Abnormal premovement brain potentials in schizophrenia

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We assessed scalp-recorded movement related potentials (MRPs) generated prior to voluntary movements in chronic, medicated schizophrenics \((n = 9)\) and age matched normal controls \((n = 9)\). MRPs were recorded in a self-paced button press task in which subjects pressed a button with either their right, left or both thumbs (experimental condition I, II and III respectively). Controls generated a slowly rising readiness potential (RP) at about 1000 ms, a negative shift (NS\textsuperscript{e}) at about 450 ms and a motor potential (MP) at about 100 ms prior to movement. The initial MRP components (RP and NS\textsuperscript{e}) were reduced in schizophrenics indicating an impairment of the voluntary preparatory process in schizophrenia. Results of the present study indicate a similarity of MRP findings in schizophrenics and reported MRPs (Singh and Knight, 1990) in patients with unilateral lesions of the dorsolateral prefrontal cortex. These findings provide further support for frontal lobe dysfunction in schizophrenia.

**Key words:** Movement-related potentials; Readiness potential; Schizophrenia; Frontal lobes; Voluntary movements; (Schizophrenia)

INTRODUCTION

Movement related potentials (MRPs) provide an electrophysiological measure of motor preparatory processes assessed with voluntary movement (Kornhuber and Deecke, 1964; Vaughan et al., 1968; Singh et al., 1990). Three premovement MRP components (the readiness potential, RP; the negative shift, NS\textsuperscript{e} and the motor potential, MP) and a post motion component (P2) of MRPs have been reliably reported (Neshige et al., 1989; Shibasaki et al., 1980; Singh and Knight, 1990).

Movement related disturbances in schizophrenics have been described in literature. For example, Kraepelin described movement disturbances in his initial definition of schizophrenia (Crow et al., 1984). In addition to abnormal saccadic eye move-

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ments (Holzman et al., 1974; Stevens, 1978), Manschreck (1986) showed that schizophrenics were unable to tap their fingers in synchrony with rhythmically occurring auditory stimuli. Schizophrenics also have difficulty in shifting attentional set from one visual field to another, possibly due to an impaired ability to shift motor programming (Rizzolatti, 1987). MRP recordings can provide an electrophysiological measure of such voluntary movements, and can index motor preparatory processes associated with voluntary movements in schizophrenia.

Recent studies have implicated neuroanatomical changes in schizophrenia. For example, schizophrenics show decreased brain weight and volume reduction of the hippocampus, amygdala, parahippocampal gyrus and pallidum internum in addition to left temporal lobe abnormalities (Flor Henry, 1969; Bogerts et al., 1985; Brown et al., 1986). Computed tomography (Farkas et al., 1984; Weinberger, 1984) and postmortem studies (Stevens, 1988; Benes et al., 1986) have further revealed that
schizophrenics have larger ventricular area than
the general psychiatric population (Owens et al.,
1985; Kelsoe and Cadet, 1988). The literature also
suggests frontal lobe dysfunction in schizophrenia
(Levin, 1984a, 1984b; Goldberg et al., 1982;
Goldberg, 1985; also see Weinberger, 1988) sup-
ported by regional Cerebral Blood flow (rCBF)
(Weinberger et al., 1985; Berman et al., 1985),
neuropsychological assessment (Kolb and
Whishaw, 1983), and EEG studies (Morhisa and
McAnulty, 1985).

The neural origin of slow movement related
potentials is not fully understood. However, evi-
dence provided by scalp topography (Vaughan
et al., 1968; Shibasaki et al., 1980), intracranial
(Neshige et al., 1989), and MRP studies on brain
damaged patients (Deecke et al., 1977, 1987;
Deecke and Kornhuber, 1978; Singh et al., submit-
ted) indicate that primary sensori-motor cortex,
 supplementary, premotor, and prefrontal cortex
(Singh and Knight, 1990) form elements of a neural
network necessary for MRP generation. MRP
recordings in schizophrenics might provide further
electrophysiological data on the involvement of
anterior cortical regions in schizophrenia.

Prior studies of MRPs in schizophrenia are
equivocal. For example, Timsit-Berthier et al.
(1973) recorded MRPs in psychiatric patients and
reported that the potentials recorded in psychotics
were characteristically different from that of neuro-
tics. Kornhuber (1983) also reported reduction of
the Readiness potential in medicated schizophreni-
cs. Similar results have been obtained by others
(Kornhuber et al., 1982; Westphal et al., 1985,
1986; Chiarenza et al., 1985). However, Adler et al.
(1989) reported normal RPs in chronic, medicated
schizophrenics and significantly enhanced MRPs
in schizophrenics with tardive dyskinesia (TD).
Thus, there is some disagreement concerning MRP
findings in schizophrenia. The present study was
designed to provide MRP data from multiple scalp
sites in stable schizophrenics in a self-paced volun-
tary task.

METHOD

Patient population
Nine chronic, medicated schizophrenics diagnosed
according to DSM-III-R (APA, 1987) criteria (all
male; mean age = 49.3 years, SD = 13.6) followed
on an ongoing basis in a V.A. outpatient clinic
participated in the study. A consensual agreement
with regard to the clinical diagnosis, severity symp-
tom rating and current mental status of each of
the patients was reached between two psychiatrists
(N.R. and J.M.K.). Eight of the patients had active
psychotic symptoms including auditory hallucina-
tions (3 patients), and delusions (5 patients). All
were receiving neuroleptic treatment (mean =
431 mg per day in chlorpromazine equivalents,
range 20 to 1000, SD = 255). All patients had
histories of multiple prior hospitalizations and an
onset of psychotic symptoms at least five years
prior to the study (mean duration of illness =
24.77, SD = 10.56 years). Patients were rated for
global severity of symptoms (mild–moderate–
severe) by clinical history and mental status exami-
nation, with one patient rated as mild and eight
patients rated as moderate. Patients with severe
symptoms were screened out due to potential
difficulties in following study protocol. Patients
with TD, drug-induced parkinsonism, history of
significant medical illness, head injury, stroke or
primary diagnosis of substance abuse were also
excluded. All subjects underwent a neurological
examination at the time of testing. None of the
patients had lateralized motor deficits, apraxia or
signs of extrapyramidal dysfunction. All patients
were right handed according to the Edinburgh
Handedness Inventory (Oldfield, 1971). All partici-
pants gave informed consent and were paid for
their participation.

Controls
Nine neurologically normal subjects (8 male; mean
age = 50.3 years, SD 10.25), with no family history
of schizophrenia or movement disorder and not
receiving any medication constituted the normal
control group. Subjects with history of substance
abuse, and psychiatric or medical disorders were
excluded. All subjects were right handed.

Recording of MRPs
MRPs were recorded according to methods
described before (Singh and Knight, 1990; Singh
et al., 1990). Briefly, recording was conducted in
a dimly lit, electrically and acoustically shielded
room. The subject was seated in a comfortable
reclining armchair and given a pushbutton (two
pushbuttons in the bimanual condition) mounted atop a cycle handle grip. Each subject was instructed to loosely grasp the handle in his or her palm and briskly press and release the button with his or her thumb. Subjects were instructed to press the button at their own pace without any external cue or control. They were warned against pressing the button too rapidly to minimize problems from overlapping of MRP epochs. Thus, the button press was self-initiated and self-paced with an inter-movement interval (IMI) ranging between 3 to 10 s in both control and schizophrenic groups (Table 1).

MRPs were recorded with Ag/AgCl electrodes placed at FP1, FPZ, FP2 (overlying superior frontal gyrus), F3, FZ, F4 (mid frontal gyrus, near superior frontal cortex), C3, CZ, C4 (precentral gyrus) and P3 and P4 (superior parietal lobule). Three additional electrodes C3a, C2a and C4a were placed over precentral areas (Homan et al., 1987). These were located 2 cm anterior to C3, CZ, and C4, respectively (between precentral and superior frontal gyrus). Multiple electrodes were used to obtain a detailed MRP scalp topography including precentral and central sites. All electrodes were referenced to linked earlobes. A ground electrode was placed on the forehead and EOG was recorded from an electrode below and slightly lateral to the inferior orbit of the eye. Individual trials with excessive muscle activity (peak to peak amplitude of 80 μV) or eye blinks (peak to peak amplitude of 80 μV) were excluded from the average. EMG responses were recorded from a pair of electrodes placed on the thenar muscle and first metacarpal-phalangeal joint of the hand involved in the task. Electrode impedances were less than 5 kOhms. EEG, EOG, and EMG were recorded using Grass P511 amplifiers. EEG and EOG were amplified (50K) and bandpass filtered from 0.01–100 Hz (time constant = 5 s). EMG activity was amplified (10K) and filtered from 10–100 Hz. Signals were digitized at a sampling rate of 128Hz/channel by a PDP11/73 minicomputer. Digitized single trial epochs were stored on magnetic tape for off-line averaging and analysis. The stored data was averaged from epochs of raw EEG beginning 1400 ms prior to the trigger and continuing for 600 ms post-motion. Trials contaminated by eye blinks, excessive EMG activity or amplifier blocking were rejected by the computer algorithms prior to averaging. Sums of 150 to 200 (total trials = 200) artifact free trials were obtained for each subject in each condition. Mean trials obtained from control and experimental groups after artifact rejection (percentage of artifact rejection: schizophrenia = 23%; control = 26%) were not significantly different (mean number of trials averaged: controls = 148 (RHP), 149 (LHP), 152 (BMP); schizophrenics = 154 (RHP), 142 (LHP), 149 (BMP)).

Behavioral measures
The mean inter-movement interval was examined between control and patient groups. All schizophrenics were subjected to Mini-mental State Examination (MMSE; Folstein, 1975).

Data reduction and analysis
Measurements of MRPs were made according to the method described previously (Singh and Knight, 1990; Singh et al., 1990). Four MRP components were identified based on individual and group mean averages. A regression line was fitted to these MRP phases. The RP was identified as the initial portion of the premovement negativity. The onset of the second component NS' (or N2a), occurred at 450 ms prior to the switch closure. The third component MP (or N2b) refers to the additional negativity generated immediately (about 100 ms) preceding the movement (Vaughan et al., 1968). The fourth component, post motion positivity (P2) was measured 180 to 220 ms post-motion. Measurements were made on the individual records using a computer assisted cursoring

<table>
<thead>
<tr>
<th>Group</th>
<th>RHP Mean (SD)</th>
<th>LHP Mean (SD)</th>
<th>BMP Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.10 (0.50)</td>
<td>3.22 (0.40)</td>
<td>3.04 (0.50)</td>
</tr>
<tr>
<td>Schizophrenic</td>
<td>4.23 (0.43)</td>
<td>4.20 (0.34)</td>
<td>4.13 (0.51)</td>
</tr>
</tbody>
</table>

Table showing mean interpress interval differences during self-paced task between control and schizophrenic. Schizophrenic patients tend to have prolonged IMIs.

*p < 0.05
RHP = Right hand press
LHP = Left hand press
BMP = Bimanual press
program. Mean MRP amplitudes were calculated in restricted windows (i.e., RP: −1000 to −500 ms; NS\(^\prime\): −500 to −100 ms; MP: −100 to 0). The MP is superimposed on the NS\(^\prime\) and NS\(^\prime\) in turn is superimposed on the RP. In order to obtain relatively isolated measures of the NS\(^\prime\) and MP components, we also used the subtraction method (Kutas and Donchin, 1980). The NS\(^\prime\) was computed as the potential difference between the N2a and N1. The MP was calculated as the potential difference between N2b and the sum of N1 and N2a components.

Isopotential maps were constructed from the normalized voltages for each subject. The electrode site values were first normalized to allow comparisons of the maps across groups and conditions with all scales ranging between 0 and 100 percent. An automated interpolation algorithm was then used to calculate the contribution of each electrode to each inter-electrode point on the map, with the contribution from each indirectly weighted as a function of the cube of the inter-electrode distance.

Data were analyzed using ANOVA with a between-group design. Each of the three components (RP, NS\(^\prime\) and MP) were analyzed separately for the two groups. T-tests were used to make specific electrode comparisons for each condition independently. Possible relationships between duration of illness and MRP amplitudes, IMIs and MRP amplitudes and drug dosage and MRP amplitude were examined by correlation methods.

**Electrophysiological Data**

**Control Group**

Controls generated a slowly increasing negativity beginning at about 1000 ms (CZ: mean = 1023) prior to switch closure (RP). The RP was symmetrical, widely distributed and maximal at fronto-central midline electrodes (CZ and C2a, Figs. 1, 2). The NS\(^\prime\) began at about 450 ms (CZ: Mean = 412) prior to the switch closure and was maximal over fronto-central regions contralateral to movement in controls (RHP: C3 vs C4, F = 4.2, p < 0.01). This effect was not significant in the LHP condition. The MP peaked at the trigger point and was maximal over contralateral sites in unimanual conditions (RHP: C3 vs C4, F = 3.57, p < 0.02). During the bimanual condition MRPs were symmetrically distributed over the scalp and there was no contralateral enhancement (C3 vs C4, F = 0.98, n.s., also see Table 2).

**Schizophrenic group**

A clear RP beginning at about 1000 ms (CZ: mean: 821 ms) prior to the button press was observed only in 2 schizophrenic patients. An NS\(^\prime\) starting at about 400–300 ms (CZ: Mean = 340) prior to the switch closure was observed in only 3 patients. An MP was observable in most patients. The MP

**RESULTS**

**Behavioral Data**

**Intermovement Interval.** The mean IMI in controls and schizophrenics was not significantly different. However, schizophrenics tended to have a prolonged IMI relative to controls (Table 1).

**Mini-Mental State Examination (MMSE).** Most schizophrenics performed well on the MMSE (Range of score: 27 to 29/30).

**Correlational Analysis.** No relationship could be established between duration of illness and MRP amplitudes (RP: r = 0.29; NS\(^\prime\): r = 0.21; MP: r = 0.19), IMIs and MRP amplitudes (RP: r = 0.19; NS\(^\prime\): r = 0.29; MP: r = 0.16) and drug dosage and MRP amplitudes (RP: r = 0.17; NS\(^\prime\): r = 0.11; MP: r = 0.23).

**TABLE 2**

<table>
<thead>
<tr>
<th>Electrodes</th>
<th>Control</th>
<th>Schizophrenic</th>
<th>Sig*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3</td>
<td>4.6 (SE = 0.82)</td>
<td>2.8 (SE = 0.82)</td>
<td>**</td>
</tr>
<tr>
<td>FZ</td>
<td>4.0 (SE = 1.02)</td>
<td>2.1 (SE = 1.05)</td>
<td>**</td>
</tr>
<tr>
<td>F4</td>
<td>4.5 (SE = 0.63)</td>
<td>2.3 (SE = 1.30)</td>
<td>**</td>
</tr>
<tr>
<td>C1</td>
<td>5.7 (SE = 0.97)</td>
<td>2.3 (SE = 1.02)</td>
<td>***</td>
</tr>
<tr>
<td>C3a</td>
<td>5.6 (SE = 0.80)</td>
<td>2.4 (SE = 0.89)</td>
<td>***</td>
</tr>
<tr>
<td>CZ</td>
<td>6.4 (SE = 0.97)</td>
<td>2.5 (SE = 0.99)</td>
<td>***</td>
</tr>
<tr>
<td>C2a</td>
<td>6.1 (SE = 0.65)</td>
<td>3.2 (SE = 0.97)</td>
<td>***</td>
</tr>
<tr>
<td>C4</td>
<td>5.1 (SE = 0.80)</td>
<td>1.8 (SE = 0.77)</td>
<td>***</td>
</tr>
<tr>
<td>C4a</td>
<td>5.7 (SE = 1.02)</td>
<td>3.0 (SE = 0.88)</td>
<td>***</td>
</tr>
</tbody>
</table>

Table showing mean amplitude (in µV) of the MP component during the bimanual button press condition in controls and schizophrenics over precentral and central leads. Significantly larger potentials were recorded in controls. The overall difference was also noted on the frontal leads. Absence of lateralization of the MP component is also evident.

***p < 0.001

**p < 0.01**

affect cognitive functions in schizophrenia, a variable not examined in the present study. However, the data indicate that the patterns of lateralization of MRPs are qualitatively different from the asymmetries in the reaction times and premotor potentials in schizophrenia (Kutas and Donchin, 1980). MRP over the left hemisphere cannot be explained by the findings of previous studies (Baltuch and Grossman, 1978; Kutas and Donchin, 1980) and must be considered a unique finding in schizophrenia.
started at about 100 ms before the button press and peaked at the trigger point (e.g., F3, C3, C3a).

Inspection of the Fig. 1 shows a nonsignificant trend toward contralateral enhancement of the MP (RHP: C3 vs C4: F(df = 1, 16) = 1.3, n.s.) and NS' (RHP: C3 vs C4: F(df = 1, 16) = 1.43, n.s.) during RHP and LHP conditions in this group. During the BMP, no differences were noted between ipsilateral and contralateral leads (C3 vs C4, F = 1.02, n.s.).

Fig. 1. Overlapped group grand-averaged waveforms from control (solid) and schizophrenic (dotted) subjects in a self-paced right hand button press. Note the contralateral enhancement of MRPs in controls as well as in schizophrenics (all subjects in both groups were right handed) and the decrement or absence of RP and NS' components in schizophrenics with relative preservation of the MP component over some leads. Also note that there is clear MRP reduction at frontal leads (F3 and F4) in schizophrenics. Arrow indicates the trigger point from which back-averaging was done. BE = below eye.
Control versus Schizophrenics

MRP scalp topography, onset latency and amplitude

In contrast to controls, the premovement negativity in schizophrenics did not onset until about 400 ms before the button press. Despite marked amplitude reductions, the scalp topographical distribution of the MP component was similar to that of normal controls (Figs. 1, 2, 3). The early and late MRP components were significantly reduced in all experimental conditions in schizophrenics. A statistically significant difference in mean amplitude was found between the two groups for the

Fig. 2. Overlapped group grand averages from control (solid) and schizophrenic (dotted) subjects in a self-paced left hand switch closure. Note the contralateral enhancement of MRPs in both the groups. The RP and NS components are either reduced or absent on most scalp sites. The MP is somewhat preserved. Also note a frontal decrement of MRPs (F3 and F4).
Fig. 3. Scalp topographical maps of the RP, NS' and MP components in the left hand button press condition. The maps reveal symmetrical distribution of the RP and contralateral preponderance of the NS' and MP components in controls and schizophrenics. A marked reduction of the RP and NS' components is evident. The MP component is relatively preserved.
TABLE 3
Statistical comparisons:

<table>
<thead>
<tr>
<th>Groups</th>
<th>F</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>Control versus Schizophrenic</td>
<td>7.91</td>
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</table>

NS*

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<thead>
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<th>Groups</th>
<th>F</th>
<th>Significance</th>
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<td>Control versus Schizophrenic</td>
<td>18.72</td>
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MP

<table>
<thead>
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<th>Groups</th>
<th>F</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control versus Schizophrenic</td>
<td>6.78</td>
<td>*</td>
</tr>
</tbody>
</table>

Mean group comparisons between controls and schizophrenics for the RP, NS' and MP components.

** < 0.01
* < 0.05

RP, NS' and MP components (see Table 3). The MRP reduction can be seen on the frontal leads in schizophrenic group (F3, FZ and F4, see Figs. 1, 2).

Specific group comparisons with respect to each of the conditions also showed a significant difference between the two groups (RHP: F = 6.95, p < 0.01; LHP: F = 9.90, p < 0.01; BMP: F = 8.80, p < 0.01). However, isolated measures of the MP component obtained by the subtraction method (Kutas and Donchin, 1980), showed no statistically significant difference between control and schizophrenic groups (LHP: F = 1.63, p = 0.55, n.s.). Thus, the schizophrenic group showed a reduction of RP and NS' components with relative preservation of the MP (F3, FZ, F4, C3a, C4a, CZa; see Figs. 1, 2, 3). The P2 component was variable in both the patient and normal control group and no significant difference emerged between the two groups (F = 2.8, n.s.).

DISCUSSION

Three premovement (RP, NS' and MP) and a post-movement (P2) component of the MRPs were generated in normal controls. The onset of premovement negativity was markedly delayed in schizophrenics and the amplitude of the RP and NS' components was either reduced or abolished in a majority of schizophrenics at frontal and central scalp sites (Figs. 1, 2). The MP component, although reduced, was observable in most subjects. MRP reduction was observed in unimanual as well as bimanual experimental conditions. Despite amplitude reduction, the scalp topographical distribution of late component in schizophrenics was similar to those of controls (Fig. 3). Like those in controls, the NS' and MP components were maximal contralaterally in unimanual conditions, and were symmetrical in the bimanual experimental condition. No difference between side of the press (RHP vs LHP) was noted both with respect to IMIs and laterality of MRPs in schizophrenics. Further, no relationship could be established between duration of symptoms and MRP amplitudes, IMIs or drug dosage and MRP amplitudes.

Despite differences in experimental design, our results in schizophrenics are consistent with the findings of other investigators (Timsit-Berthier et al., 1973; Kornhuber, 1983; Westphal et al., 1985, 1986; Chiarenza et al., 1985) who showed abnormal MRPs in schizophrenics. However, our results are opposite to the findings of Adler et al. (1989) who reported normal RPs in chronic, medicated schizophrenics and significantly enhanced MRPs in schizophrenics with TD. Differences of results may be due to the differences in the task employed and patient population studied. Our group of patients (8/9) had active psychotic symptoms which might have contributed to the impairment of the RP component in these patients. In addition, the extent of the influence of antipsychotic medication on MRPs in the current and previously reported studies needs further investigation.

In the current study, no significant difference emerged between the performance of control and schizophrenics on the experimental task. However, schizophrenics had a trend to prolonged interpress interval relative to controls, consistent with problems of initiation and slowness observed in these patients (Levin, 1984a,b). Schizophrenic patients showed no clinical evidence of apraxia, sequencing difficulties or elementary motor disturbances. In addition, none of the patients had muscle weakness or difficulty in pressing the button so MRP reductions are not likely due to decreased button press force. Moreover, force is reported to
affect the late MP component with early components (RP and NS) largely unaffected by force variations (Kristeva et al., 1990). Abnormality of MRPs cannot be attributed to attentional deficits in these patients because of high scores obtained by these individuals on MMSE which do not indicate severe attentional problems in these patients. However, the possibility of reduced motivation (this variable has been shown to affect MRPs, McAdam and Seal, 1971) in these patients cannot be ruled out. Furthermore, schizophrenics show lack of planning, initiation, (Levin, 1984a) and problems with temporal organization (Klonoff et al., 1970; DePue et al., 1975) on behavioral tasks. MRPs have been associated with psychological constructs such as readiness, preparation, initiation, planning, volition and intention to act (Kornhuber and Deecke, 1964; Libet et al., 1982; Kutas and Donchin, 1980). Abnormal MRPs in schizophrenics might relate to deficits in these processes in schizophrenia.

The frontal cortex is involved in initiation, planning and regulation of voluntary movements (Fuster, 1980; Luria, 1980). Frontal lobe dysfunction has been reported in neuropsychological studies of schizophrenia (Kolb and Whishaw, 1983; Heattan et al., 1978). Also, frontal EEG abnormalities (Morihsa and McAnulty, 1985) and hypofrontality of glucose metabolism has been observed in schizophrenics (Farkas et al., 1984). Recent rCBF studies have found reduced activity in the dorsolateral frontal cortex in medicated and medication-free schizophrenics engaged in the frontal lobe mediated Wisconsin Card Sorting Test (Weinberger et al., 1985; Berman et al., 1985). These findings are supported by studies showing decrease in the frontal lobe volume in schizophrenia (Andreasen et al., 1989, 1990). Intracranial recordings and human lesion data have indicated discrete MRPs in pre- and postcentral gyrus with additional contribution from supplementary and premotor cortices. Further, abnormal MRPs recorded from patients with Parkinson’s disease are interpreted as dysfunction of supplementary area (SMA) in these patients primarily because the SMA derives its major input from the basal ganglia (Deecke et al., 1977; Deecke and Kornhuber, 1978). In addition, MRP recordings from patients with prefrontal cortex lesions have reported significant MRP decrement in these patients. This indicates that in addition to supplementary, motor and premotor areas, prefrontal cortex areas 8, 9 and 46 are involved in MRP generation (Singh and Knight, 1990). The MP component was partially preserved in schizophrenics as well as in patients with prefrontal lesions. The similarity of MRP findings in schizophrenics and prefrontal lesioned subjects provide further support for frontal lobe dysfunction in schizophrenia. MRP reductions in frontal sites could be due to direct loss of prefrontal or premotor generators or to decrease in prefrontal modulation of MRP generators in distant sites. Additional concurrent measures of frontal activity such as rCBF or PET would be needed to address this issue.

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