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Left temporal deficit of P300 in patients with schizophrenia: effects of task

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Abstract

P300 is often, but not always, observed to be more reduced over left than right temporal lobes in patients with schizophrenia. The possibility that task differences contribute to the inconsistency in the literature was explored in this study. ERPs were collected from 17 right-handed men with schizophrenia (DSM-IIIIR) and 11 right-handed healthy male community controls, performing three auditory oddball tasks — respond to a target tone by: (1) counting; (2) pressing a response button with the right index finger; or (3) pressing a response button with the left index finger. Although patients with schizophrenia had smaller and later P300 amplitudes than controls, they did not have smaller P300s over the left temporal scalp (T3) than over the right (T4). P300 recorded over the left (C3) and right (C4) motor cortices indicated sensitivity to responding hand, with greater negativity being associated with contralateral button pressing. Failure to find P300 asymmetry is not related to the presence or absence of a button pressing task, or the hand used for button pressing. Rather, P300 asymmetry may be related to structural neuroanatomical asymmetries. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Schizophrenia; Event-related potentials (ERPs); P300; Lateral asymmetry; Task

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1. Introduction

While there is general agreement that the P300 component of the event-related potential recorded parietally at midline (Pz) is reduced in patients with schizophrenia (Ford, 1999), there is less agreement over whether this reduction is laterally symmetric (McCarley et al., 1997). One group of investigators has found *symmetric* reduction of P300 recorded in two samples of patients with schizophrenia recruited from a Veterans Affairs hospital (Pfefferbaum et al., 1989, 1991; Ford et al., 1994c), as well as from severely ill patients recruited from a state hospital (Ford et al., 1999). Symmetrical temporal site reduction in P300 has also been reported in other laboratories (Michie et al., 1990; Stefansson and Jonsdottir, 1996; Umbricht et al., 1998). However, a finding of greater P300 amplitude reduction over left than right temporal lobes in schizophrenia (Morstyn et al., 1983) has been consistently confirmed by subsequent studies in the same laboratory in patients with schizophrenia off-medication (Faux et al., 1993), first episode patients (Salisbury et al., 1998), and in patients with schizophrenia spectrum disorders (Salisbury et al., 1996). Left lateralized P300 reduction in schizophrenia has also been reported by other investigators (Strik et al., 1994a,b; Heidrich and Strik, 1997; Turetsky et al., 1998; Bruder et al., 1999).

Possible explanations for the discrepant findings include differences in acquisition or analysis of ERPs (Faux et al., 1990; McCarley et al., 1991; Pfefferbaum et al., 1991) as well as differences in sample characteristics, particularly the degree of asymmetry in temporal lobe gray matter deficits (e.g. McCarley et al., 1993; O'Donnell et al., 1999), overall amplitude of P300 (Hill and Weisbrod, 1999), or handedness of subjects (Holinger et al., 1992). Other factors that have been considered include task difficulty (Salisbury et al., 1994; Weisbrod et al., 1997), and whether or not a button press response is required (Bruder et al., 1996): in general, studies requiring a button press have not shown P300 asymmetry in patients with schizophrenia, with some exceptions (e.g. Turetsky et al., 1998).

A variety of methodological differences

between studies using count and button press tasks preclude a clear assessment of whether button press alone is responsible for the presence or absence of left temporal lobe P300 deficits in patients with schizophrenia. In this study, right handed patients with schizophrenia and right handed healthy controls performed an auditory oddball task under three conditions: count targets; press a button with right hand; and press a button with left hand. If scalp asymmetries associated with button pressing were responsible for suppressing an asymmetric P300 in patients, an asymmetry should be seen in the count condition.

2. Materials

2.1. Subjects

Demographic and clinical characteristics of the subject groups are provided in Table 1. All subjects were right-handed (Crovitz and Zener, 1962) and provided written informed consent.

2.1.1. Patients

Patients ($n = 17$) were medically healthy men who met diagnostic criteria for chronic schizophrenia according to the Diagnostic and Statistical Manual-III-Revised (DSM-III-R) (American-Psychiatric-Association, 1987) and did not have a history of significant head injury (loss of consciousness ≥ 30 min or neurological sequelae), current alcohol or substance dependence, past or present epilepsy, psychosurgery or other non-schizophrenic illness that would affect the central nervous system. At the time of testing, 15 were in-patients on a research psychiatric ward at the Veterans Affairs Palo Alto Health Care System, and two were currently living in the commu-

Table 1
Means and standard deviations for age, education and BPRS for each group

Groups	Age (years)	Education (years)	BPRS
Patients ($n = 17$)	38.9 \pm 11.2	13.9 \pm 1.4	39.7 \pm 7.4
Controls ($n = 11$)	40.3 \pm 8.1	16.4 \pm 2.5	–

nity and being followed as outpatients. Patients participated in a standard auditory oddball ERP paradigm when they had been stable for at least 2 weeks on either typical ($n = 13$) or atypical ($n = 3$) antipsychotic medication or had been medication-free for 2 weeks ($n = 1$). Within 3.4 days of ERP testing (range: 0–11 days), patients were assessed by two trained raters using the Brief Psychiatric Rating Scale (BPRS), a semi-structured interview yielding measures of symptom severity (Overall et al., 1967).

2.1.2. Controls

Controls ($n = 11$) for this study included men recruited from the neighboring community. Some had participated previously in other electrophysiological (Ford et al., 1994b,c) studies from our laboratory. Subjects who responded to recruitment advertisements were initially screened over the phone. Those willing to participate and passing this screen were invited into the laboratory where they were further screened by a psychiatric interview [Schedule for Affective Disorders and Schizophrenia-Lifetime (SADS-L) (Endicott and Spitzer, 1978) or Structured Clinical Interview for DSM-III-R (SCID)] (Spitzer et al., 1989). Prospective controls were excluded if they met criteria for substance abuse in the past year, or life-time history of other psychiatric disorder.

2.2. ERP recording and analysis

Subjects were tested on an auditory oddball task which took approximately 10 min to conduct and consisted of a series of 320 standard tones and 80 target tones with a fixed interstimulus interval of 1.5 s. Standard tones were 500 Hz, 70 dB SPL, 50-ms duration and occurred on 80% of the trials. Target tones were 1000 Hz, 70 dB SPL, 50-ms duration and occurred on 20% of the trials. Tones had a shaped rise and fall time of 5 ms. Stimuli were presented in a Bernoulli sequence held constant across subjects. The task was repeated three times with different instructions each time: count the target tones (Count); press the reaction time button with right hand to target tones, giving equal importance to speed and accuracy (Press Right); press the reaction time button

with left hand to target tones, giving equal importance to speed and accuracy (Press Left). The order of conditions was counter-balanced across subjects.

EEG was recorded from Fz, Cz, Pz, Oz, A1, T3, C3, C4, T4, and A2 electrodes and referenced to a sternovertebral electrode with a balancing circuit to minimize EKG artifacts (Stephenson and Gibbs, 1951). Vertical EOG was recorded from electrodes placed above and below the right eye, and horizontal EOG from electrodes placed at the outer canthus of each eye.

2.2.1. Data screening

Single trials were individually screened by computer algorithm before being included in the averages. First, trials on which EEG at any electrode site saturated the A/D converter ($> \pm 250 \mu\text{V}$) were rejected. Next, single trials at each electrode were individually corrected for the effects of eye blinks and eye movements (Gratton et al., 1983; Miller et al., 1988). Trials with button presses occurring before 100 ms or after 1150 ms were excluded as were those with incorrect button presses. Each averaged ERP waveform comprised 30 or more trials.

2.2.2. Peak identification

Before peak identification, EEG was filtered with a 0.5-Hz (down 3 dB) high pass filter (Coppola, 1979) and with a 12.4-Hz (down 3 dB) low pass filter (Ruchkin and Glaser, 1978). For the analyses presented here, P300 was measured by finding the peak between 275 and 600 ms at each lead, and averaging the amplitude over a 50 ms window centered on that latency; similar to that reported by the McCarley group (Salisbury et al., 1994).

2.2.3. Statistical analyses

Partially repeated measures analyses of variance were performed to determine effects on P300 amplitude and latency of Group (patient vs. control); Task (Count, Push Left, Push Right); Antero-Posterior topography [frontal (Fz, F3, F4, F7, F8), central (Cz, C3, C4, T3, T4), and parietal (Pz, P3, P4, P5, T6)]; and Lateral topography [midline (Fz, Cz, Pz), left (F3, C3, P3), far left (F7,

T3, T5), right (F4, C4, P4), far right (F8, T4, T6)] on P300 amplitude. Additional analyses were performed on subsets of the data to answer specific questions: Push Left vs. Push Right task using only C3 and C4 sites (to determine whether responding hand affected P300 amplitude laterality); and all tasks at T3 and T4 only, to determine effects of Task and Group at T3 and T4 where greatest lateralized P300 reduction in patients with schizophrenia has previously been reported. For these analyses, the factor of Side (left vs. right) was analyzed. To correct for violations of the sphericity assumption, Geisser-Greenhouse corrections were used for factors containing three or more levels.

Mean reaction time (RT) and error data were also subjected to repeated measures analyses of variance for the factors of Group and Task.

3. Results

3.1. Behavioral data

Reaction times were slower in patients (435 ms) than in controls (331 ms) ($F_{1,26} = 7.99$, $P < 0.01$). Patients (7.5%) tended to make more errors than controls (<1%) ($F_{1,26} = 3.92$, $P < 0.06$). Neither RTs nor error rates were affected by Task (Push Left vs. Push Right) nor did the Group effect interact with Task.

3.2. Overall analysis of variance of ERP data

As can be seen in Fig. 1, in which ERPs for controls and patients with schizophrenia are overlaid, P300 was smaller in patients than in controls ($F_{1,26} = 4.28$, $P < 0.05$). The expected parietal distribution of P300 was significant [Antero-Posterior ($F_{2,52} = 39.36$, $P = 0.0001$)] as was the Lateral distribution ($F_{4,104} = 163.2$, $P = 0.0001$), reflecting larger P300s closer to the midline. Task did not significantly affect P300 amplitude ($F_{2,52} = 1.77$, ns). The interactions of Group with Task, Antero-Posterior or Lateralized topographies were not significant.

P300 was later in patients (389 ms) than in controls (352 ms) ($F_{1,26} = 5.13$, $P < 0.04$), an ef-

fect that appeared strongest at frontal sites as revealed in a Group by Antero-Posterior interaction ($F_{2,52} = 4.79$, $P < 0.02$). There was no effect of Task on P300 latency, and no other significant interactions among the variables.

3.3. Task, group, and responding hand effects at C3 and C4

To specifically address the effect of responding hand on P300 asymmetry, data from C3 and C4 were analyzed for the Push Right and Push Left conditions. P300 at the side contralateral (e.g. C3) to the responding hand (e.g. right) was smaller than P300 ipsilateral (e.g. C4) to the responding hand ($F_{1,1} = 17.05$, $P = 0.0003$), indicating that there is negativity associated with pressing that is contralateral to the responding hand. The Group by Side interaction was not significant ($F_{1,26} = 2.46$, $P = 0.13$). These effects can be seen in Fig. 2.

3.4. Task and group effects at T3 and T4

Fig. 2 represents data from right and left scalp sites, overlaid for the three different tasks to emphasize the asymmetries in P300, and Fig. 3 summarizes the main effects seen at T3 and T4. To statistically assess the differences at the temporal sites, data from T3 and T4 were analyzed and revealed trends for P300 reduction in patients ($F_{1,26} = 4.201$, $P = 0.051$). Although there was a slight tendency for P300 at T3 to be smaller than at T4 ($F_{1,26} = 4.192$, $P = 0.051$), this asymmetry was not different in patients and controls (Group \times Side: $F_{1,26} = 0.19$, $P = 0.66$). There was no main effect of Task and no interactions between Task, Side, or Group. When only data from the counting condition were included, there was no evidence of different asymmetries in the patients and controls ($F_{1,26} = 0.66$, $P = 0.42$). Of the 17 patients, 16 had little or no (-1.0 – 1.0 μ V) P300 difference between T3 and T4, while one patient had a difference of -2.0 μ V, indicating smaller P300s over left than right sites. Similarly, of the 11 controls, nine had little or no difference, while two controls had differences of -2.0 and -3.0 μ V.

ERPs to Counted Target

— Control
 — Schizophrenic

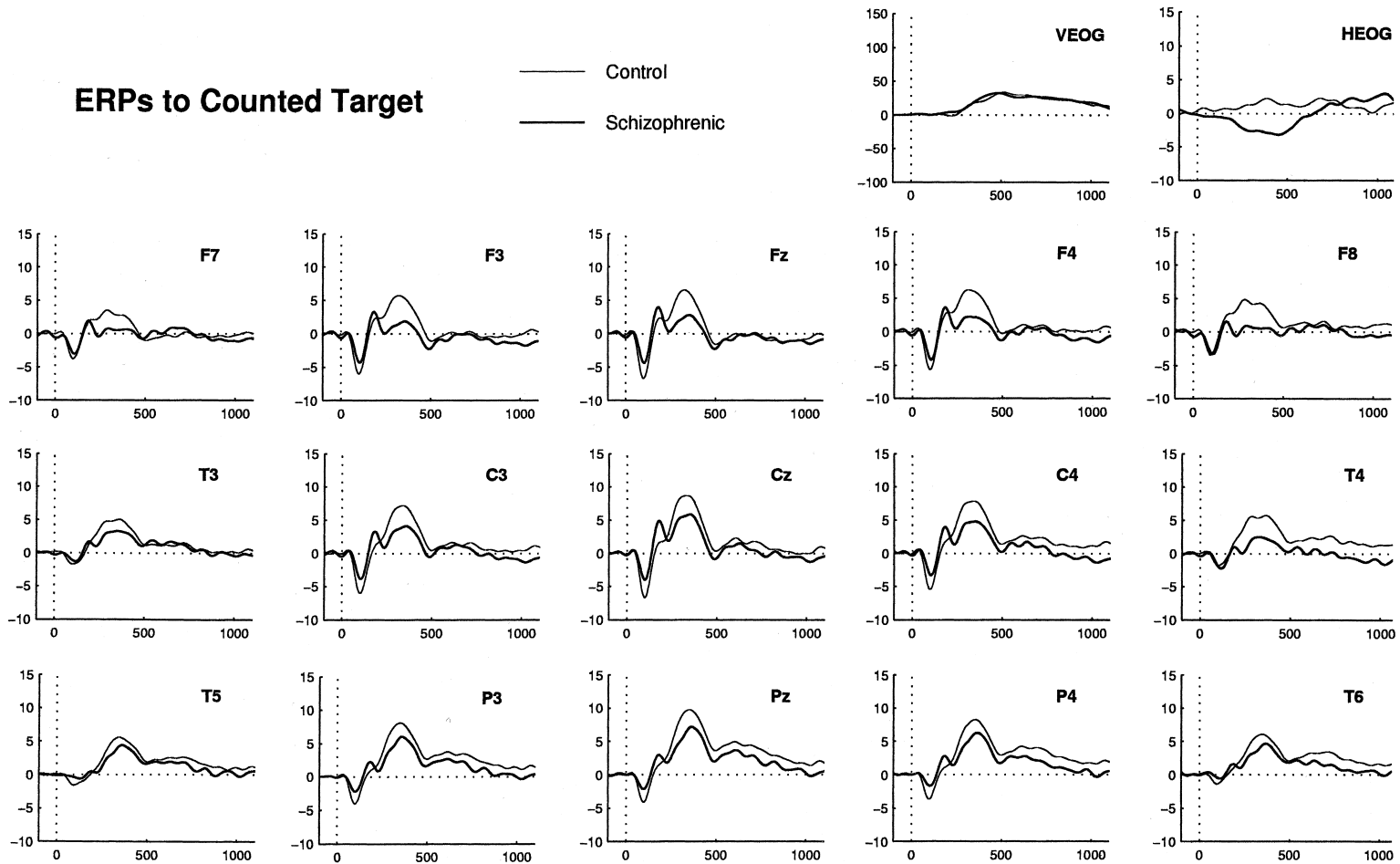


Fig. 1. Grand averages for normal controls ($n = 11$) (thin line) and patients with schizophrenia ($n = 17$) (thick line) for ERPs to the target tone during the Count task. (y-axis, μV ; x-axis, ms.) VEOG and HEOG have been mathematically removed from the ERPs but are shown here for illustrative purposes.

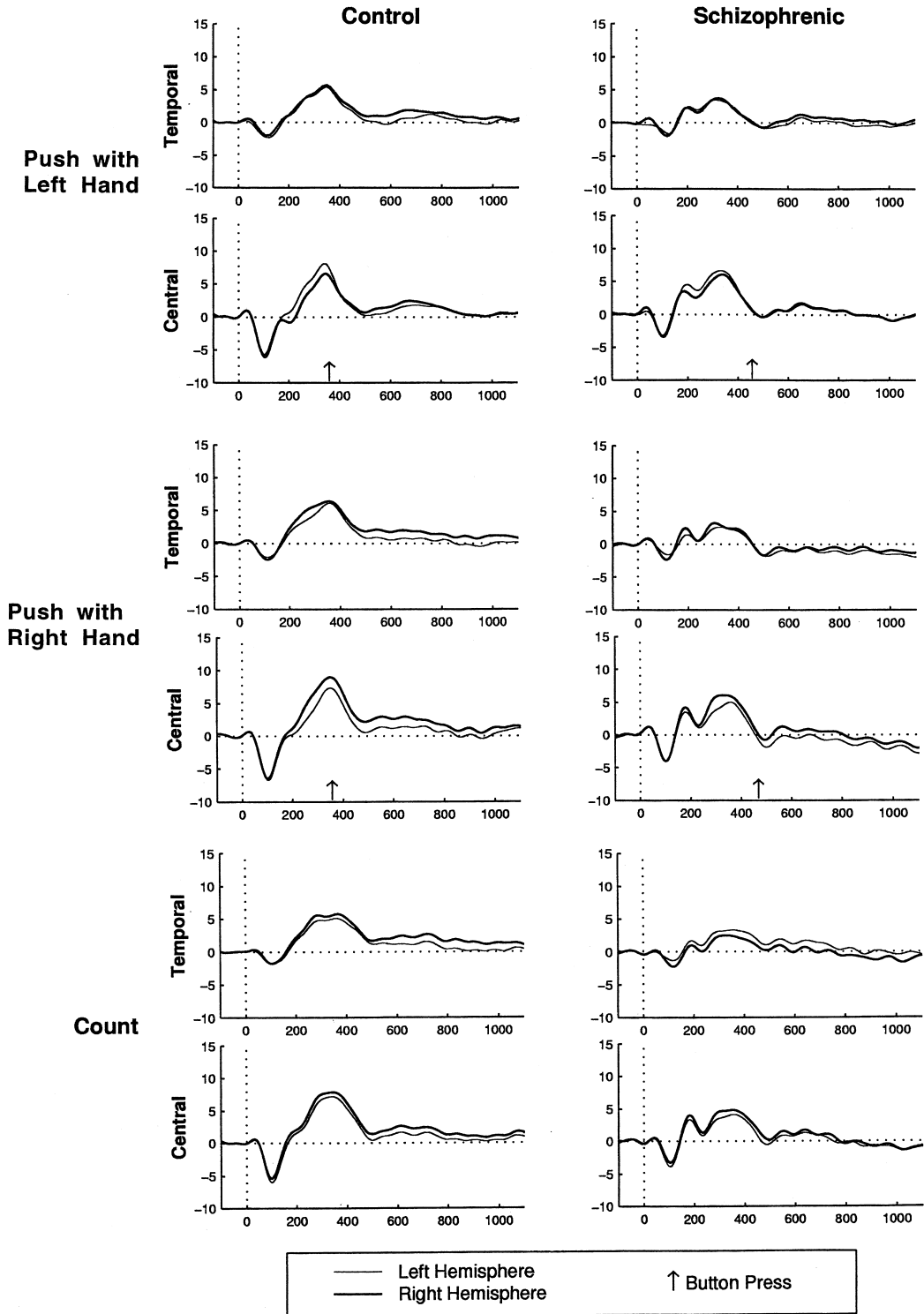


Fig. 2.

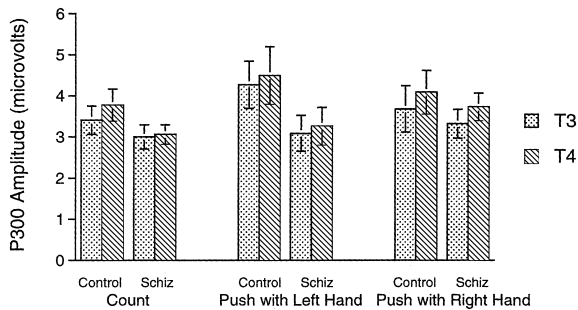


Fig. 3. P300 amplitude at T3 (dotted) and T4 (shaded) from normal controls (left) and patients with schizophrenia (right) for each of the three study tasks.

4. Discussion

These data suggest that P300 asymmetry seen in schizophrenics (e.g. McCarley et al., 1993) as well as the failure to find it (e.g. Ford et al., 1994c), is not related to task differences. Even when patients were counting the oddball tone, P300 did not reveal the T3 < T4 asymmetry seen by other groups using this task. Furthermore, there was no evidence that pressing obscured a P300 asymmetry in schizophrenia; P300 was equally symmetric regardless of whether subjects were responding to the oddball tone with their left or right hands, or simply counting. While P300 in patients with schizophrenia in this study lacked asymmetry, it was smaller than P300 elicited from controls, as was expected (see Ford, 1999).

Neuroanatomical differences between the patients studied by different laboratories may explain the difference in P300 asymmetry. P300 amplitude has been correlated with gray matter volume, with larger P300s being associated with more gray matter (Ford et al., 1994a), and fMRI studies suggest that parietal temporal activation is associated with P300 production in normal subjects (Menon et al., 1997). In addition, temporal asymmetries in P300 amplitude in schizophrenia

have been associated with MRI measures of temporal lobe structural asymmetries (McCarley et al., 1993). Although no MRI data are reported for the patients in this study, some of these patients have also participated in separate structural brain imaging studies in which no temporal lobe asymmetries were noted (Zipursky et al., 1994).

Our study of P300 lateralization included comparisons of manual and count responses, and right and left hand responses. In normative studies, other investigators have noted larger P300s during counting than button pressing (Polich, 1987) and right lateralization of P300 during button pressing, particularly at frontal and central sites (Alexander et al., 1995, 1997). In the latter two reports however, responding hand was counterbalanced over subjects, limiting any analysis of the role of motor potentials, the slow negative cortical potentials, contralateral to the moving hand, that develop prior to and peak just before a button press is made. Because the neural activity reflected in motor potentials is related to the movement and not to the stimulus, motor potentials are better estimated by synchronizing activity to the response than to the stimulus. However, to the extent that the response is tightly coupled to the stimulus, movement potentials can be seen in stimulus synchronized ERPs as well. Readiness potentials (RPs) are a type of movement potential that are more negative contralateral to the responding hand, and develop approximately 200 ms before the movement is made (Deecke et al., 1969; Tarkka and Hallett, 1990). RPs are more marked in right than left handed subjects (Kutas and Donchin, 1974) and contribute to lateralization of P300s in normal subjects (Tenke et al., 1998). In the data reported here, hand of pressing produced the predicted effect on P300 amplitudes at C3 and C4 in both groups, e.g. P300 recorded over the left scalp site was more negative when subjects were responding with their right hand. An RP can be seen in the C3 and C4 tracings in

Fig. 2 Grand averages for normal controls (on left) and patients with schizophrenia (on right) shown separately for the Push with Left Hand, Push with Right Hand, and Count tasks, with recordings from the left scalp overlaid on those from the right. For each task, ERPs from the temporal sites (T3 and T4) are plotted above those from the central sites (C3 and C4). Mean RTs are shown by arrows on the X-axis for the Push with Left Hand and Push with Right hand tasks. (y-axis, μ V; x-axis, ms.)

Fig. 2, starting approximately 200 ms before the response is made. Although the RP is reduced in patients with schizophrenia (Dreher et al., 1999), it does not appear to be differentially reduced over the right hemisphere and, therefore, would not be expected to contribute to P300 asymmetry in schizophrenia. The data reported here support that finding.

Thus, discrepancies between studies with regard to asymmetric reduction of P300 amplitude recorded over temporal sites in patients with schizophrenia do not appear to be due to motor potentials associated with a button pressing task, but are more likely to be related to neuroanatomical differences between populations studied in different laboratories (O'Donnell et al., 1999).

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