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Source distribution of neuromagnetic slow-wave activity in schizophrenic patients—effects of activation

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Abstract

When slow waves in the EEG delta and theta frequency range appear in the waking state, they may indicate pathological conditions including psychopathology. The generators of focal slow waves can be mapped using magnetic source imaging. The resulting brain maps may possibly characterize dysfunctional brain areas. The present study examined the stability of the density and distribution of MEG slow waves during three conditions—rest, mental arithmetic and imagery—in 30 schizophrenic patients and 17 healthy controls. Schizophrenic patients displayed a higher density of delta and theta generators primarily in temporal and parietal areas. The group difference was not affected by the particular conditions. The focal concentration of delta and theta slow waves did not differ between patients with and without neuroleptic medication, whereas the prominence of theta dipoles in the temporal area correlated with neuroleptic dosage. The relative amount of temporal slow waves was correlated with the negative symptoms score (PANSS-N) suggesting that temporal dysfunction may be related to negative symptomatology. Results suggest that the distribution of slow-wave activity, measured in a standardized setting, might add diagnostic information about brain abnormalities in schizophrenia.

Keywords: Schizophrenia; Magnetoencephalography; Delta; Theta; Dipole density; Negative symptoms

1. Introduction

If prominent during the waking state, slow waves generated in a circumscribed brain region typically characterize pathological or dysfunctional neural tissue. Focal slow waves appear in the vicinity of structural lesions like cerebral infarcts, contusions, local infections, tumors, developmental defects, degenerative defects or subdural hematomas (Niedermeyer and Lopes da Silva, 1987; Lewine and Orrison, 1995; Matsuoka, 1990; Vieth et al., 2000; De Jongh et al., 2001). Since enhanced activity in lower EEG-frequency bands has also been reported in a variety of psychopathological conditions (for schizophrenia, see, for instance, Winterer and Herrmann, 1995; Shagass, 1991; Rockstroh et al., 1997), we have previously suggested that dysfunctional brain areas in psychiatric patients might be indicated by the concentration of focal magnetic slow waves (Rockstroh et al., 2000). In schizophrenic patients, we found slow-wave generators in the magnetoencephalogram (MEG) to be more frequent in association cortices, mostly in temporal

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and parietal regions (Fehr et al., 2001). Given that focal slow-wave concentration is related to neuropsychological dysfunctions in schizophrenic patients, brain mapping of focal slow-wave generators may add information about possible neurophysiological correlates of psychopathology. However, the dependency of this phenomenon on the particular context, state of activation or mental task activity of a patient and its interaction with psychoactive medication needs to be thoroughly explored before further consideration from the perspective of diagnostic usefulness.

Previous reports of enhanced electric slow waves in psychiatric patients over posterior, frontal-midline and frontal-temporal regions (Schober et al., 1996; Fernandez et al., 1995; Iramina et al., 1996; Nakashima and Sato, 1992) did not distinguish focal generators from more widespread slow activity, i.e., they did not differentiate likely indices of pathological brain activity from those that appear in the intact brain under various conditions of activation and mental load. A first indication that the slow waves in schizophrenic patients may be of a particular nature came from a study by Elbert et al. (1992) which showed not only enhanced delta power in schizophrenic patients, but also a different form of these slow waves and the embedding EEG time course between groups.

On this background, the present study explored the stability of focal magnetic slow waves across three different conditions of mental activation, designed to enhance either left (mental arithmetic) or right parieto-temporal (spatial imagery) brain hemispheric activation. We wanted to know to what extent the topographical pattern of slow-wave activity may serve as a marker of cortical dysfunction during the waking state irrespectively of the type of the particular mental activity during which the measurement is obtained. Effects of task or activation would make it difficult to establish a diagnostic tool based on focal slow-wave mapping. Another possible complication may come from the impact of medication. General slowing of EEG frequencies has been reported as a consequence of neuroleptic medication (Koshino et al., 1993, Malow et al., 1994), but also normalizing' effects (Canive et al., 1996, 1998; Saletu et al., 1994). Therefore, the possible relationship between the focal clustering of slow waves and neuroleptic medication was also addressed.

The data reported here result from a larger long-term project that attempts to examine the diagnostic usefulness of focal slow-wave mapping. Further outcome will be reported elsewhere. For the resting state only, a fraction of the presently reported data from a subsample of 16 patients was included in Fehr et al. (2001). As there were no differences between the original 16 and the presently added 14 patients in the outcome measures, they are pooled here in one group.

2. Methods and materials

2.1. Subjects

Thirty patients (12 females) aged 31.6 ± 8.9 years with the DSM-IV diagnosis of a schizophrenic disorder were compared to 18 healthy subjects (2 females). After one control subject had to be excluded because of artifact-contaminated data, the mean age of the group of 17 controls was 32.4 ± 11.2 years.

All patients, inpatients of the university research ward at the local Center of Psychiatry, were asked by the psychiatrist or psychologist in charge whether they would be willing to participate in the study. Diagnoses were given by the psychiatrist/psychologist in charge on the bases of ICD-10 diagnostic criteria. As summarized in Table 1, the majority of patients met the diagnosis of paranoid–hallucinatory subtype ($N=22$; three patients were diagnosed as undifferentiated, two as disorganised; two patients met the criteria of a schizophreniform disorder and one of a schizoaffective disorder. Additional diagnoses—mostly of drug dependence—were given to six patients.

The psychopathological status of each patient was assessed on the day of the experiment by the psychologist/psychiatrist in charge by means of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) (average scores PANSS-P: 15.8 ± 4.9, range 8–26; PANSS-N: 21.2 ± 6.7, range 9–33; PANSS-G: 37.8 ± 12.0, range 25–87) (see Table 1 for individual symptom scores). Twenty-one patients were under neuroleptic medication at the time of the assessment, 12 receiving typical neuroleptics only, 3 atypical neuroleptics only and 5 a combination of typical and atypical neuroleptics (see also Table 1). The patient with schizoaffective disorder received a combination

Table 1
ICD-10 diagnoses, type of medication (INN) and PANSS scores for the 30 schizophrenic patients

Patient	ICD-10	Medication	PANSS-P	PANSS-N
1	F20.0	none	26	13
2	F20.0, F12.1	none	13	25
3	F20.0, F12.1	none	17	17
4	F20.3	clozapin, flupentixol	15	20
5	F20.0	none	22	33
6	F20.1	none	14	22
7	F20.0	none	Not available	Not available
8	F20.0, F19.1	none	10	14
9	F20.0	perphenazin, levopromazin	14	9
10	F20.0	perphenazin	16	13
11	F20.0	haloperidol, levopromazin	15	24
12	F20.8	haloperidol	11	25
13	F20.0	clozapin	Not available	Not available
14	F20.0	clozapin, melperon	25	19
15	F20.0, F12.2	flupentixol, chlorprothixen	8	24
16	F20.0,	flupentixol	9	13
17	F20.1	none	22	26
18	F20.0	haloperidol	10	22
19	F25.0	lithium, chlorprothixen	Not available	Not available
20	F20.0	perphenazin	14	16
21	F20.0	haloperidol, clozapin	11	21
22	F20.8	chlorprothixen, atypical	22	13
23	F20.3	risperidon, chlorprothixen	15	30
24	F20.0	clozapin	22	31
25	F20.0, F12.1	fluphenazin, perphenazin	20	25
26	F20.0	none	Not available	Not available
27	F20.0	haloperidol, chlorprothixen	15	14
28	F20.3	risperidon	17	29
29	F20.0, F10.1, F19.1	haloperidol, chlorprothixen	13	17
30	F20.0	haloperidol perphenazin	18	30

Each PANSS scale comprises seven items with scores ranging from 1 (not apparent) to 7 (maximal strength of symptom). Thus, sum scores can vary between 7 (asymptomatic) to 49.

of lithium and chlorprothixene. Two patients received additional anticholinergics. The average daily dosage was 144.99 ± 163.6 mg CPZ eq (CPZ eq were determined after Jahn and Mussgay, 1989; the atypical neuroleptics used, clozapine and risperidone, were adjusted for the CPZ eq according to the same table with 0.9 and 8, respectively). Nine patients were unmedicated at the time of the measurement, because they had refused neuroleptic treatment until their admission. For all patients, it was ascertained that patients did not use any psychoactive substances other than nicotine during their inpatient treatment. Duration of illness varied between 1 and 107 months (mean 22.04 ± 29.37 months).

Control subjects, recruited by announcements in the hospital and the university, were interviewed by a trained psychologist and were only accepted if they did not report any history of psychiatric illness for themselves or first degree relatives, if they did not report head injury or other neurological disorders affecting the brain, and if they did not report to be under current psychoactive medication or regular drug use or abuse. In all subjects, handedness was assessed by a modified version of the Edinburgh Handedness Questionnaire (Oldfield, 1971) asking subjects to demonstrate hand use on various actions (like using a broom, brushing teeth, writing, etc.). Five patients proved to be left-handed, while all controls were determined as right-handed. Prior to the experiment, subjects were familiarized with the recording environment, informed about the procedure and gave written consent to participate in the experiment, for which they received a financial bonus of about US$10.

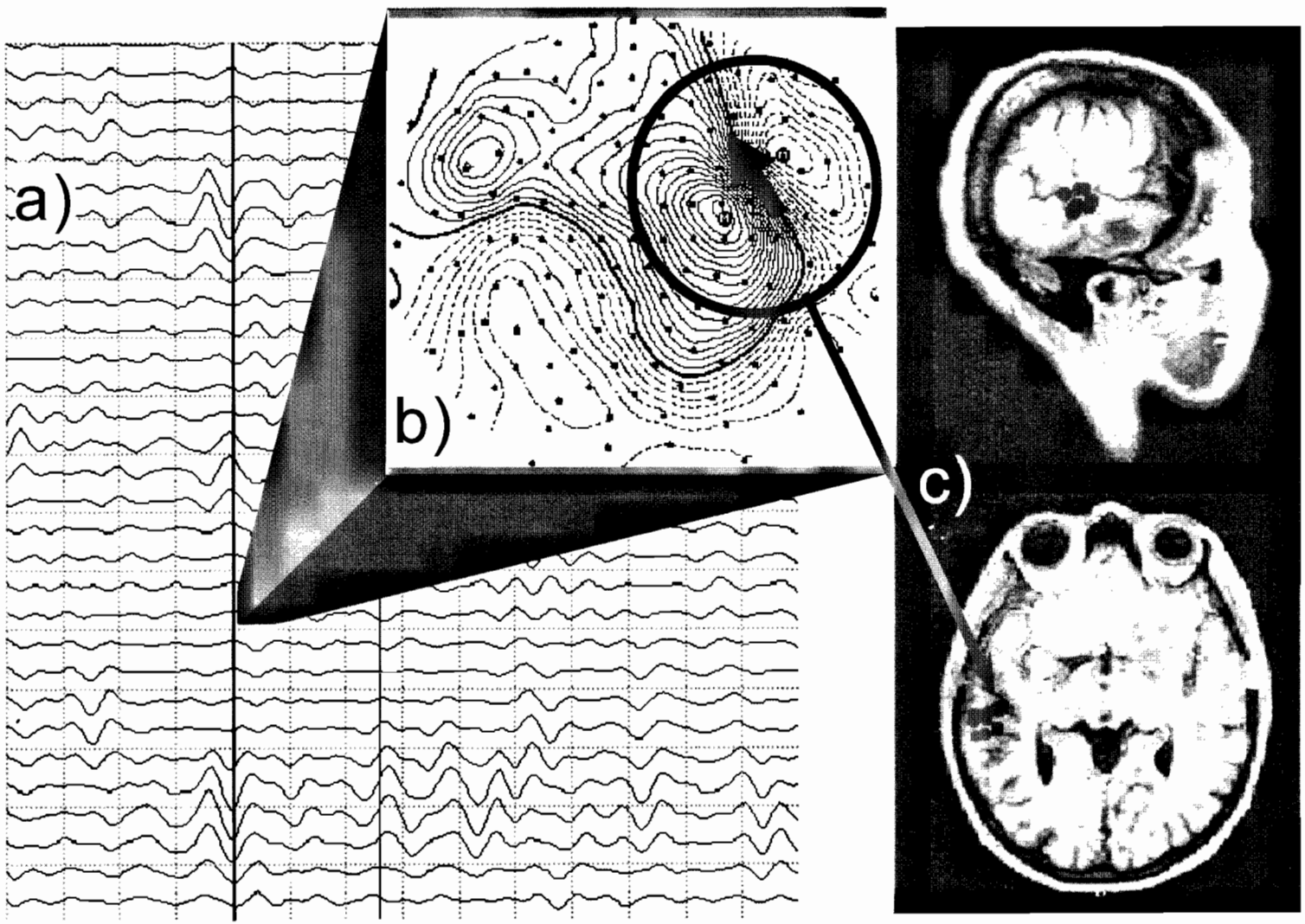

Fig. 1. Determination of dipole density. (a) Selection of MEG traces. Large-amplitude slow waves can be observed in a subset of channels. (b) Contour plot. The algorithm detects a regional dipolar source which can be fitted with an equivalent current dipole model (GOF > 0.90 required). (c) Localization of the dipolar activity and determination of number of dipoles located within predefined brain regions per unit time. Note that a high goodness for the dipole fit is required only for a subset of 37 channels (e.g., within the circle indicated in (b)) and that activity may or may not appear simultaneously at other sensors.

2.2. Data collection

Using a 148-channel whole-head neuromagnetometer (MAGNES™ 2500 WH, 4D Neuroimaging, San Diego, USA), the MEG was measured during three periods of 5 min each. In the *resting* condition, subjects were asked to relax but to stay awake and not to engage in any specific mental activity. In the *mental arithmetic* condition, subjects were asked to translate the words of a common German folksong letter by letter into numbers (a corresponding to 1, b to 2, c to 3, etc.) and total them up. In the *mental imagery* condition, subjects were asked to imagine as vividly as possible walking a well-known and recently strolled footpath, e.g., through the hospital area. Breaks separated the three recording periods and allowed subjects to move. MEG recordings were obtained in a supine position, and subjects were asked to fixate upon a colored fixation mark on the ceiling of the magnetically shielded room throughout the recording in order to avoid eye- and head-movement. A video camera installed inside the chamber allowed monitoring the subject's behavior and compliance at any time throughout the experiment. For the mental arithmetic condition, compliance was assessed by comparing the result of totaling up the word sums and the position in the song that was reached by the subject at the end of the 5-min period. For the mental imagery condition compliance was assessed by asking the subject to describe the imagined tour in detail.

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 (EOG) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye. The electrocardiogram (EKG) was monitored via electrodes attached to the right collarbone and the lowest left rib. A Synamps amplifier (NEUROSCAN) served for the recording of EOG and EKG.

2.3. Data reduction and analysis

For each of the three 5-min recording epochs the data were band-pass filtered by a second order filter in the delta (1.5–4.0 Hz) and theta (4.0–8.0 Hz) band. The number of sample points was reduced by factor 16 prior to further analysis, each sample point representing an epoch of about 20.8 ms. Artifact-free time segments 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 100 fT < (RMS=($\sqrt{(1/n\sum(x_1)^2)}$)) < 300 fT and a goodness of fit (GOF) greater than 0.90 were accepted for further analysis. These restrictions should ensure that neither artifacts nor small amplitude biological noise would affect the results, and that only dipolar fields that were generated by focal sources were analyzed. Since artifact-free epochs varied in length, the percentage of data time points per second that could be fitted by the dipole model in a particular area was submitted to the statistical analyses (see Fig. 1 for an illustration of steps in data reduction).

The distribution of dipole density was assessed by dividing the total brain volume into 10 regions, five in each hemisphere: prefrontal, frontal, temporal, parietal and occipital. Effects of conditions and diagnosis on the pattern of dipole densities in the delta and theta

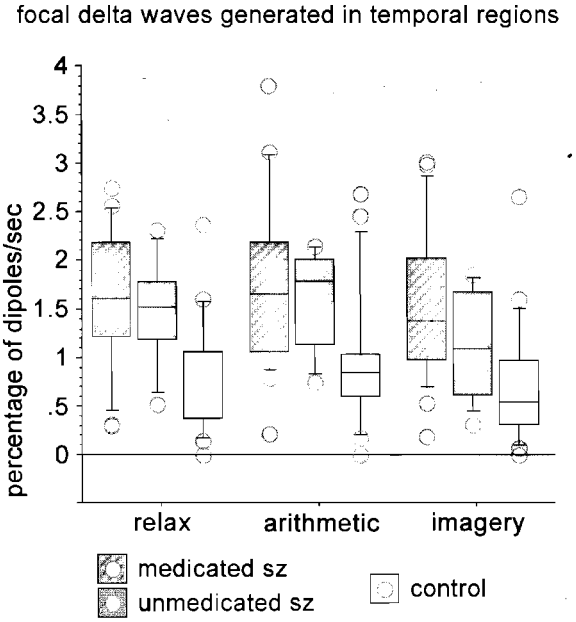

Fig. 2. Boxplot for the percentage of delta dipoles per second (ordinate) for the group of controls and the groups of schizophrenics with and without medication. The three different conditions (abscissa: resting, arithmetic, imagery) produce similar differences between groups in temporal regions, with many schizophrenic subjects exhibiting values outside the range of controls.

range were evaluated by analyses of variance with the between-subjects factor GROUP and the within-subjects factors CONDITION, AREA (comparing prefrontal, frontal, temporal, parietal, and occipital dipole densities) and HEMISPHERE (comparing the left- and right-hemispheric areas). For interactions with degrees of freedom larger than 1, the degrees of freedom were corrected using the Greenhouse–Geisser procedure to account for possible violations of the sphericity assumption.

3. Results

Schizophrenic patients exhibited more focal delta activity (i.e., a higher percentage of delta dipoles per second) than controls, group differences being most pronounced in temporal and parietal areas [GROUP $\times$ AREA $\times$ HEMISPHERE, $F(4,180)=3.01$, $p<0.05$; GROUP, $F(1,45)=6.41$, $p<0.05$; for temporal areas, GROUP, $F(1,45)=10.75$, $p<0.01$; for parietal areas, GROUP, $F(1,45)=5.47$, $p<0.05$]. This result was equally prominent for all conditions, i.e., there was no interaction of group with task (Fig. 2 and Table 2). Temporal delta was equally prominent in medicated ($N=21$) and nonmedicated ($N=9$) patients (Fig. 2).

Table 2
Mean ($\pm$ S.D. in brackets) percentage of delta dipoles per second of artifact-free epochs in the two groups (p = schizophrenic patients, c = controls) for the three conditions (resting, mental arithmetic and mental imagery)

	Resting		Mental arithmetic		Mental imagery	
	p	c	p	c	p	c
Left prefrontal	1.13 (1.00)	1.13 (1.25)	1.48 (1.36)	1.53 (1.50)	1.18 (0.99)	1.19 (1.18)
Right prefrontal	1.27 (0.98)	0.82 (0.59)	1.56 (1.55)	1.07 (0.90)	1.58 (1.14)	0.74 (0.74)
Left frontal	0.89 (0.61)	0.59 (0.48)	0.81 (0.75)	0.65 (0.51)	0.77 (0.50)	0.60 (0.50)
Right frontal	0.99 (1.00)	0.62 (0.45)	1.07 (1.22)	0.63 (0.60)	1.11 (0.98)	0.62 (0.45)
Left temporal	1.60 (0.92)	0.73 (0.77)	1.66 (0.98)	0.89 (0.82)	1.35 (0.82)	0.67 (0.76)
Right temporal	1.54 (0.68)	0.82 (0.55)	1.76 (0.73)	1.00 (0.69)	1.44 (0.76)	0.77 (0.62)
Left parietal	1.52 (1.32)	0.62 (0.52)	1.04 (0.90)	0.69 (0.49)	1.16 (0.86)	0.64 (0.42)
Right parietal	1.52 (1.20)	0.69 (0.43)	1.08 (0.85)	0.80 (0.58)	1.16 (0.90)	0.86 (0.65)
Left occipital	0.72 (0.86)	0.36 (0.40)	0.68 (0.73)	0.44 (0.51)	0.70 (0.94)	0.39 (0.48)
Right occipital	0.72 (0.71)	0.43 (0.62)	0.59 (0.44)	0.47 (0.69)	0.62 (0.57)	0.58 (0.90)

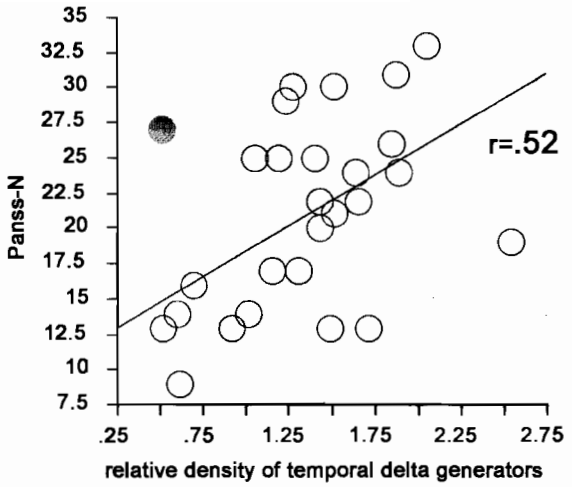

Fig. 3. Correlation between the relative density of temporal delta dipoles (percentage temporal dipoles per second divided by the average percentage of dipoles per second across all brain regions) and the amount of negative symptoms as measured by the PANSS-N scale. The correlation is significant even if one subject with a high dipole density in all areas (indicated by the dark dot) is included.

The temporal percentage of delta dipoles per second relative to the total amount (averaged across all areas) correlated positively with the negative symptoms ($r=0.42$, $P<0.05$; excluding one subject with a relative large amount of delta dipoles in all other regions and, therefore, a lower fraction of temporal activity would increase the correlation coefficient to $r=0.52$, Fig. 3).

In both groups, mental arithmetic produced a somewhat higher amount of focal slow waves than rest and imagery in temporal [CONDITION, $F(2,90)=4.51$, $p<0.05$] and prefrontal [CONDITION, $F(2,90)=4.83$, $p<0.05$] areas.

Patients also produced a significantly greater percentage of theta dipoles per second than controls, group differences being again most pronounced in temporal and parietal areas compared to prefrontal, frontal and occipital areas [GROUP $\times$ AREA $\times$ HEMISPHERE, $F(4,180)=5.11$, $p<0.01$; GROUP, $F(1,45)=5.73$, $p<0.05$; for temporal areas, GROUP, $F(1,45)=7.97$,

$p<0.01$; for parietal areas, GROUP, $F(1,45)=4.27$, $p<0.05$]. While the prominence of temporal theta activity did not differ significantly between medicated and nonmedicated patients ($F<1$), the patients with higher daily medication displayed more pronounced temporal theta prominence ($r=0.51, p<0.01$).

Effects of mental activation on theta dipole density were similar in both groups (interactions n.s.) with higher density of theta dipoles during spatial imagery than during the other two conditions [CONDITION, $F(2,90)=3.41, p<0.05$]. Imagery reduced and mental arithmetic increased parietal theta activity, while both activation conditions reduced frontal theta activity relative to rest [CONDITION × AREA, $F(8.360)=4.92, p<0.01$].

4. Discussion

The present findings underscore the previous report (Fehr et al., 2001) of more frequent generators of focal slow waves (in the delta and theta bands) in schizophrenic patients. This activity prevails in temporal and parietal areas. A generator within the temporal lobe may be oriented such that its volume currents project to frontal scalp regions (like, e.g., the generators of the auditory evoked N100). In this case EEG recordings would pick up activity over frontal regions. The group-specific distribution of focal slow waves appeared under all conditions of mental activation. Mental activation changed the pattern of focal slow-wave activity relatively little, only in prefrontal areas, and to a similar degree, whereas the prominent difference between groups in temporal brain regions was not affected at all. Thus, a disease-specific pattern of focal slow-wave activity and the effect of activation on slow waves seem to add together. It might be possible that characteristics in the course of brain activity over time might allow to tease apart these two different types of slow-wave activity, given that nonlinear measures add to the differentiation between groups (Elbert et al., 1992).

The accentuation of focal slow wave in the temporal regions correlated with the negative symptoms score. If these focal waves do indicate dysfunctional brain tissue, then the present results add to structural and functional evidence of temporal abnormalities in schizophrenia (McCarley et al., 1999; Shenton et al., 2001) in addition to the equally often reported frontal dysfunction. Indications of temporal dysfunctions have been obtained from imaging (Deicken et al., 1995; Hirayasu et al., 1999) and event-related potential studies (Faux et al., 1990; McCarley et al., 1993). If we consider volume reduction in the temporal lobe (Johnstone et al., 1989; McCarley et al., 1999) as an indication of dysfunction comparable to a lesion, enhanced slow-wave activity arising from these regions is a conceivable finding.

Patients with and without neuroleptic medication did not differ in the temporal enhancement of slow-wave (delta and theta) activity, whereas temporal theta prominence correlated with daily dosage of neuroleptics. This does not seem to support findings of a general slowing of EEG frequencies as a consequence of neuroleptic medication (Koshino et al., 1993; Malow et al., 1994), but might be considered in line with the finding of increased EEG theta activity concomitant with an increase in haloperidol plasma levels in patients who responded to the treatment (Czobor and Volavka, 1991). However, pharmaco-EEG studies have mostly reported 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 theta bursts (Kubicki and Herrmann, 1996), but no relationship between temporal enhancement of slow-wave generators and medication. Therefore, we assume a rather weak impact of neuroleptic medication on the diagnosis-specific pattern of slow-wave generators. Moreover, an indirect relationship between focal slow waves and severity of illness is indicated by the negative symptom score, while the impact of neuroleptic medication was not supported by a significant correlation between the two latter measures.

Group differences were also statistically meaningful for the theta band. However, the magnitude of effects was less pronounced, possibly, because focal theta activity was affected by medication and the type of task. Increased power in the EEG theta frequency band has been found with different mental tasks including, for instance, the encoding of material that was later successfully retrieved (Klimesch et al., 1996, 1997, 2001; Doppelmayr et al., 1998; Yamamoto and Matsuoka, 1990). Although the type of task differs between those studies and the present one, a common element in memory encoding and

retrieval and the imagination of a well-known path from memory might be associated with enhanced theta activity. Thus, the present analysis confirms that mental imagery activates theta sources and indicates that the sources of this activity are confined to prefrontal brain areas.

Tasks had been selected to specifically activate either the left or the right hemisphere. Contrary to our expectation though, the distribution of delta and theta dipole densities was not asymmetrical and did not vary with the task in a hemisphere-specific manner. This suggests that delta and theta dipole densities are not task-related—like activity in the gamma band. Thus, we have to conclude the tasks selected for hemisphere-specific mental activation and the measure selected as indication of (dys)function did not fit most favorably.

In sum, the present results support previous EEG and MEG studies regarding the evidence of an activation-invariant pattern of prominent temporal slow-wave activity in schizophrenics. The distribution of focal slow-wave clusters might add diagnostic information, the more so as recent results from our laboratory indicate a diagnostic specificity of the presently reported pattern for schizophrenia when contrasted with depression (Wienbruch et al., submitted for publication). An abnormal activity in the temporal association cortices seems to vary with negative symptoms, while it seems possible that abnormal activity in other areas could represent other aspects of the schizophrenic symptomatology. It might be worthwhile to examine the clinical usefulness of this additional information.

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