.

(5) The results of the MEG measurement of spontaneous cerebral activity remained stable in the retest.

A comparison of the present study with a methodologically analogous application of the DDP revealed similar findings in a recently published MEG study by Fehr et al. (2001). They described an elevation in the low frequency range (1.5–4 and 4.0–8 Hz) mainly in the left frontal, posterior and temporal regions in schizophrenic patients compared with controls. The elevation in absolute dipole values in the 2–6-Hz frequency range found during magnetoencephalography also complements earlier electroencephalographic findings in schizophrenics that showed frequency increases for slow activity (Canive et al., 1996, 1998; Clementz et al., 1994; Matsusura and Yoshino, 1994; Sponheim and Clementz, 1994).

In addition, in the slow frequency range we found a correlation between patients with positive symptoms and a pronounced slow wave activity in the temporoparietal region. In their recent study Fehr et al. (2001) also described that positive symptoms which were clustered with focal slow waves in the delta and theta bands were mainly located in the frontal and right temporal areas, whereas posterior slow wave activity appeared to be unrelated to any specific schizophrenic symptoms. In electroencephalographic studies, correlations between low frequency activity and psychopathological findings indicated a possible correlation with schizophrenic negative symptoms (e.g. formal thought disorders and poor therapeutic outcome, mainly in the lateral and posterior regions; Rappelsberger et al., 1994). A close correlation between schizophrenic negative symptoms and an increase in theta/delta activity in the EEG was also noted by Gattaz et al. (1992). An evaluation of these differing results, however, will be possible when further series of MEG examinations have been carried out. The increase in beta wave activity shown in the present examination proved to be gender specific, with a predominance found for female gender. An increase
in beta wave activity, in particular within the 25–30-Hz range, however, has been described within the framework of so-called “choppy activity” in schizophrenic patients, irrespective of gender (Davis, 1939).

The gender effect observed in the present study might, however, also be related to the strict subtyping of the group investigated and is thus not directly applicable to a non-subtyped group of schizophrenia patients. With regard to the intensity of absolute dipole values, magnetoencephalography revealed an influence of long-term parameters (disease duration, cumulative neuroleptic dosage) on the beta wave range, but not of current psychopathological findings.

In contrast, the correlation between the above mentioned and the concentration of the absolute dipole values was identifiable in the slow activity range and in positive symptoms. To summarize the results obtained may be explained by the following hypothesis: The current severity of the condition has an effect on slow wave activity, while the long-term parameters of the disease have an effect on fast wave activity. A further major result of the investigation is the fact that schizophrenic males differ significantly from all other groups in terms of the dipole localization in the left hemispherical-temporoparietal region both on slow and fast activity ranges. In comparison with already known markers of schizophrenia, the present results confirm not only the gender specificity within the schizophrenic group, but also, and in particular, the temporoparietal localization of the findings. At various investigative levels, the left temporoparietal region in particular has been described as a vulnerable site in schizophrenia patients. Sauer et al. (1998) described dipole abnormalities left hemispherically in male (p = 0.02) and right hemispherically in female patients with schizophrenia when compared to controls. Furthermore, Pearlson and Barta (1997) reported a bilateral narrowing of the upper section of the posterior left temporoparietal lobe in 46 schizophrenic patients and Russel and Early (1997), employing hexamethylpropyleneamine oxime (HMPAO)-SPECT, has demonstrated a significant perfusion deficiency in the left temporal lobes of schizophrenics. In rCBF-studies on schizophrenics, Ganguli and Carter (1997) detected increases in perfusion in the frontal upper temporoparietal lobe regions on both sides. He was, however, unable to find any correlation with medication, demographic variables or handedness. Sabri and Schreckenberger (1997), having employed HMPAO-SPECT on the brain, reported a positive correlation between the bitemporal rCBF elevation and formal disorders of the mental process in schizophrenic patients, but not in patients with hallucinations or delusions.

Klemm et al. (1996) noted a statistically significant hypoperfusion in the temporal region of schizophrenics that correlated with positive symptoms of schizophrenia. Tune et al. (1996) demonstrated in schizophrenia patients an inverted relationship between reduced temporal lobe volume and elevated levels of striatal dopamine D2 density. In qualitative MRI measurements in schizophrenics developing the disease in advanced age, Barta and Powers (1997) described a reduction in median temporal lobe volumes. Electroencephalographic studies also showed deviations from normal within the temporal region of schizophrenics, in particular a decrease in alpha activity and an increase in beta wave activity.

Gender is known to be a confounding factor at both phenomenal and neurobiological levels in schizophrenic patients. As a rule, men usually have a poorer premorbid performance than women, are younger at disease onset, suffer a more severe course, and respond less well to medication (Goldstein et al., 1989; Häfner and Reiderer, 1989). Gender differences, including an obvious enlargement of the right temporal lobe in male schizophrenic patients, have also been found in neuropsychological investigation as well as in neuroanatomical studies (Gür and Gür, 1990; Manoach, 1994). In view of the basis of the clear, highly significant temporoparietal localization site observed exclusively in males in our group, it would appear that within the investigated subtype of paranoid hallucinatory psychoses, there is a gender-specific effect that takes the form of a left temporoparietal dipole concentration. The simultaneous concentration of various frequencies in the same left hemispheric region can be expressed by the collective term “dipole concentration effect” (DCE). In the particular context of numerous publications, assuming a left hemispherical dysfunction in schizophrenia, the findings recorded here would appear to be of some significance. The use of the new technique supports
existing evidence pointing to a region of the human brain, which, usually within a gender and subtyped group, assumes the significance of a vulnerable zone. Irrespective of gender, however, the overall group of paranoid hallucinatory schizophrenics differed from the group of healthy subjects in the bi-hemispherical increases in the absolute dipole values in both the fast and slow wave activities, thus providing strong support for the existing hypothesis of an aetio-pathogenic effect of neuronal dysfunction in this disease.

References


