Source Distribution of Neuromagnetic Slow Waves and MEG-Delta Activity in Schizophrenic Patients

Thorsten Fehr, Johanna Kissler, Stephan Moratti, Christian Wienbruch, Brigitte Rockstroh, and Thomas Elbert

Background: *Schizophrenic patients exhibit more activity in the electroencephalographic delta and theta frequency range than do control subjects. Using magnetic source imaging (MSI) our study aimed to explore this phenomenon in the magnetoencephalogram (MEG), the distribution of its sources, and associations between symptom profiles and sources of low-frequency activity in the brain.*

Methods: *Whole-head MEG recordings were obtained from 28 schizophrenic patients and 20 healthy control subjects during a resting condition. The generators of the focal magnetic slow waves were located employing a single moving dipole model. Distributed or multiple delta and theta sources were captured by the minimum norm estimate.*

Results: *Both localization procedures showed slow wave activity to be enhanced in schizophrenic patients compared with control subjects. Focal slow wave activity differed most between groups in frontotemporal and in posterior regions. Slow wave activity was associated with symptom characteristics in that positive symptoms varied with frontal delta and theta activity.*

Conclusions: *Results indicate that activity in low-frequency bands in schizophrenic patients exceeds the activity of control subjects in distinct areas, and that this focal clustering of neuromagnetic slow waves may be related to psychopathologic characteristics.* Biol Psychiatry 2001; 50:108–116 © 2001 Society of Biological Psychiatry

Key Words: Schizophrenia, magnetoencephalography, slow waves, delta, theta, dipole modeling

Introduction

Neuronal information processing requires synchronized activity of neural cell assemblies. Large-amplitude slow wave activity is an indicator of widespread synchronization of many neurons in rest. Consequently, this activity characterizes a brain with little ongoing information processing. In this respect, electroencephalographic (EEG) delta (1–4 Hz) activity appears to characterize brain states with little ongoing information processing, such as slow wave sleep or coma. If prominent during the waking state, focal slow waves may characterize circumscribed pathologic or dysfunctional brain regions. Examples are abnormal brain waves in the vicinity of a structural lesion. Typical lesions producing focal slow activity include cerebral infarcts, contusions, local infections, tumors, developmental defects, degenerative defects, or subdural hematomas (Lewine and Orrison 1995; Niedermeyer and Lopes da Silva 1987). Slow waves may not only result from neurologic disease but also appear in certain psychopathologic conditions. Our study aimed to explore whether the evaluation of the spatial distribution of generators of this brain activity would allow the assessment of dysfunctional brain regions, which might ultimately provide a diagnostic aid in psychiatry.

Atypically enhanced activity in the delta and theta EEG frequency bands has frequently been reported in schizophrenic patients, whereas alpha activity is often attenuated in these patients (Rockstroh et al 1997; Shagass 1991; Winterer and Herrmann 1995); however, results vary considerably between studies. Inconsistencies may result from different patient samples (acute or chronic states, medicated or unmedicated, younger or older subjects, prominent negative or positive symptoms, diagnostic categories, etc.) and different data collection procedures (eyes open vs. eyes closed, spatial resolution, artifact rejection procedures, etc.; for an overview, see Tauscher et al 1995). Across studies, there is agreement that slow wave activity is generally enhanced in schizophrenic patients compared with control subjects in both acute and chronic states. Moreover, some studies suggest that theta and delta activity might be more pronounced in patients with dominating negative symptoms than in those with positive symptoms (Harris et al 1997; Saletu et al 1990).

Descriptions of the scalp distribution of the slow activity in schizophrenia differ between studies. A predominance of delta and theta activity has been reported over posterior scalp sites (e.g., Harris et al 1997; Ulrich and Otto 1984; Westphal et al 1990), but also at central (Karson et al 1987, 1988), left lateral (Schellenberg et al

1989), frontal (Gattaz et al 1992), or frontotemporal (Serafetinides 1984) electrodes. Some studies emphasize that the distribution of slow wave activity is generally diffuse or variable (Elbert et al 1992; Fenton et al 1980; Galderisi et al 1991; Macmahon and Walter 1938). One reason for this inconsistency may be that both distributed activity and focal slow waves from various brain regions contribute to the power of slow-frequency bands. In addition, volume conduction, the number of electrodes, and the electrode chosen as reference may blur the distribution of slow wave activity. A focal slow wave that affects a reference electrode may, for instance, be misinterpreted as widespread scalp activity.

The use of magnetic source imaging circumvents some of these problems because magnetic fields are largely unaffected by volume conduction in the brain. Furthermore, magnetoencephalography (MEG) is reference free. For equivalent current dipoles in a homogenous sphere, the sources of activity in the brain can be modeled better compared with the EEG. In previous studies employing magnetic source imaging, Canive and colleagues (1996) found bitemporal slow waves and high delta and theta activity in four schizophrenic patients (out of 11 patients during washout of neuroleptic medication). In two of the patients, slow wave generators were localized in the left-temporal plane; in the other two, generators were distributed throughout the temporal and inferior parietal lobes. Similarly, Canive et al (1998) modeled dipolar activity in the delta and theta band (2–6 Hz) in three out of five schizophrenic patients in left temporal ($n = 2$) and parietal ($n = 1$) cortical regions and in the superior planum temporale. These results suggest that augmented slow wave activity may not be characteristic for all schizophrenic patients and that localization of slow wave generators may be variable. In the patients with augmented slow waves, higher scores on psychopathology (Positive and Negative Syndrome Scale [PANSS]) were found.

With this background, our study aimed to examine in a larger patient group whether low-frequency activity in MEG is concentrated in specific areas and whether focal low-frequency activity is related to schizophrenic symptoms.

Our study employed magnetic source imaging to determine the source locations of focal slow waves and the generators of slow wave activity at multiple locations in schizophrenic patients and in healthy control subjects. The source distribution of focal slow waves was determined by scanning for fits of a single moving equivalent dipole; multiple sources of slow activity were modeled by the minimum norm estimate (MMN). We hypothesized that schizophrenic patients would exhibit a higher frequency of focal slow waves than control subjects at distinct locations. If slow wave activity indicates dysfunctional brain processes, group differences should be found mainly in frontal and temporal areas, which are assumed to be involved in schizophrenic psychopathology (Chua and McKenna 1995; McCarley et al 1996; Rockstroh et al 1997). To explore the potential psychopathologic relevance of slow wave activity in schizophrenia, we analyzed the relationship between the distribution of slow wave activity sources and psychopathology scores by means of a principal component analysis. Factors should be extracted that could be used to describe this relationship between slow wave activity in distinct areas and schizophrenic symptomatology.

Methods and Materials

Subjects

Twenty-eight inpatients (six women, mean age 30.9 ± 9.6 years) were recruited from the research unit of the university at the local Center of Psychiatry. They were compared with 20 healthy subjects comparable to the patient group with respect to age and gender distribution (five women, mean age 34.4 ± 11.3 years). Groups did not differ in the amount of formal school education (with an average 11.0 years of education in the patient and 11.95 years in the control group; $t (1,46) = 1.05$, $p = .3$).

In all subjects, handedness was assessed by a modified version of the Edinburgh Handedness Questionnaire (Oldfield 1971), which asks subjects to demonstrate hand use on various actions (such as using a broom, brushing teeth, writing, etc.). Twenty-one patients proved to be right-handed and seven left-handed, whereas all control subjects were determined as right-handed according to the test. (We are aware that the difference in the distribution of right- and left-handers in the two groups could have affected our results. This possibility was examined by comparing the results of two analyses, one including and one excluding the left-handed patients. As the pattern of results did not differ between the two analyses, results will be reported for all subjects.)

Patients met a DSM-IV diagnosis of either paranoid or disorganized schizophrenia. The psychiatrist or psychologist in charge made diagnoses based on the Present State Examination (PSE) and an interview considering DSM-IV criteria. Twenty-three patients received standard neuroleptics, four of these together with atypical neuroleptics; four patients received atypical antipsychotic medication alone; and one patient was unmedicated. The mean daily dosage of chlorpromazine equivalents for the group of 27 medicated patients was 231.71 ± 167.38. Because a number of patients received several different neuroleptic substances, the mean daily dosage of chlorpromazine equivalents (CPZ eq) was estimated for the entire group, and CPZ eq for standard and atypical neuroleptics were combined. We determined CPZeq following Jahn and Mussgay (1989). For our sample, atypical neuroleptics comprised clozapine and risperidone. Because the effects of risperidone are described as closely resembling those of clozapine (Benkert and Hippius 1996), the CPZ eq of 0.9 for clozapine was adopted for both substances.

Duration of illness varied between 1 and 107 weeks around a mean of 30.1 weeks. We ascertained that none of the patients used or abused any drug (except for nicotine) during the inpatient
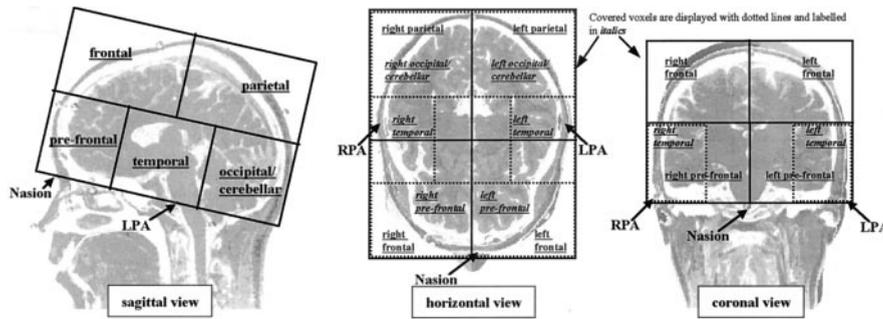
Figure 1. Ten regions for which dipole densities were determined and averaged for statistical comparison are illustrated relative to a schematic brain.

treatment. The psychopathologic status of each patient was assessed on the day of the experiment by the psychologist or psychiatrist in charge by means of the Brief Psychiatric Rating Scale (BPRS; Lukoff et al 1986; Overall and Gorham 1962; average score: 44.9). For 26 patients, symptom rating were available based on the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1981; average score: 53.8), and the PANSS (Kay et al 1987; average scores PANSS-P: 14.9; PANSS-N: 20.2; PANSS-G: 35.5).

Control subjects were only accepted if they did not report any history of psychiatric illness or regular drug use or abuse and were not under current medication.

All subjects were familiarized with the recording environment, informed about the procedure, and gave written consent to participate in the experiment. Participants were paid the equivalent of about $10 US.

Data Collection

The MEG was measured using a 148-channel whole-head neuromagnetometer (MAGNES 2500 WH, Biomagnetic Technologies, San Diego, CA) during a 5-min resting period. Subjects were asked to stay awake and not to engage in any specific mental activity while looking at a colored fixation mark on the ceiling of the magnetically shielded room to avoid eye and head movement. Compliance was assured by observation via a video camera (installed inside the chamber) that allowed us to monitor the subject's behavior at any time throughout the experiment. The MEG was recorded with a 678.17 Hz sampling rate, using a band-pass filter of 0.1–200 Hz. For artifact control, eye movements (electro-oculogram) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye using a Synamps amplifier (NEUROSCAN, Sterling Virginia). The electrocardiogram (ECG) was monitored via electrodes attached to the right collarbone and the lowest left rib.

Data Reduction and Analysis

For the 5-min recording, the number of sample points was reduced by factor 16, and the data were band-pass filtered in the delta (1.5–4.0 Hz) and theta (4.0–8.0 Hz) band before further analysis. Two distinct source localization methods were used as described below. The dipole density method was used because of its sensitivity for both deeper and superficial, focal sources (indicated by dipolar magnetic field patterns), and the minimum-norm-estimate (MNE) method was used to explore multiple superficial sources.

DIPOLE DENSITY ANALYSIS. Artifact-free time segments of varying lengths were determined by visual inspection. Single equivalent current dipoles in a homogeneous sphere were fitted for each time point in the selected epochs. Only dipole fit solutions at time points with a root mean square (RMS $= (\sqrt{(1/n\Sigma(x_i)^2)})) > 100$ fT < 300fT and with a goodness of fit greater than 0.90 were accepted for further analysis. These restrictions should ensure that neither artifacts nor small-amplitude biological noise affect the results and that only truly dipolar fields generated by focal sources were analyzed.

For statistical analysis, the total brain volume was divided into the following five regions in each hemisphere (see Figure 1): prefrontal, frontal, temporal, parietal, and occipital. The number of dipole fits per second in a particular region was determined.

MINIMUM-NORM ESTIMATE. An explorative analysis of multiple sources was performed on magnetic activity field patterns in the delta and theta band. A period of 30 sec that was low on artifacts was determined for each subject. The global field power (GFP: $\Sigma(x_i)^2$) was calculated for each time point. A minimum global field power of 3000 [ft^2] was required to exclude noise-induced activity patterns, and a maximum of 18,000 [ft^2] to exclude artifacts. Activity patterns that correlate with a typical eye-blink pattern were excluded as well.

The MNE (Hämäläinen and Ilmoniemi 1984; Hauk et al 1999) is an inverse method reconstructing the primary current that underlies an extracranially recorded time-locked brain potential. The procedure is based on the assumption that the data vector d, which contains the recorded scalp potential at given electrode sites, can be described as the product of the leadfield matrix L, which specifies the electrode's sensitivity to the sources, the source current vector j (cf., Grave de Peralta Menendez et al 1997), and a noise component ε. Because L and d are known, and ε is estimated with an accuracy of $p < .05$, the MNE for j is the mathematically unique solution of the equation which minimizes the squared current density ($j^2 = \min$). This solution is obtained by multiplying the pseudoinverse of the leadfield matrix L with the data. Given the high number of electrodes and the presence of noise, spatial regularization is performed with the factor λ. This algorithm allows sources to be omitted, if they do not contribute to the measured scalp potential. A priori information about the number or locations of cortical sources is not required. The dependence of the accuracy of inverse solutions on the depth of the source is addressed by the present MNE algorithm as follows: A three-dimensional source space consisting of four

concentric shells (80%, 60%, 40%, and 20% of sensor radius) is computed as an approximation of the brain volume. Hauk and coworkers have shown that deeper shells are associated with less suppression of deep sources, but more blurring (Hauk et al 1999). For our analyses, solutions for the shell at 60% sensor radius (L2-norm) were determined as a compromise between blurring and depth sensitivity. Eighty-seven locations on this shell were selected; the MNE amplitudes at these sites were computed and averaged across the 30-sec epoch. For statistical analyses, the MNE were averaged further across 10 regions, left and right prefrontal, left and right frontal, left and right temporal, left and right parietal, and left and right occipital.

Group differences of the dipole density solutions and of the MNE were evaluated by analyses of variance (ANOVA) with the between factor GROUP (schizophrenic patients vs. healthy control subjects) and the within-subjects factor REGION (10 regions). Where appropriate, significance levels are reported with Huynh-Feldt adjusted degrees of freedom to compensate for violations of the sphericity assumption. Sources of interactions were verified by post hoc least significant difference tests (LSD tests).

The relationship between symptom ratings (total SANS-score for negative symptoms, PANSS-P for positive symptoms) and slow wave activity was examined by means of a principal component analysis (PCA), extracting main components with varimax rotation. (StatSoft, 1998. STATISTICA für Windows [Computer-Programm-Handbuch]. Tulsa, OK: StatSoft). Only factors with an eigenvalue > 1 were accepted. A relationship between slow wave activity and medication was evaluated by correlation between the chlorpromazine equivalents and overall dipole density and MNE, respectively, for the delta and the theta band.

Results

Dipole Density Analysis

The percent of single-current dipoles fitted for the selected time points according to the criteria mentioned above is displayed in Figure 2 for each region, separately for the delta and for the theta bands. For the delta frequency band, the number of focal slow waves fitting a single dipole model was generally higher for patients than for control subjects (main effect GROUP, $F[1,46] = 8.9, p < .01$). This enhancement was particularly pronounced in left frontal and bilaterally in temporal and posterior regions (GROUP $\times$ REGION, $F[9,414] = 3.0, p < .05$; see Table 1, top, for post hoc comparisons between group for the 10 selected brain regions).

In the theta frequency band as well, more dipoles could be fit to the data in schizophrenic patients (GROUP $F[1,46] = 6.6, p < .05$). Again, the spatial distribution of the dipoles differed between the groups (GROUP $\times$ REGION, $F(9,414) = 2.8, p < .05$): The number of dipoles in schizophrenic patients significantly exceeded the one in control subjects, primarily for left frontal and for left and right posterior regions (see Table 1, bottom, for post hoc comparisons). In the delta frequency band, 24

of the 28 patients exhibited dipole densities at least one standard deviation above control subjects in at least one region; this was also true in the theta band for 23 patients.

Minimum-Norm Estimates

Although focal slow waves indicated by dipolar magnetic field patterns were evaluated by the dipole density analysis, the MNE are additionally sensitive to waves generated at multiple locations. The MNE indicated higher dipole moments of the neural generators of delta activity in patients than in control subjects (GROUP, $F[1,45] = 19.13, p < .001$) without significant group-specific distribution (GROUP $\times$ REGION, $F[9,405] = 0.74$; Huynh-Feldt $p = .53$). Post hoc analyses confirmed this group difference for all regions (see Table 2, top, and Figure 3).

Patients also displayed higher MNE for theta activity than did control subjects (GROUP, $F[1,45] = 12.94, p < .001$). Although Figure 3 suggests that the group difference was most prominent in parietal and the left temporal regions, the interaction GROUP $\times$ REGION ($F[9,405] = 1.76$) did not reach significance (Huynh-Feldt $p = .15$; see Table 2, bottom, for post hoc statistics).

The impact of medication on the amount and distribution of slow wave activity (delta and theta band) was explored by correlation analysis. Although we are aware of the preliminary and vague nature of correlations with CPZ eq, this approach was chosen instead of a comparison of subgroups with typical and atypical neuroleptics, or even with and without medication, because of the insufficient number of subjects within each subgroup and because many patients received a combination of typical and atypical neuroleptics. The only significant correlation with CPZ eq indicated higher values in the theta frequency band in right temporal (for dipole densities: $r = .41, p < .05$; for MNE: $r = .43, p < .05$) and right frontal (MNE: $r = .45, p < .05$) to covary with higher medication.

Relationship Between Slow Wave Activity and Symptomatology: Principal Component Analysis

For the 26 patients for whom symptom ratings were available, the principal component analysis (PCA) including dipole densities and PANSS-P scores for positive symptoms and SANS-A for negative symptoms explained 83% of the total variance in the delta band (three factors) and 80% in the theta band (three factors). For minimum-norm estimates, the PCA explained 79% of variance in the delta band (three factors) and 85% in the theta band (four factors; see Table 3).

For the dipole densities, the PCA showed a relationship primarily between positive symptoms and prefrontal, frontal, parietal, and right temporal delta activity (factor 1 in Table 3, top). For the theta band, this relationship is
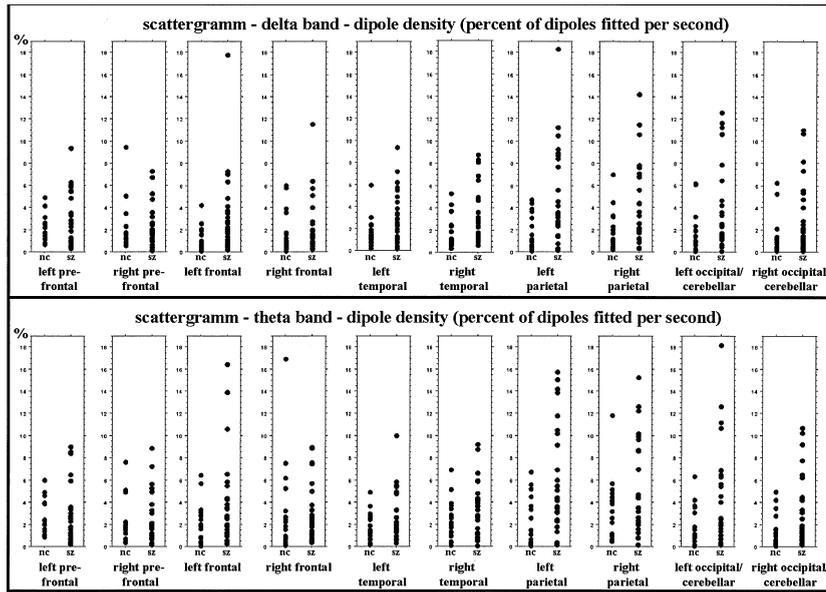
Figure 2. Distribution of individual dipole densities in the delta (top) and theta (bottom) frequency band, plotted separately for schizophrenic patients (sz) and normal control subjects (nc), showing the 10 regions of dipole density estimation. Each dot represents a single subject; the ordinate represents the percent of mean single dipoles fitted per second.

supported by factor 2. For the minimum-norm estimates, the three-factor solution in the delta band indicated a relationship between positive symptoms and prefrontal, frontal, and parietal delta activity (factor 2). For the theta band, factor 2 disclosed a weak negative relationship between positive symptoms and occipital theta activity. Thus, positive symptoms seem to be related to slow wave activity in frontal, parietal, and right hemispheric regions, whereas negative symptoms seem not to be related to any specific area. There was no significant correlation between neuroleptic dosage and the positive or negative symptom scores.

Discussion

We applied two methods in our study to estimate the distribution and sources of slow wave activity in schizophrenic patients and healthy control subjects from MEG recording during a resting state. One method focused on the number of dipoles in the delta and theta frequency bands in different brain regions, that is, source distribution of focal slow wave activity; the other method estimated the distribution of multiple sources of slow wave activity. Both methods provided similar results, that is, more sources of activity in the delta and theta band in schizophrenic than in healthy subjects. The finding of enhanced slower activity in schizophrenic patients is consistent with results from EEG analyses. In our study, we confirmed this finding with magnetic source imaging analysis. In addition, the dipole density analysis suggests that the regional distribution of slow wave activity differs between schizophrenic patients and control subjects, in that a higher number of slow wave generators was observed in certain areas. In contrast, the minimum-norm solution substantiated a widespread enhancement in slow wave activity. The similarity of the results obtained from the two different analysis procedures suggests that focal slow waves were identified by both methods and may therefore be an important source of variance explaining group differences. Moreover, the considerable proportion of slow waves that fit a single dipole model in patients supports the presence of focal slow wave generators.

Patients exhibited more pronounced slow wave activity in several brain regions. On a group level, differences

Table 1. Significance Level of Group Differences in Dipole Density of the Delta Band and the Theta Band for the Different Regions

	Prefrontal		Frontal		Temporal		Parietal		Occipital	
	L	R	L	R	L	R	L	R	L	R
Delta band (1.5–4.0 Hz)										
p	.19	.56	.00[b]	.22	.02[a]	.01[b]	.00[b]	.01[b]	.00[b]	.00[b]
Theta band (4.0–8.0 Hz)										
p	.38	.5	.01[b]	.90	.09	.06	.00[b]	.00[b]	.00[b]	.01[b]

L, left; R, right.
[a] $p < .05$.
[b] $p < .01$.

Table 2. Significance Level of Group Differences in Minimum-Norm Estimates of the Delta Band and the Theta Band for the Different Regions

	Prefrontal		Frontal		Temporal		Parietal		Occipital	
	L	R	L	R	L	R	L	R	L	R
Delta band (1.5–4.0 Hz)										
p	.00[b]	.00[b]	.00[b]	.00[b]	.00[b]	.00[b]	.00[b]	.00[b]	.00[b]	.00[b]
Theta band (4.0–8.0 Hz)										
p	.10	.43	.01[a]	.07	.00[b]	.01[b]	.00[b]	.00[b]	.00[b]	.00[b]

[a] $p < .05$.
[b] $p < .01$.

were most pronounced in left frontal, posterior, and temporal regions, which is in line with the results of Canive et al (1998). If the presence of delta and theta generators can be taken as indication of dysfunctional brain tissue, the results from both sets of analyses suggest that schizophrenia does not simply affect a single cortical area but is related to a network of dysfunctional areas. Areas with higher slow wave activity in schizophrenic than in control subjects included those (left frontal and temporal areas) that have been linked to schizophrenic pathology in different methods of inquiry.

The individual variation in the localization of slow wave generators within the patient group may also contribute to the group level difference in many areas. Canive et al (1996, 1998) described a variable localization of slow wave generators in the few subjects they studied. One reason for an interindividual variability of region-specific prominence of slow wave activity might be symptom characteristics. We explored this possibility by relating the regional distribution of slow wave activity to schizophrenic symptoms by means of PCA. The results indicated that positive symptoms clustered with focal slow waves in the delta and theta band mainly in frontal and right temporal areas, whereas posterior slow wave activity appeared to be unrelated to any specific schizophrenic symptoms. Using the multiple-source model, we found a positive factor loading of positive symptoms on a common factor for frontal and parietal delta activity. This may also indicate a predominance of focal clustering of slow wave activity in patients with prevalent positive symptoms. Regional specificity of the slow wave activity determined from the scalp-recorded EEG previously has been related to clinical characteristics. For instance, Rappelsberger et al (1994) found increased delta in posterior regions in schizophrenic patients with thought disorder. Harris et al (1997) showed enhanced delta and theta activity over posterior and right lateral regions and associated frontal delta activity with poor therapeutic outcome. If slow wave activity results from dysfunctional states of cortical tissue, our results would suggest frontal dysfunction when positive symptoms prevail.

Alternative explanations for our results of group-spe-

cific and focal clustering of slow wave activity have to be considered. Indications of EEG slowing, in particular reduced power in the alpha frequency band, and increased activity in the theta range or occasional slow waves, have been reported as correlate of drowsiness and transition to sleep (e.g., Badia et al 1994; Hasan and Broughton 1994; Ogilvie et al 1994; Matejcek 1982; Morikawa et al 1997; Tanaka et al 1998; Kubicki and Herrmann 1996). In addition, neuroleptics are known to have dampening effects, particularly at the beginning of the treatment. Using video monitoring, our study controlled for drowsiness by assuring that subjects did not close their eyes and fall asleep. Furthermore, the high number of eye blinks affecting the EEG of schizophrenic patients might argue
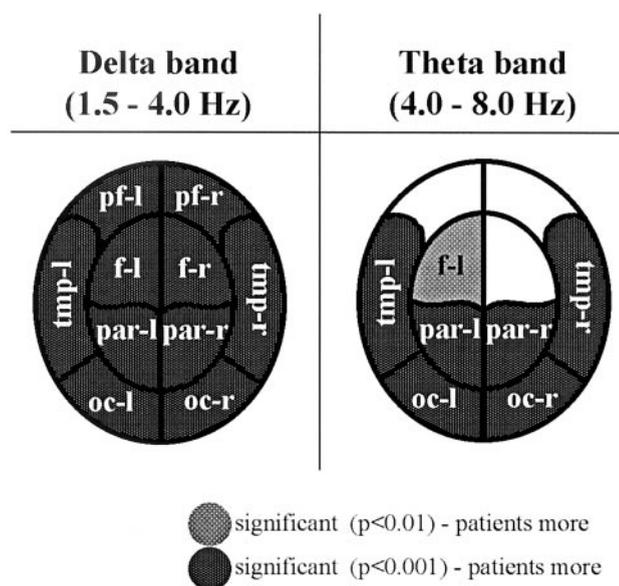

Figure 3. Schematic illustration of the statistical differences between groups in the minimum-norm estimate for the delta (left) and theta (right) frequency bands, determined for the 10 regions. (pf-l: left prefrontal; pf-r: right prefrontal, f-l: left frontal, f-r: right frontal; tmp-l: left temporal, tmp-r: right temporal; par-l: left parietal, par-r: right parietal; oc-l: left occipital, oc-r: right occipital). Darker shading indicates higher levels of significance.

Table 3. Factor Loadings of the Variables with the Factors Extracted by Principal Component Analysis (PCA) Separately for the Delta Band and the Theta Band, the Dipole Density (DD) Values and the Minimum-Norm Estimates (MNE), and Symptom Values for Negative (SANS) and Positive (PANSS–P) Symptoms

PCA	Delta Band (1.5–4.0 Hz)			Theta Band (4.0–8.0 Hz)			
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3	Factor 4
DD							
F-L	0.95	0.02	0.08	0.04	0.90	0.01	
F-R	0.93	0.14	0.17	0.22	0.92	−0.11	
PAR-L	0.55	0.70	0.02	0.81	0.43	−0.11	
PAR-R	0.48	0.68	−0.01	0.81	0.34	−0.08	
PF-L	0.84	0.31	−0.01	0.10	0.85	0.07	
PF-R	0.83	0.35	0.03	0.24	0.90	−0.06	
TEMP-L	0.36	0.83	0.13	0.78	0.42	−0.04	
TEMP-R	0.59	0.68	0.14	0.54	0.53	0.16	
OC-L	0.01	0.95	−0.06	0.90	0.00	0.11	
OC-R	−0.05	0.91	−0.06	0.94	−0.06	0.05	
PANSS-P	0.62	−0.36	−0.41	−0.37	0.43	0.61	
SANS	0.14	−0.05	0.95	−0.16	0.20	−0.85	
Eigenvalues:	4.57	4.20	1.16	4.18	4.18	1.18	
Variance:	0.38	0.35	0.10	0.35	0.35	0.10	
MNE							
F-L	0.34	0.85	0.23	0.69	−0.12	0.61	−0.12
F-R	0.13	0.93	0.05	0.95	−0.07	0.14	−0.07
PAR-L	0.71	0.50	0.19	0.15	0.23	0.89	0.00
PAR-R	0.67	0.60	0.09	0.78	0.16	0.47	0.08
PF-L	0.30	0.87	0.04	0.87	0.00	0.21	0.01
PF-R	0.09	0.82	−0.15	0.98	0.07	−0.07	0.07
TEMP-L	0.65	0.38	0.32	0.15	0.19	0.82	0.04
TEMP-R	0.81	0.36	−0.08	0.86	0.34	0.16	−0.01
OC-L	0.95	0.02	0.06	−0.05	0.91	0.28	0.00
OC-R	0.92	0.07	−0.02	0.23	0.92	0.05	−0.02
PANSS-P	−0.24	0.58	−0.34	0.15	−0.37	0.08	−0.72
SANS	0.03	0.06	0.92	0.13	−0.28	0.08	0.79
Eigenvalues:	4.06	4.25	1.19	4.60	2.14	2.26	1.18
Variance:	0.34	0.35	0.10	0.38	0.18	0.19	0.10

Variables: F-L, left frontal; F-R, right frontal; PAR-L, left parietal; PAR-R, right parietal; PF-L, left pre-frontal; PF-R, right pre-frontal; TEMP-L, left temporal; TEMP-R, right; OC-L, left occipital/cerebellar; OC-R, right occipital/cerebellar.

against a prominent state of drowsiness. Nevertheless, it cannot be ruled out that the present resting condition without any attention-demanding task might have induced drowsiness. Moreover, a dampening effect of neuroleptics cannot be ruled out, although the schizophrenic patients were most often tested at the end of their inpatient stay, which was hopefully beyond the phase of pronounced medication-induced sleepiness. Pharmaco-EEG studies have demonstrated the relationship between drug effect, modulation of the alpha and theta/delta EEG frequency bands, and the state of vigilance (e.g., Matejcek 1982; Ott et al 1982). Because none of these studies determined slow wave activity from MEG, direct comparison with and conclusions for our results are difficult; however, those studies, in which the EEG was recorded from many electrodes, revealed evenly distributed activity (Badia et al 1994; Morikawa et al 1997) or a "flat table distribution" of theta activity (Hasan and Broughton 1994), sometimes with anterior predominance of alpha activity or theta

bursts (Hasan and Broughton 1994; Kubicki and Herrmann 1996). An asymmetry of slow frequencies induced by drowsiness or sleep was not reported. Thus, the bilateral posterior concentration of slow wave dipoles in schizophrenic patients in our study would be in line with these findings, whereas the left-frontal focus of delta dipoles would argue against drowsiness as the main explanation for the pattern of focal concentration of slow wave activity.

Neuroleptic medication provides another possible source of influence. The various effects of neuroleptic medication on the human EEG/MEG present a problem in the interpretation of data of any study like ours. General slowing of EEG frequencies has been reported as a consequence of neuroleptic medication (Koshino et al 1993; Malow et al 1994) or, more specifically, increased theta activity concomitant with an increase in haloperidol plasma levels has been reported in patients who responded to the treatment (Czobor and Volavka 1992). Nonetheless, other studies described the effects

of medication as normalizing (e.g., Canive et al 1996, 1998; Saletu et al 1990, 1994).

The insufficient control of the influence of medication in our study (given the insufficient number of nonmedicated patients and the insufficient number of patients with atypical neuroleptics only) must be considered a problem for the interpretation of results. The correlation between chlorpromazine equivalents and right frontotemporal slow wave activity is certainly insufficient to allow any conclusion about the effect of medication on slow wave activity—the more so because precise indicators, the plasma levels, were not available for our sample. The comparison of groups of nonmedicated and medicated patients is a major goal for further studies.

Final conclusions about medication effects on brain activity will be difficult. For instance, medication is assumed to affect the dopaminergic and serotonergic systems, which are distributed over many brain regions. It is not clear to what extent neuroleptic medication might affect one cerebral hemisphere more than another and how this might consequently influence the focal concentration of slow wave activity. Furthermore, the amount of medication varies with the severity of the illness. Although the neuroleptic dosage did not correlate with symptom scores in our study, it cannot be ruled out that those more impaired patients with higher symptom scores received higher doses of neuroleptics. In this case, the correlation of positive symptom scores and slow wave activity as determined by the PCA could have been affected indirectly by medication. The interrelationship of medication and symptomatology also impairs the foremost control of medication effects. For instance, differences of slow wave activity in patients on and off neuroleptics might be the consequence of medication effects but also the consequence of symptom differences.

Our results are promising in several respects. Data obtained from a relatively large number of subjects substantiate and extend previous reports on the amount and localization of MEG slow waves in schizophrenic subjects. In 86% of the schizophrenic patients, a number of delta dipoles above the mean plus one standard deviation of control subjects was found in at least one region. For the focal theta dipoles, the respective number was 82%. The PCA suggested a relationship between symptom characteristics and the origin of slow wave activity in the brain. If regional slow wave activity is related to abnormal functioning of the generating neuronal tissue, these results suggest a potential diagnostic value of the dipole density and the minimum-norm analyses. Brain regions that exhibit enhanced numbers of focal and distributed slow waves can be determined on an individual basis. This may provide the grounds to examine, for example, the diagnostic specificity of distributed and focal slow wave activity

by comparing groups of patients with different diagnoses, or the state-dependence of these patterns by comparing patients in the acute and remitted state. Our study is insufficient in these respects but may provide methods for other studies. Such studies are necessary before speculations about the diagnostic and therapeutic usefulness of the present method can be validated, and the advantage of monitoring the regional distribution of slow waves presented here could become a useful indicator of the effectiveness of diagnostic tools and therapeutic interventions.

References

Andreasen NC (1981): *Scales for the assessment of negative symptoms (SANS).* Iowa City: University of Iowa Press.

Badia P, Wright K, Wauquier A (1994): Fluctuation insingle-Hertz EEG activity during the transition to sleep. In: Ogilvie RD, Harsh JR editors. *Sleep Onset.* Washington, DC: American Psychological Association, 201–218.

Benkert O, Hippius H (1996): *Psychiatrische Pharmakotherapie* (6th ed). Heidelberg: Springer.

Canive JM, Lewine JD, Edgar JC, Davis JT, Torres F, Roberts B, et al (1996): Magnetoencephalographic assessment of spontaneous brain activity in schizophrenia. *Psychopharmacol Bull* 32:741–750.

Canive JM, Lewine JD, Edgar JC, Davis JT, Miller GA, Torres F, Tuason VB (1998): Spontaneous brain magnetic activity in schizophrenic patients treated with aripiprazole. *Psychopharmacol Bull* 34:101–105.

Chua SE, McKenna PJ (1995): Schizophrenia—A brain disease? *Br J Psychiatry* 166:563–583.

Czobor P, Volavka J (1991): Level of haloperidol in plasma is related to electroencephalographic findings in patients who improve. *Psychiatry Res* 42:129–144.

Elbert T, Lutzenberger W, Rockstroh B, Berg P, Cohen R (1992): Physical aspects of the EEG in schizophrenics. *Biol Psychiatry* 32:595–606.

Fenton GW, et al (1980): EEG spectral analysis in schizophrenia. *Br J Psychiatry* 136:445–455.

Galderisi S, Mucci A, Mignone ML, Maj M, et al (1991): CEEG mapping in drug-free schizophrenics: Differences from healthy subjects and changes induced by haloperidol treatment. *Schizophr Res* 6:15–23.

Gattaz WF, Mayer S, Ziegler P, Platz M, et al (1992): Hypofrontality on topographic EEG in schizophrenia: Correlations with neuropsychological and psychopathological parameters. *Eur Arch Psychiatry Clin Neurosci* 241:328–332.

Grave de Peralta Menendez R, Hauk O, Gonzalez Andino S, Vogt H, Michel C (1997): Linear inverse solutions with optimal resolution kernels applied to electomagnetic tomography. *Hum Brain Mapping* 5:454–467.

Hämäläinen M, Ilmoniemi RJ (1984): *Interpreting Measured Magnetic Fields of the Brain: Estimates of Current Distributions. Technical Report* TKK-F-A559:1984.

Harris A, Gordon E, Anderson J, Ritchie G, et al (1997): Change in quantified electroencephalography (QEEG) with medication and altered clinical state in the same subjects with schizophrenia. *Schizophr Res* 23:87–89.

Hasan J, Broughton R (1994): Quantitative topogrpahic EEG mapping during drowsiness and sleep onset. In: Ogilvie RD, Harsh JR editors. *Sleep Onset.* Washington, DC: American Psychological Association, 219–236.

Hauk O, Berg P, Wienbruch C, Rockstroh B, Elbert T (1999): The minimum norm method as an effective mapping tool for MEG analysis. In: Yoshimoto T, Kotani M, Kuriki M, Karibe H, Nakasato N, editors. *Recent Advances in Biomagnetism (Proceedings of the 11th conference on biomagnetism).* Sendai, Japan: Tohoku University Press, 213–216.

Jahn T, Mussgay L (1989): Die statistische Kontrolle möglicher Medikamenteneinflüsse in experimentalpsychologischen Schizophreniestudien. *Z Klin Psychol Psychopathol Psychother* 18:257–267.

Karson CN, Coppola R, Daniel DG, Weinberger DR (1988): Computerized EEG in schizophrenia. *Schizophr Bull* 14:193–197.

Karson CN, Coppola R, Morihisa JM, Weinberger DR (1987): Computed electroencephalographic activity mapping in schizophrenia: The resting state reconsidered. *Arch Gen Psychiatry* 44:514–517.

Kay SR, Fiszbein A, Opler LA (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13:261–276.

Koshino Y, Murata I, Morata T, Omori M, Hamada T, Miyagoshi M, Isaki K (1993): Frontal intermittent delta activity in schizophrenic patients receiving antipsychotic drugs. *Clin Encephalogr* 24:13–18.

Kubicki S, Herrmann WM (1996): The future of computer-assisted investigation of the polysomnogram: Sleep microstructure. *Clin Neurophysiol* 13:285:294.

Lewine JD, Orrison WW (1995): Magnetoencephalography and magnetic source imaging. In: Orrison WW, Lewine JD, Sanders JA, Hartshorne MF, editors. *Functional Brain Imaging.* St. Louis, MO: Mosby-Year Book, 404.

Lukoff D, Nuechterlein KH, Ventura J (1986): Manual for Expanded Brief Psychiatric Rating Scale (BPRS) [Appendix A]. *Schizophr Bull* 12:594–602.

Macmahon JF, Walter WG (1938): The electro-encephalogram in schizophrenia. *J Ment Sci* 84:781–787.

Malow BA, Reese KB, Sato S, Bogard PJ, Malhotra AK, Su TP, Pickar D (1994): Spectrum of EEG abnormalities during clozapine treatment. *Electroencephalogr Clin Neurophysiol* 91:205–211.

Matejcek M (1982): Vigilance and the EEG: Psychological, physiological and pharmacological aspects. In: Herrmann WM, editor. *Electroencephalography in Drug Research.* Stuttgart: Gustav Fischer, 407–510.

McCarley RW, Hsiao JK, Freedman R, Pfefferbaum A, Donchin E (1996): Neuroimaging and the cognitive neuroscience of schizophrenia. *Schizophr Bull* 22:703–725.

Morikawa T, Hayashi M, Hori T (1997): Auto power and cohenrence analysis of delta-theta band EEG during waking-sleeping transition. *Electroencephalogr Clin Neurophysiol* 103:633–641.

Niedermeyer E, Lopes da Silva F (1987): *Electroencephalography: Basic Principles, Clinical Applications and Related Fields* (2nd ed). Baltimore: Urban & Schwarzenberg.

Ogilvie R, Battye RA, Simons IA (1994): Are there changing CNS priorities in sleepiness and sleep? EEG and ERP evidence. In: Ogilvie RD, Harsh JR, editors. *Sleep Onset.* Wahsington, DC: American Psychological Association, 269–287.

Oldfield R (1971): The assessment and analysis of handedness. The Edinburgh Inventory. *Neuropsychologia* 9:97–113.

Ott H, McDonald RJ, Fichte K, Herrmann WM (1982): Interpretation of correlations between EEG-power-spectra and psychological performance variables within the concept of "subvigilance," "attention" and "psychomotoric impulsion." In: Herrmann WM, editor. *Electroencephalography in Drug Research.* Stuttgart: Gustav Fischer, 227–248.

Overall JE, Gorham DR (1962): The Brief Psychiatric Rating Scale. *Psychological-Reports* 10:799–812.

Rappelsberger PD, Lacroix K, Steinberger KT (1994): EEG Amplituden und Kohärenzanalysen bei medikamentenfreien Schizophrenen. *Z Elektroenzephalogr, Elektromyogr* 25:144–150.

Rockstroh B, Elbert T, Berg P (1997): Die Untersuchung von Strukturen und Funktionen des Gehirns in der experimentellen Psychopathologie am Beispiel der Schizophrenien. In: Rockstroh B, Elbert T, Watzl H, editors. *Impulse für die Klinische Psychologie.* Göttingen: Hogrefe, 1–29.

Saletu B, Kuefferle B, Anderer P, Gruenberger J, et al (1990): EEG-brain mapping in schizophrenics with predominantly positive and negative symptoms: Comparative studies with remoxipride/haloperidol. *European-Neuropsychopharmacology* 1:27–36.

Saletu B, Kuefferle B, Grunberger J, Foldes P, Topitz A, Anderer P (1994): Clinical EEG mapping and psychometric studies in negative schizophrenia: Comparative trials with amisulpride and fluphenazine. *Neuropsychobiology* 29:125–135.

Schellenberg R, Knorr W, Beyer H, Kropf S, et al (1989): Multivariate EEG power spectral analysis in acute schizophrenics. *Int J Psychophysiol* 8:85–91.

Serafetinides EA (1984): EEG lateral asymmetries in psychiatric disorders. *Biol Psychol* 19:237–246.

Shagass C (1991): EEG studies of schizophrenia. In: Steinhauer SR, Gruzelier JH, et al, editors. *Neuropsychology, Psychophysiology, and Information Processing. Handbook of schizophrenia.* Amsterdam: Elsevier Science, 39–69.

Tanaka H, Hayashi M, Hori T (1998): Topographic mapping of electroencephalography coherence in hypnagogic state. *Psychiatry Clin Neurosci* 52:147–148.

Tauscher J, Schindler S, Rappelsberger P, Kasper S (1995): EEG-Veränderungen bei schizophrenen Erkrankungen—eine kritische Übersicht./EEG changes in schizophrenic disorders: A critical review. *Fortschr Neurol Psychiatr* 63:162–169.

Ulrich G, Otto W (1984): Zur Bedeutung intermittierender rechts-posterior betonter langsamer Wellen im EEG psychiatrischer Patienten./The significance of slow waves occurring intermittently with right-posterior accentuation in the EEGs of psychiatric patients. *Fortschr Neurol Psychiatr* 52:48–62.

Westphal KP, Groezinger B, Diekmann V, Scherb W, et al (1990): Slower theta activity over the midfrontal cortex in schizophrenic patients. *Acta Psychiatr Scand* 81:132–138.

Winterer G, Herrmann WM (1995): Über das Elektroenzephalogramm in der Psychiatrie: Eine kritische Bewertung. *Z Elektroenzephalogr, Elektromyogr* 26:19–37.