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RESEARCH ARTICLE

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Planning dysfunction in schizophrenia: impairment of potentials preceding fixed/free and single/sequence of self-initiated finger movements

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Abstract To test the hypothesis of a planning dysfunction in schizophrenia using a precise temporal definition, the readiness potential (RP), a negative cortical wave preceding self-initiated movements and reflecting motor preparation processes, was studied in patients under stable medication and in controls. The supplementary motor area (SMA), known to be involved in the generation of the RP, has also been implicated in movement selection (fixed versus free) and complexity (single versus sequence). This is the first study using RP for the assessment of the influence of these factors on motor preparation in schizophrenics. Our results show that schizophrenics' RP amplitude is significantly lower than in controls at central and contralateral electrodes. However, RP amplitude increases with task difficulty in both groups, offering important new insight into classical SMA hypoactivation in schizophrenics performing motor tasks. Topographic analysis shows that RP amplitude is, for both groups, significantly higher in sequence than in single movements at fronto-central sites and higher for free than for fixed movements at centro-parietal sites. Finally, RP onset occurs significantly later in schizophrenics than in controls. These results support the view of a motor-preparation and decision-making dysfunction in schizophrenia. They are interpreted within the framework of a fronto-striatal disorder in this disease.

Key words Electrophysiology · Schizophrenia · Readiness potential · Motor planning · Frontal Cortex

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Abbreviations *EEG* Electroencephalography · *ERP* event related potentials · *MI* primary motor cortex · *MRCPs* movement-related cortical potentials · *NS'* negative slope · *RP* readiness potential · *SMA* supplementary motor area · *PFC* prefrontal cortex · *EOG* electrooculogram

Introduction

Planning dysfunction in schizophrenia

Dysfunction of dopamine (DA)-modulated cortico-subcortical loops has been supposed to mediate part of the physiopathology of schizophrenia (Swerdlow and Koob 1987; Robbins 1990; Grace 1991, 1993; Gray et al. 1991; Weinberger 1993a, b; Frith 1992; Deutsch et al. 1993; Gray and Joseph, 1995). This disease can partly be considered as a glutamate-mediated disruption in the balance between DA afferents to frontal cortex and nucleus accumbens (NAc) (Tassin et al. 1982; Carlsson 1990; Tassin 1995). A fronto-striatal dysfunction in schizophrenia should be revealed in planning tasks, because loops between frontal cortex and basal ganglia are supposed to constitute the neurobiological substrate of planning, whether cognitive, motor or language-related. This hypothesis has been partially supported by brain imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

Indeed, Günther et al. (1994) have used PET to show that during performance of simple and complex sequences of finger movements, both medicated and neuroleptic-free negative schizophrenics have significantly lower regional glucose metabolism in frontal regions and higher-than-normal metabolism in the thalamus and basal ganglia. In the same finger-to-thumb opposition task, Schröder et al. (1995) used fMRI to show that schizophrenics have lower activation of sensorimotor cortices and SMA than normals. Hypofrontality is also reported in cognitive planning tasks known to involve the frontal lobes (Weinberger et al. 1986, 1992; Goldberg and Weinberger

1988; Weinberger and Berman 1988; Buchsbaum et al. 1992; Sullivan et al. 1994). However, hypofrontality has not been reported systematically in schizophrenia in some verbal fluency tasks, in which schizophrenics' performance matched with controls (Frith et al. 1995). This discordance cannot only be attributed to heterogeneity in the schizophrenic population, but also to heterogeneity in the controls. Indeed, compared with their normal homozygotic twins, schizophrenics do show decreased frontal cortex activation while performing the Wisconsin card-sorting test, even if performance per se did not differ between twins (Berman et al. 1992). In fact, it can now be reliably argued that motor and cognitive tasks that depend on frontal lobe function produce depressed frontal lobe activation in schizophrenic patients – particularly those with negative signs (Guy et al. 1986; Kemali et al. 1987; Braff et al. 1991; Wolkin et al. 1992; Ingvar 1995; Malla et al. 1995; Spence et al. 1997). Importantly, this hypofrontality would not be a long-term effect of neuroleptics or of illness chronicity (Andreasen et al. 1992).

In addition to these deficits revealed by PET and fMRI, there is a large variety of event-related potential (ERP) abnormalities in schizophrenic patients: N100, N200, mismatch negativity (MMN), P300, N400, RP and contingent negative variation (CNV) have all been shown to be smaller than in controls (Pritchard 1986; Rockstroh et al. 1989; Cohen 1991; Wagner et al. 1996). In particular, attenuation of the late CNV component (which includes but is not restricted to motor preparation) in schizophrenics may be related to their frequent perturbation in the initiation and execution of goal-directed actions. Further support for this assumption comes from the low amplitude of the readiness potential (RP) that precedes voluntary single-finger movements (Timsit-Berthier 1973; Timsit-Berthier et al. 1978; Chiarenza 1985; Westphal et al. 1986; Singh et al. 1992; Karaman et al. 1997) and from the hypoactivation of contralateral motor areas, as revealed by electroencephalograph (EEG)-mapping methods (Günther et al. 1991; Günther, 1992). These results could either support the hypothesis of a specific cortical disturbance (such as in the prefrontal cortex, PFC) or of a more generalized cortical dysfunction (Javitt 1995).

Premovement potentials in normals

Source(s) of the RP

Movement-related cortical potentials (MRCPs) are generated prior to, during and after the execution of self-paced voluntary movements. They are recorded by back-averaging EEG activity time-locked to muscle activation onset. Human volitional self-initiated movements are preceded by two premovement potentials: the RP, or Bereitschaftspotential, and the negative slope (NS') (Kornhuber and Deecke 1965). The RP and NS' extend, respectively, from –2 s to –0.5 s and from –0.5 to –60 ms prior to movement onset (Shibasaki et al. 1980). Four hypotheses have been proposed to explain the origins of the RP and NS' that are generated prior to unilateral hand movements. Two hypotheses implicate only one structure for the generation of both RP and NS': bilateral activation of either SMA (Tarkka et al. 1994; MacKinnon et al. 1996), or primary motor cortex (MI) (Cheyne and Weinberg 1989; Kristeva et al. 1991; Bötzel et al. 1993; Toro et al. 1993; Böcker et al. 1994). The two alternative hypotheses implicate SMA and MI, but assume different time courses of activation. The first hypothesis states that the RP originates bilaterally from both SMAs and reflects neural activity associated with the preparation of movement, whereas the NS' potential is generated by the contralateral MI (Deecke et al. 1976, 1987; Boschert 1983; Tanji et al. 1985, 1994; Deecke 1990; Lang et al. 1990, 1991; Jahanshahi et al. 1995). The second hypothesis proposes that RP and NS' are both generated by bilateral activation of MI and SMA with an equivalent time-course (Ikeda 1992, 1993; Rektor et al. 1994).

It is now admitted that SMA is activated during the generation of the RP, but temporal precedence or simultaneity of SMA and MI activation remains an open question. As noticed by Praamstra et al. (1995), simultaneous activity of the SMA and MI does not necessarily exclude the possibility that the SMA subserves a supramotor function. This study will not directly address the question of RP localization. However, a comparison of RP variations with PET and fRMI results, according to groups (normals and schizophrenics) and parameters (mode of movement selection and complexity), should indicate whether: (1) the reported cerebral activation changes are related to events that occur during motor preparation; and (2) the main generators of the RP vary with groups and/or the parameters explored (complexity and mode of movement selection).

SMA functions

The SMA has been implicated in complex versus simple motor tasks, internal versus external motor initiation, and freely selected versus fixed (memory-guided) movements. We briefly review arguments supporting these different hypotheses.

Complexity factor: is the RP amplitude larger for sequential than for single movements?

In the generation of a sequence of finger movements, Lang et al. (1989) used EEG to show that both the negativity and regional density of the inward-directed current flow significantly increased over the frontocentral midline (SMA) for complex versus simple sequences, whereas no differences were observed over either the ipsi- or contralateral MI. They interpreted this result as an increase in SMA activation and no change in MI activation with task complexity. Some ERP studies also supported

the view that sequential movements cause higher RP amplitudes than single movements (Benecke et al. 1985; Lang et al. 1988, 1989; Simonetta et al. 1991); others have not (Ikeda et al. 1993; Praamstra et al. 1995).

The effect of complexity has also been reported in PET studies for which greater SMA activation occurred during execution of a learned motor sequence than during simple repetitive movements (Orgogozo and Larsen 1979; Roland et al. 1980, 1982; Deiber et al. 1991; Shibasaki et al. 1993). More recently, a positive correlation between regional cerebral blood flow (rCBF) and sequence complexity was found in the controlateral rostral SMA (pre-SMA) and associated pallido-thalamic loop (Boecker et al. 1998).

Electrophysiological studies in monkeys showed that neural activities related to motor preparation are found in MI, SMA and pre-SMA (Evarts et al. 1984; Lecas et al. 1986; Riehle and Requin 1989). However, with more complex preparatory processes, only SMA and pre-SMA neurons were involved (Tanji et al. 1980). Furthermore, Tanji et al. (1994) found some pre-SMA and SMA neurons that were exclusively active relative to a particular ordering of forthcoming memory-guided movements, and others that were preferentially active during the interval between two specific movements. These neurons would therefore contribute a signal regarding the order of forthcoming sequential movements and help to retrieve appropriate action according to a memorized order.

These results can be interpreted as the expression of a gradient of activation from the pre-SMA, particularly active in tasks requiring temporal sequencing of multiple movements, to MI, mostly involved in the execution of the motor task itself. Thus, they support the hypothesis of a higher RP for sequential than for single movements. Furthermore, the time course and slope of the first component of the RP in humans closely resembles the preparatory related activity recorded from cells in the SMA of behaving monkeys, whereas the second component (NS') resembles the movement-related activity characteristic of a large number of MI neurons (Tanji et al. 1985; Alexander and Crutcher 1990; Romo and Schultz 1992).

Is the RP amplitude larger for internally than externally triggered movements?

The most reproducible result concerning the role of the SMA, in particular its rostral part (pre-SMA), is its involvement in internally versus externally triggered movements (Libet et al. 1982; Goldberg 1985; Passingham 1987, 1993; Deiber et al. 1991; Frith et al. 1991; Wise et al. 1991; Playford et al. 1992; Tanji et al. 1994; Jahanshahi et al. 1995). Distinct cerebral structures are expected to control these different types of movement. Goldberg (1985) has proposed that a medial premotor system (SMA) mediates self-initiated movements, whereas a lateral system (centered on the lateral premotor cortex) mediates externally triggered movements. The lateral premotor cortex receives inputs from the inferior parietal lobule and subcortical inputs from the cerebellum via distinct areas of the thalamus; the SMA receives inputs from the superior parietal lobule and subcortical inputs from the basal ganglia. These two routes to MI could thus subserve distinct motor functions. This hypothesis seems to be confirmed by experiments with monkeys that have shown that: (1) during the pre-movement period, the SMA neurons are particularly activated in self-initiated versus externally triggered movements whereas the opposite is true for premotor cortex neurons (Mushiake et al. 1990, 1991); and (2) the removal of the medial premotor cortex (SMA) impairs self-initiated movements, but affects tone-paced performance to a lesser extent (Thaler et al. 1995). Conversely, monkeys with lateral premotor lesions are less impaired in making self-initiated versus externally triggered movements (Thaler et al. 1995). Furthermore, performance of animals with lesions of the medial premotor cortex is improved when external cues prompt the retrieval of an appropriate action (Chen et al. 1995). These results in monkeys are in agreement with results in Parkinson's disease, showing that, relative to self-initiated movements, SMA deficits are not as marked when external cues are provided to guide movements (Flowers 1976; Stern et al. 1983; Cunnington et al. 1995).

Despite these findings, anatomical studies question the concept of two routes to action (Matelli et al. 1989; Darian-Smith et al. 1990) and, instead, suggest a continuous functional gradient. Similarly, PET studies making the distinction between internally and externally generated movements support the concept of a medial premotor system, but do not show evidence of a lateral system. Indeed, in self-initiated movements, there is a clear activation not only of the SMA but also of the dorsolateral prefrontal cortex (DLPFC), anterior cingulate and lateral premotor cortex (Deiber et al. 1991; Frith et al. 1991; Papa et al. 1991; Playford et al. 1992; Jahanshahi et al. 1995; Rao et al. 1997). The contralateral thalamus and putamen have also been shown to be significantly activated in self-initiated movements (relative to rest) in normals (Jahanshahi et al. 1995; Rao et al. 1997).

Influence of the movement selection mode: is the RP amplitude larger for free than fixed movements?

In the RP paradigm, all the movements are self-initiated and thus do not require an external cue. Therefore, the distinction between internally versus externally generated movements is recast as a distinction between fixed (i.e. repetition of the same movements for all trials) and free movements (i.e. freely chosen movements for all trials). Fixed movements can also be considered memory guided (reproduction), whereas free movements imply self generation. In normal subjects, RP amplitude is larger preceding free than fixed single movements of a joystick or presses of a button (Praamstra et al. 1995; Touge et al. 1995).

This study investigates whether the mode of movement selection, which has been shown by PET and EEG to influence SMA activity in normals, also modulates the RP in schizophrenics. In addition, single versus sequential movements will be tested in order to examine: (1) the implications for the frontal cortex during complex movements; (2) purported planning dysfunction in schizophrenia; and (3) the relative and interactive effects of mode of selection and complexity. Additive effects of complexity and mode of movement selection could make an SMA contribution to the RP easier to identify. More specifically, we expected to find: (1) significantly lower RP amplitudes in schizophrenics versus controls for all tasks and particularly for the free-sequence task (which requires more planning); (2) a larger RP in both groups for free versus fixed movements and for sequences versus single movements; and (3) longer RP latencies in schizophrenics than in controls for all tasks, reflecting motor preparation impairment in schizophrenia.

Materials and methods

A similar experiment has previously been performed with normal subjects (Praamstra et al. 1995). Our paradigm was approved by the ethics commission of the Medical University of München (Ludwig-Maximilian Universität). All subjects gave their informed consent prior to inclusion in the study.

Subjects

Eleven schizophrenics under stable medication (4 males, 7 females) were selected according to the ICD 10 international classification. The mean duration of hospitalization was 97.4 days (SD 54.70). Subjects' characteristics are given in Table 1. Patients with a history of drug dependence, head trauma, alcoholism or who manifested tardive dyskinesia were excluded from the study. Controls were matched to patients according to age and gender. They had no movement disorder and no previous history of psychiatric or neurological disease. All the subjects were right handed. The mean age was 38.9 years (SD 7.98 years) for controls and 39.1 years (SD 10.04 years) for schizophrenics.

Tasks and design

Subjects had to place the index, middle, third and small fingers of their right hand on four keys of a computer keyboard. The experiments consisted of four tasks:

1. Fixed single-key press: subjects pressed the key under the index finger at self-paced rate of one response every 4–5 s.
2. Fixed sequences: subjects pressed the four designated keys in the fixed order – index, middle, third and small.
3. Free single-key press: subjects chose one of the four keys every 4–5 s without repeating the same finger successively.
4. Free sequences: subjects chose sequences of four free-key presses without repeating the same sequence successively.
   In all conditions, each finger corresponded to a specific key.

The order of testing was from conditions 1–4, without randomization or counterbalancing order across subjects in each group. This progression from the easy task to the more difficult ones was done to facilitate the schizophrenics' comprehension and execution. Additional oral instructions to slow down or speed up the rhythm of movement were given during the task to achieve a delay of 4–5 s between two key-presses in single tasks and between two sequences in sequences tasks. The timing of successive key-presses was required to be as fast as possible during the sequence tasks. Furthermore, reminders were given by the experimenter when necessary (especially for schizophrenics) to avoid eye blinks at least 2 s before key press. Short pauses were allowed during each task when the subject requested or when too many artifacts were recorded on-line. The recording phase ranged from 15 min to 20 min to provide at least 50 artifact-free responses. The total number of trials was not considered; only the number of artifact-free trials was of importance. Erroneous trials (repeating the same key press, or repeating the same sequence in the free conditions) were rejected from the final averaging.

Procedure

Subjects were seated in a reclining comfortable armchair in a noise- and light-protected room. They received verbal instructions

Table 1 Schizophrenics' characteristics. Diagnosis: *DS* depressive schizophrenia; *PS* paranoiac schizophrenia; *SS* schizophrenia simplex. Medication: *Dx* doxepin; *OL* olanzapin; *Cl* clozapin; *Be* benperidol; *Bi* biperiden; *Ri* risperdal; *Ca* carbamazepin; *Lo* lorazepam; *Le* levopromazin; *Hal* haloperidol

Gender	Age (years)	Diagnosis	ICD 10	Medication (4× per day) (mg/day)	Signs
F	24	DS	F 25.1	Dx 0-25-0-100 OL 0-0-0-12.5	Mixed
F	53	PS	F 20.0	Cl 50-50-100-100	Mixed
M	35	DS	F 25.1	Dx 0-0-0-100 OL 0-0-0-15	Mixed
M	33	PS	F 20.0	Be 10-10-10-10	Mixed
F	27	PS	F 20.0	Ri 6-0-0-0 Bi 4-0-0-0	Positive
F	38	PS	F 20.0	Bi 4-0-0-0	Positive
M	33	PS	F 20.0	Be 5-5-10-10 Ca 0-0-0-600	Mixed
F	56	PS	F 20.0	Bi 4-0-4-0	Positive
F	34	PS	F 20.0	Hal 0-0-0-10 Le 100-100-100-100 Bi 4-0-0-0 Ca 0-0-0-600	Positive
M	46	SS	F 20.6	OL 0–0-0-10 Dx 25-0-25-100	Negative
F	40	PS	F 20.0	OL 0-0-0-15 Be 4-2-4-0	Mixed

read by the experimenter. For the free-selection tasks, the instructions stressed that movements should be chosen arbitrarily, i.e., without use of the same finger across two successive trials. Furthermore, it was expressly requested that subjects change sequences from trial to trial to avoid short cyclic repetition of the same sequences. Subjects had to practice each type of movement a few times to ensure that they made brisk movements at the desired rate. They were instructed to fixate on a square (1 cm^2) on the center of a screen, placed 1 m from their eyes. Subjects were given encouragement by the experimenter particularly given the difficulty experienced by the schizophrenics to concentrate on fixating on the square.

Data acquisition and apparatus

The EEG activity was recorded with Ag/AgCl electrodes from 10 positions of the 10–20 system (Fz, Cz, Pz, C1, F3, C3, P3, F4, C4, P4). Electrodes were attached using collodion after careful cleaning of the skin. Horizontal and vertical electrooculograms (EOG) were recorded from the outer canthi of both eyes and from sites above and below the two eyes to control for eye-movement artifacts. Additionally, artifacts were controlled using electrodes at Fp1 and Fp2. Linked electrodes attached to both earlobes served as reference. Bipolar EMG was recorded using Ag/AgCl electrodes attached to the flexor side of the right forearm. The EEG was filtered with a time constant of 5 s and a low-pass filter set at 30 Hz. Signals were digitized on-line with a sampling frequency of 128 Hz per channel, a dynamic range of ±150 μV, and a resolution of 7.8 ms per sample point (400 points). Electrode impedance was kept below 5 kΩ. Data were stored on the hard disk of the EEG brain-mapping system and analyzed off-line with Evoked Potential Software.

Data analyses

To define point 0 of a trial, movement-onset triggers were manually placed where the EMG signal began to rise. Additionally, triggers sent at each key press were used when the EMG was not clearly visible. The interval (for averaging the sweeps) selected to study the RP was 2 s before point 0 and 1.2 s after (7.8×400 ms). RP curves were obtained by averaging at least 50 artifact-free sweeps. For sequences, the onset triggers were placed at the beginning of the first EMG activity. Baseline was corrected from –2000 ms to –1900 ms.

RP onset (RPO) latency was defined as the beginning of the negative potential rise. According to Shibasaki et al. (1980), negative slope (NS') can be defined in normal MRCPs as a late negative slope (prior to actual motor potential) that is steeper than the earlier RP slope and contralateral to the moving hand. Functionally, NS' seems to indicate a terminal increase of lateral premotor system activation prior to movement onset. Peak of NS' was quantified as the maximum negative amplitude prior to movement onset. Negative slope onset (NSO) was defined at the point were NS' began to rise (approximately 500 ms before EMG activity). It has to be noted that NSO results have to be interpreted with caution, given that the point were NS' begins to rise is often difficult to determine, especially in schizophrenics. Amplitudes of the early RP were calculated at Cz and C1 at NSO. Motor preparation was supposed to be reflected by the RPO and early RP amplitude; decision-making was supposed to be reflected by NS' onset and peak of NS' amplitude.

Statistical analysis

Analysis of amplitudes

Multivariate analysis of variance (MANOVA) of the early RP amplitude (amplitude of NS' at the time of its onset) was confined to electrodes Cz and C1, with group (schizophrenics versus controls) as a between-subjects variable, and mode of movement selection (fixed versus free conditions) and movement complexity (single movement versus sequence) as within-subjects factors.

For topographical analysis, comparisons of the peak of NS' amplitude were confined to electrodes Fz, Cz, Pz, C1 and C3. The interval from –500 ms to 0 ms, corresponding to the NS' was selected as the main epoch for statistical analysis. MANOVA of the peak of NS' amplitude was conducted with group as the between-subjects variable, and mode of movement selection and movement complexity as the within-subjects factor.

To further quantify temporal differences in the shape of the RP across groups and conditions, mean amplitudes were calculated for successive time windows (–1000 ms to –900 ms, –900 ms to –800 ms, –800 ms to –700 ms, –700 ms to –600 ms, –600 ms to –500 ms, –500 to 0 ms and 0 ms to 500 ms). The time windows are numbered from 1 to 7. MANOVA of RP amplitude was performed for each time window at electrodes Fz, Cz, Pz, C1 and C3 with group, mode of selection and complexity as variables.

In all of the analyses of amplitude, the three following one-sided hypotheses were tested: (1) amplitudes are greater in normals than in schizophrenics; and for both groups that: (2) sequence induces greater amplitudes than single movements; and (3) free-selected movements induce greater amplitudes than fixed movements.

Analysis of latencies

MANOVA of RPO was conducted at Cz, with group (schizophrenics versus controls) as a between-subjects variable, and with mode of movement selection (fixed versus free conditions) and complexity (single movement versus sequence) as within-subjects factors. MANOVA of NSO was conduced at Cz, with group (schizophrenics versus controls) as a between-subjects variable, and with mode of movement selection (fixed versus free conditions) and complexity (single movement versus sequence) as within-subjects factors.

We tested the two one-sided hypotheses: (1) RPO starts sooner in controls than in schizophrenics; and (2) NSO starts sooner in controls than schizophrenics. For all tasks, the significance level was set at $P<0.05$.

Results

Task performance

Schizophrenics generally presented difficulties at the beginning of the tasks but were able to press the keys correctly after a few minutes of training. Visual inspection of the EMG recordings revealed no substantial differences in strength and speed of finger movements between patients and controls. On-line control of sequence execution was done by monitoring the fingers. When repetition of the same finger occurred in a sequence, the experimenter instructed the subject not to press the same finger twice in one sequence.

General wave form and distribution of the RP

The general wave form of the grand mean RP at Cz for each group and condition is given in Fig. 1. Maps of RPO, NSO and NS' peak are displayed in the bottom panel of Fig. 1. The general wave form of the RP does not differ in normals across the various conditions. In schizophrenics, the RP rises much more slowly than in controls, has lower amplitudes and is less structured. The more striking characteristics of schizophrenic RPs are: (1) delayed onset and low amplitudes and (2) persistence

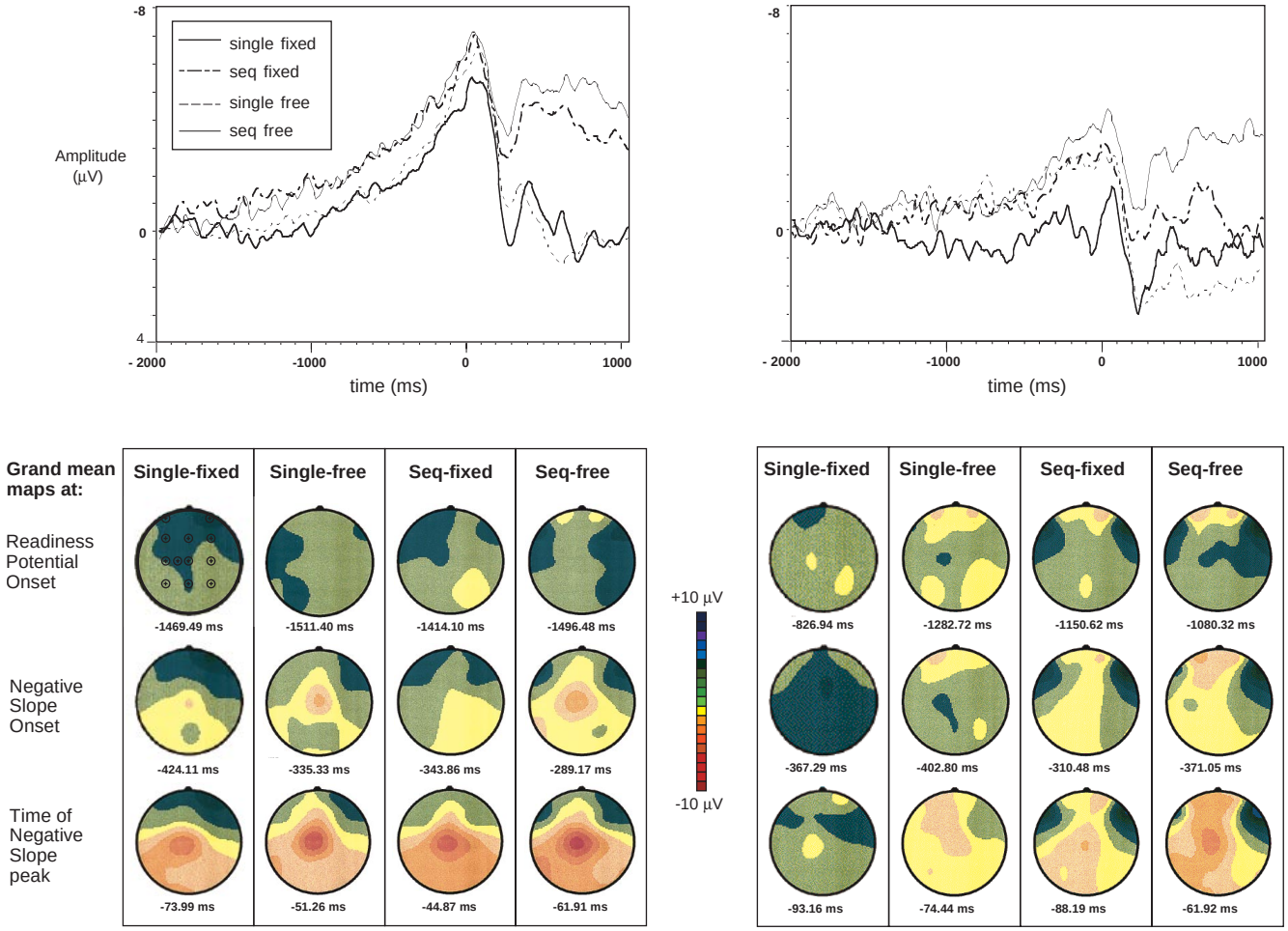

Fig. 1 On the *left*: *Top*: superposition of grand mean readiness potential (RP) of single-fixed, single-free, sequence-fixed, sequence-free conditions, representing potentials preceding right-hand movements recorded at electrode Cz in controls. The time scale extends from 2000 ms before to 1000 ms after movement onset. *Bottom:* grand mean maps of controls in the four conditions displayed at the time of readiness potential onset (*RPO*), negative slope onset (*NSO*) and peak of negative slope. Note the increased recruitment of the supplementary motor area (*SMA*) with time and difficulty of the task. On the *right*: *Top*: superposition of grand mean RP of single-fixed, single-free, sequence-fixed, sequence-free conditions, representing potentials preceding right-hand movements recorded at electrode Cz in schizophrenics. Note: (1) their lower and more noisy RP amplitudes than in controls; and (2) the conservation of an increased SMA recruitment as a gradient of task complexity. *Bottom*: grand mean maps of schizophrenics in the four conditions displayed at the time of RPO, NSO and peak of negative slope. Even if the pattern of activation is more diffuse than in controls, a gradient of SMA activation appears when time and difficulty of the task increase

(as in controls) of a monotonically increasing amplitude that emerges at Cz as the task becomes progressively more complex (from single-fixed, single-free, sequence-fixed to sequence-free).

For both groups, in addition to these effects that occur before movement, there are differences between single movements and sequences that appear during the movement execution: with sequential, but not with single movements, the RP is followed by a performance-related negativity. Classically, when a large degree of cortical control has to be exercised during a movement, negativity is not resolved immediately after movement onset but, rather, is maintained throughout the movement. This sustained negativity has been named the movement-monitoring potential (Deecke et al. 1984). Distribution of the RP is displayed in Figs. 2 and 3 and conforms to general characteristics established in previous studies.

Amplitudes of the early RP

Analysis of the amplitude of the early RP (corresponding to the amplitude of NS' at the time of its onset) was performed at electrodes Cz and C1 (see Table 2). MANOVAs of the early RP show that the amplitudes are significantly greater in controls than in schizophrenics at Cz [$F_{(1,20)}$=3.99, P<0.05], and in both groups, greater at Cz for sequences than for single movements [$F_{(1,20)}$=4.49, P<0.05] and greater at C1 for free than for fixed movements [$F_{(1,20)}$=3.82, P<0.05]. There was no interaction between any of the factors for the amplitude of the early RP analysis.

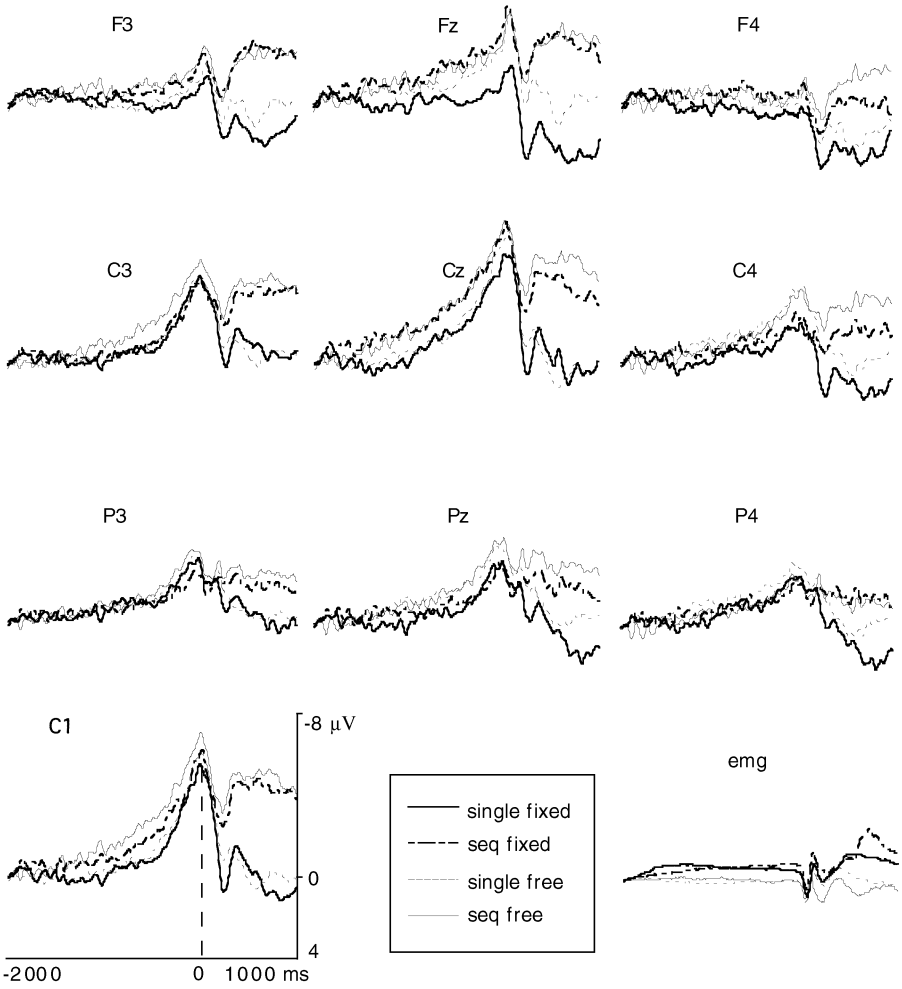

Fig. 2 Superposition of grand mean readiness potential (RP) in conditions 1–4 at all electrode sites, representing potentials preceding right-hand movements in controls. The time scale extends from 2000 ms before to 1000 ms after movement onset

Table 2 Amplitude of the early readiness potential (RP) expressed as µV (+SE of the mean)

	Single-fixed	Sequence-fixed	Single-free	Sequence-free
At electrode Cz				
Cnt	–0.44 (0.68)	–1.65 (0.99)	–0.74 (0.71)	–2.07 (0.75)
Sz	2.24 (1.14)	0.45 (1.13)	–0.10 (0.90)	–0.02 (0.98)
At electrode C1				
Cnt	–0.01 (0.74)	–0.76 (1.07)	–0.39 (0.65)	–2.03 (0.55)
Sz	1.18 (0.69)	0.88 (1.14)	–0.04 (0.92)	–0.09 (1.12)

NS' peak amplitudes

Mean maximal NS' amplitude (NS' peak) is given in Table 3 for each group and condition at Fz, Cz, C1, C3 and Pz. Maximal NS' amplitude reflects the maximal intensity of synchronous activation of neuron populations. It is obtained at the vertex for both groups and in all conditions, except for the first task in schizophrenics (for which the maximal amplitude is at C3).

MANOVA of NS' peak amplitudes shows that amplitudes are significantly greater: (1) in normals than in schizophrenics at Cz [$F_{(1,20)}$=3.43, P<0.05], C1 (F=3.20, P<0.05) and C3 (F=3.26, P<0.05); and for both groups, greater: (2) in free than in fixed movement tasks at Cz (F=6.28, P<0.05), C1 (F=7.05, P<0.05) and Pz (F=12.63, P<0.01); and, (3) in sequence than in single movement tasks at Cz (F=4.56, P<0.05), C1 (F=3.54, P<0.05) and Fz (F=5.04, P<0.05). For all electrodes, there were no interactions between any of these factors.

Time course of the RP

Figure 4 summarizes the MANOVAs of mean RP amplitudes in each of the seven time windows from –1 s to –0.5 s (in intervals of 100 ms), from –0.5 s–0 s and from 0 s–0.5 s. The F-values per window are given in Fig. 4 for significant corresponding P-values. A group effect (lower RP in schizophrenics than in normals) starts 700 ms before movement (fourth time window at Cz). A com-

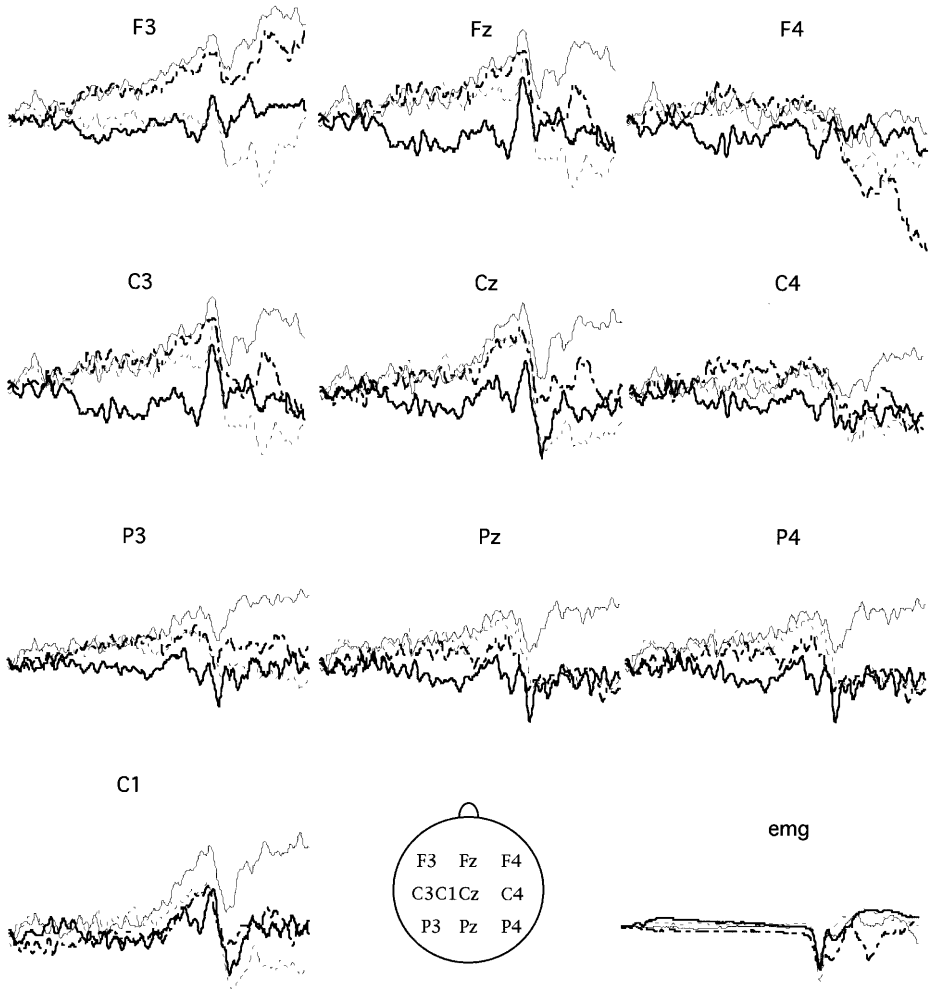

Fig. 3 Superposition of grand mean readiness potential (RP) in conditions 1– 4 at all electrode sites, representing potentials preceding right-hand movements in schizophrenics. The time scale extends from 2000 ms before to 1000 ms after movement onset

Table 3 Mean peak of negative slope (NS') amplitude (+SE of the mean) for the four successive tasks in each group (μV). *Cnt* Controls; *Sz* Schizophrenics

	Single-fixed	Sequence-fixed	Single-free	Sequence-free
Electrode Cz				
Cnt	–5.05 (0.98)	–6.45 (1.43)	–5.75 (0.56)	–6.79 (1.10)
Sz	–1.43 (1.76)	–4.01 (1.03)	–4.00 (0.84)	–5.66 (1.18)
Electrode C1				
Cnt	–4.96 (1.29)	–5.74 (1.21)	–5.68 (0.59)	–6.55 (1.12)
Sz	–2.00 (1.12)	–3.18 (1.16)	–3.46 (1.06)	–5.06 (1.31)
Electrode C3				
Cnt	–4.08 (0.78)	–3.61 (0.89)	–4.23 (0.76)	–5.22 (1.30)
Sz	–2.28 (0.84)	–2.20 (1.02)	–2.86 (0.79)	–2.75 (0.99)
Electrode Pz				
Cnt	–3.56 (0.82)	–3.01 (0.95)	–4.03 (0.40)	–4.92 (1.12)
Sz	–1.23 (0.92)	–2.22 (0.89)	–3.25 (0.89)	–3.57 (0.99)
Electrode Fz				
Cnt	–1.12 (0.47)	–3.76 (0.96)	–1.91 (0.93)	–2.97 (0.89)
Sz	–1.29 (1.09)	–3.56 (1.23)	–2.83 (0.59)	–3.53 (1.15)

plexity effect (greater RP for sequences than for single movements) starts simultaneously at Fz, Cz, C1 and Pz 600 ms before movement onset and is more pronounced at fronto-central electrodes. A mode of movement selection effect (greater RP for free than for fixed movements) starts at Pz as early as 1000 ms before movement onset.

RPO latencies

RPO reflects the starting time of movement preparation. The mean times (ms) of RPO (+SE) are, for the four successive tasks: –1469.49 (52.96), –1511.40 (52.16), –1414.1 (64.81), and –1496.48 (72.81) for controls and –826.94 (95.77), –1282.72 (97.13), –1150.62 (116.24), and –1080.32 (102.10) for schizophrenics.

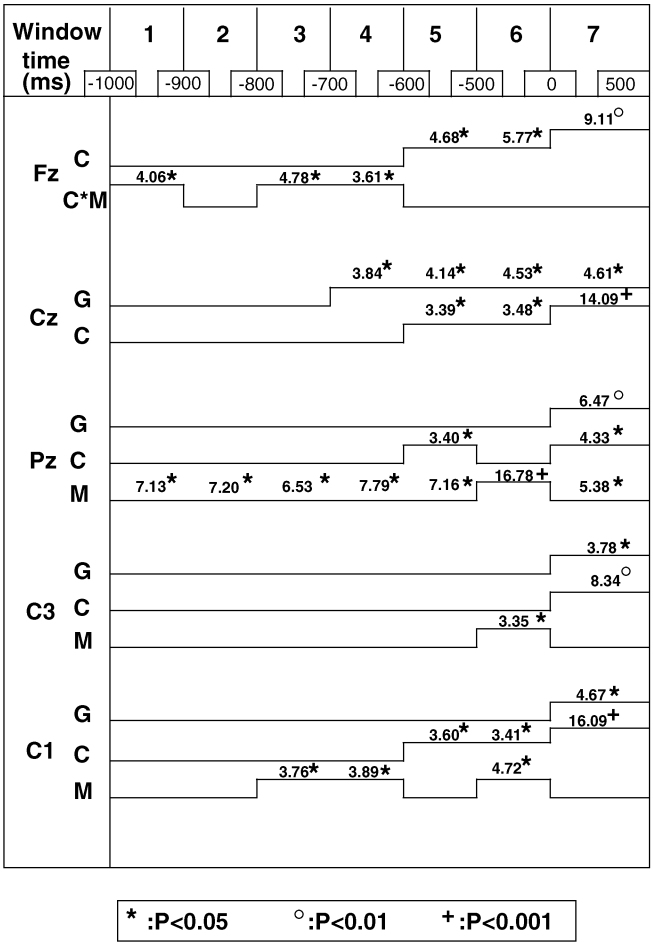

Fig. 4 Summary of analyses across time of group effect (*G*), complexity effect (*C*) and mode of selection effect (*M*) at electrodes Fz, Cz, Pz, C3 and C1. The time scale represents 1000 ms before and 500 ms after movement onset. The interval from –1000 ms to –500 ms was analyzed in five separate time windows of 100 ms each. The interval from –500 ms to 500 ms was analyzed in 2 separate time windows of 500 ms each. Separate analyses of variance were carried out for each window on the mean amplitudes of the RP for group, complexity and mode of selection factors (two-sided hypothesis)

MANOVA results reveal that RPO occurs later in schizophrenics than in controls [$F_{(1,20)}$=27.62; P<0.001] and that there is a significant interaction between group, complexity and mode of movement selection [$F_{(1,20)}$=5.40; P<0.05]. This interaction is further analyzed by *t*-tests of paired differences in RPO, which reveal significant effects only in schizophrenics for the single-fixed versus sequence-fixed tasks (t=3.12, P<0.05) and for the single-fixed versus single-free tasks (t=2.31, P<0.05).

NS' latencies

NS' reflects the initiation of movement, or go signal (Libet et al. 1982). Mean times (ms) of the NSO and SE of the mean for the four successive tasks at electrode Cz were: –424.11 (45.37), –335.33 (36.69), –343.86 (40.21), and –289.17 (37.88) for controls and –367.29 (37.29), –402.80 (43.10), –310.48 (42.59), and –371.05 (27.48) for schizophrenics. A MANOVA revealed significantly later NSO for free movements compared with fixed ones [$F_{(1,20)}$=4.90; P<0.05]. There were no group or complexity effects and no interactions.

Discussion

RP and NS' amplitudes: interpretation

Except for the single-fixed task in schizophrenics, for whom the maximal amplitude was obtained at C3, NS' peak was maximal at Cz for both groups in all conditions. Usually, the NS' component is reported to be maximal over the contralateral precentral region in controls. The small number of subjects and the lack of lateralization in schizophrenics could explain this discrepancy (Günther et al. 1994, 1995; Schröder et al. 1995; Mattay et al. 1997).

Our results show, first, lower RP amplitudes at Cz in schizophrenics than in normals, which can be interpreted as a motor preparation deficit. Second, relative to controls, schizophrenic subjects show significantly lower NS' peak amplitude at central and contralateral electrodes (Cz, C1 and C3), which can be considered a decision-making process deficit. Third, in both groups, higher RP and NS' amplitudes are obtained for sequential versus single movements and for freely selected versus fixed movements, which supports the importance of movement complexity and mode of selection in SMA/MI activation. Taken together, these results reflect a focal deficit of activation around the SMA/MI in schizophrenia, which can either be interpreted in terms of a fronto-striatal dysfunction (or, more generally, of impaired SMA-basal ganglia loops) or in terms of a fronto-parietal gradient of perturbation. Indeed, a diffuse cortical perturbation cannot be excluded, because RP shows greater between-group variance at its generation site than at other sites. We now further discuss each of our three results.

RP is smaller in schizophrenics than in controls

The fact that the RP is smaller in schizophrenics than in normals has been reported previously for single fixed movements (Timsit-Berthier 1973; Chiarenza 1985; Westphal et al. 1986) and is extended here to complex and free movements. Previous PET and fMRI studies showed that the mesial frontal and contralateral sensorimotor areas were not activated in schizophrenics performing a fixed sequence of finger movements (Günther et al. 1994, 1995; Schröder et al. 1995; Mattay et al. 1997). Our EEG findings show that activation of these areas is not completely impaired in schizophrenics, particularly when complexity and mode of movement selection are combined.

The between-groups differences appear to be significant as early as 700 ms before EMG onset at electrode

Cz. This allows a clear distinction between the intervals preceding and during movement, adding important new insights to PET and fMRI results. NS' peaks are significantly higher in normals than in schizophrenics at electrodes Cz, C1 and C3. However, we cannot conclude from this that there is a localized deficit in schizophrenia. Indeed, significant differences in NS' peak amplitudes occur at sites for which the NS' peak is at its highest amplitude (Cz, C1 and C3), but not at frontal and parietal sites, where the amplitude is lower.

RP is greater for sequences than for single movements

Greater RPs for sequences versus single movements have been described in normals: (1) for sequences that start with the same movement as the single movement task; (2) when the comparison is between sequences and the simultaneous extension of two fingers (Benecke et al. 1985; Simonetta et al. 1991; Kitamura et al. 1993a, b). Yet, there are also reports of no differences in RP amplitudes for sequences versus single movements (Lang et al. 1988, 1989; Praamstra et al. 1995).

Our MANOVA of RP amplitudes as a function of time shows that complexity effects become significant at electrodes Fz, Cz, and C1 as early as 600 ms before EMG onset. This complexity effect is larger at Fz than at central sites (Cz and C1). This is in accordance with studies that show a larger and earlier RP over the anterior part of the frontal lobes when measured during writing and drawing than when measured during single finger movements, for which the RP is larger at the vertex (Schreiber et al. 1983). Furthermore, there is an early Pz activation (from –600 ms to –500 ms before EMG onset). Although this effect is no more significant during NS' (from –500 ms to 0 ms), it is in the direction of PET results from normals that show activation of frontal as well as parietal cortex during a self-paced sequential finger-opposition task (Wessel et al. 1995). This parietal cortex activity likely occurs because of feedback activation due to proprioception present: (1) in the finger-movement task but not the rest condition of the PET study; and, (2) in the sequence task more than in the single movement task of the present study. Thus, our results provide new information about the magnitude of activation from frontal to central and parietal cortex during self-initiated sequences versus single movements.

RP is larger for free than for fixed movements

Analysis of the NS' peak amplitudes shows significant effects of selection mode at sites Cz, C1 and Pz. In contrast, analyses of different time windows implicate electrode C1, Pz, C3 but not Cz. These differences are due to the fact that the statistical analysis in each time window is based on time-averaged values, while the analysis of NS' peak amplitude is performed on a value observed at a specific time.

The selection effect is present at Pz 1000 ms before EMG onset and appears at C1 800 ms before EMG onset over the contralateral hemisphere. One possible interpretation for the early effect that selection mode shows at Pz depends on the involvement of parietal cortex in extrapersonal space – in the free conditions, the fingers are always changing, whereas in the fixed condition they are not. This clearly shows an influence of selection mode even before movement occurs in normals and schizophrenics. Praamstra et al. (1995) likewise reported in normals a selection effect that started 800 ms before EMG onset. Their study grouped electrodes by rows and, thus, could not statistically determine the site at which the selection effect began; nevertheless, inspection of their results confirms a larger involvement of parietal than PFC for free versus fixed movements. PET studies also revealed significant bilateral activation of parietal area 40 for self-initiated movements, relative to rest (Deiber et al. 1991; Jahanshahi et al. 1995).

The result that freely selected movements cause higher NS' peak amplitudes than fixed ones does not necessarily imply that the mode of movement selection modulates the RP. As noted by Kitamura et al. (1993b), there is a substantial difference in RP amplitude associated with extension of the middle finger versus extension of the index finger. This difference could be related to greater difficulty of the former movement due to anatomy. The first two fixed tasks started with pression of the index finger; however, this was not necessarily the case for the last two free tasks. Thus, movements could differ in anatomical characteristics that determine the NS' peak amplitude, independently of the selection mode (fixed or free). To rule out this possibility, for each of the possible movements in a free-selection condition, Praamstra et al. (1995) examined the same movement in a fixed control condition. This procedure was not used in our study because it would have required three tasks in addition to our four existing ones, which would have been too long and difficult for schizophrenics. We thus suppose that finger-related differences in amplitudes are not affected by schizophrenia but depend, instead, only on anatomy and subjects' skills. This hypothesis is justified in light of EMG activity which does not reveal between-group differences (see Figs. 2 and 3).

Internally versus externally triggered movements: comparison of fixed versus free movements

Even if the fixed condition tasks do not correspond to the externally triggered conditions of other studies, it is interesting to compare activity at Cz, which is supposed to be related to SMA activity, and activity at more lateral C1 and C3 electrodes, which are related to lateral premotor or motor cortex. Our results showed an effect of selection mode at both C1 and Cz. This does not validate the distinction between the two routes to MI (Goldberg 1985). As noted previously, even PET and fRMI studies, which present a much finer spatial resolution than elec-

trophysiology, have failed to support this dichotomy (Deiber et al. 1991; Playford et al. 1992; Jahanshahi et al. 1995). They have even shown SMA participation in visually and auditory triggered simple motor tasks (Grafton et al. 1996; Van Oostende et al. 1997). Thus SMA activation would not be confined to internally generated movements.

Furthermore, for both groups, free movements did not produce significantly larger RP amplitudes at Fz than fixed movements. This can be compared with Jahanshahi et al.'s (1995) RP study of normals, which did not report significantly larger RP amplitudes at Fz for self-initiated versus externally triggered movements. However, PET studies revealed significant DLPFC activation in normals during self-initiated movements when compared with externally triggered ones (Deiber et al. 1991; Frith et al. 1991; Papa et al. 1991; Playford et al. 1992; Jahanshahi et al. 1995). This discrepancy between EEG and PET results concerning frontal activation in self-initiated versus externally-triggered movements in normals could be attributed to task differences associated with the two techniques. Furthermore, PET studies in fixed versus free conditions remain to be performed in normals and schizophrenics to allow for a comparison of rCBF activation to our EEG results.

Latencies: interpretation

A functional interpretation of RP and NS' onset has been proposed by Libet et al. (1982), who suggested that two volitional processes contribute to the RP in self-initiated movements. The first process starts 1 s or more before EMG onset and is related to the preparation to act (early RP). The second process starts at approximately 500 ms before EMG onset, is associated with the decision-making process or endogenous intention to act (go signal), and corresponds to the late RP in terms of its timing (or NS' for Shibasaki et al. 1980). This interpretation has been supported recently by two experimental results. First, due to the absence of internally guided decision making, the NS' for externally triggered movements is significantly lower than for self-initiated movements. Second, in an externally triggered condition with irregular rhythm, there is neither decision making nor the possibility of anticipating the precise onset of the stimulus, thus no early or late RP (Jahanshahi et al. 1995).

Schizophrenics' RP starts significantly later than that of controls, which reflects delayed movement preparation. This provides evidence for a planning dysfunction and of late SMA activity involvement in schizophrenics. The significant three-way interaction of group, complexity, and mode of movement selection [$F_{(1,20)}$=5.40; P<0.05] in the analysis of RPO can be attributed to significant effects obtained in schizophrenics for single-fixed versus sequence-fixed tasks (t=3.12, P<0.05) and for single-fixed versus single-free tasks (t=2.31, P<0.05).

With respect to the NS' onset, the absence of a significant between-groups difference can be interpreted as the absence of perturbation in the timing of the decision process. Furthermore, the fact that free movements induce later NS' onset than fixed ones can be explained by the time required for the choice of movement selection in free conditions. Thus, the distinction between fixed and free conditions could be useful for distinguishing the latest stage involved in choosing a self-initiated movement.

Heterogeneity and medication of schizophrenics

Two important and general questions about the influences of heterogeneity and medication of schizophrenics on the RP remain to be analyzed. Hypofrontality has been associated with negative symptoms of schizophrenia, whereas hyperactivity of the mesolimbic pathway has been associated with positive symptoms (Guy et al. 1986; Kemali et al. 1987; Breier et al. 1990; Braff et al. 1991). It has been proposed that patients with negative symptoms have difficulty in making self-initiated movements, while patients with positive symptoms are more impaired in making externally triggered movements (Frith 1992). In our study, the groups were not distinct enough to distinguish the effects of symptoms. A recent finding reveals significant RP differences according to symptoms. Indeed, in a simple motor task, Karaman et al. (1997) reported that the RP is reduced in patients with positive symptoms, whereas the NS' is reduced in patients with negative symptoms.

The second usual and yet unresolved question concerns the role of medication on the RP. Schizophrenics were exposed to long-term and cumulative anti-dopaminergic drugs, which might lead to functional changes that cause abnormal RP findings. Although schizophrenics with manifest tardive dyskinesia were excluded from our study, some patients showed soft drug-induced parkinsonian symptoms. However, these soft signs do not seem to have influenced either EMG activity or the after-movement positive wave. Indeed, the RP is resolved immediately following movement in our group of schizophrenics, which is not the case in patients with severe parkinsonian symptoms (Cunnington et al. 1995).

Recently, Karaman et al. (1997) failed to observe significant RP amplitude differences between medicated and drug-free schizophrenics. However, haloperidol administration reduces the peak NS' amplitude in normals (Dick et al. 1987). Neuroleptic administration also increases basal ganglia metabolism (De Lisi, 1985; Buchsbaum et al. 1992), which could therefore affect SMA activity and RP amplitudes. Thus, further studies need to be carried out to confirm the lack of effect of neuroleptics on RP amplitudes in schizophrenics.

Comparison of RP in Parkinson's disease and schizophrenia

Qualitative comparison of RP in Parkinsonians, schizophrenics and controls shows that in both of the patient groups, the RP onset is later, while the peak NS' ampli-

tude is lower than in controls (Deecke et al. 1977; Barrett et al. 1986; Simpson and Khuraibet 1987; Dick et al. 1989; Tarkka et al. 1990; Feve et al. 1992; Vidailhet et al. 1993; Jahanshahi et al. 1995; Touge et al. 1995). The delayed RP onset indicates a delayed beginning of SMA/MI activation, whereas abnormal RP amplitude can be interpreted as a reduced SMA/MI activity. Behaviorally, the delayed RP onset reflects impaired timing of the preparatory phase of movement, whereas the lower NS' amplitude reflects impaired decision making. Specific to patients with severe parkinsonian symptoms is an impaired termination of RP following the motor response (Cunnington et al. 1995, 1997).

The parameters of movement selection and complexity have been studied in Parkinson's disease. With respect to the mode of selection, two studies indicate that the RP is not modulated by this parameter in Parkinson's disease (Touge et al. 1995; Praamstra et al. 1996); this can be attributed to impaired processes involved in self-selection of movements. This could be a major difference between Parkinson's patients and schizophrenics, given that our study reported a larger RP for free than for fixed movements at centro-parietal sites, in controls and schizophrenics, taken as a group. With regard to complexity, deficits in the performance of sequential movements have been reported in Parkinson's disease, although the RP has not been compared between single and sequences of movements (Benecke et al. 1987; Georgiou et al. 1993).

In conclusion our study reports that schizophrenics' RP is smaller than in controls for all tasks, revealing a global motor preparation deficit. These motor deficits are not specific to complex movements (sequence-free) but are even present for the simplest movement preparation (single-fixed). Furthermore, our study reports for the first time that RP amplitude increases with task difficulty for both groups, indicating that schizophrenics exhibit the same order of frontal activation as controls. Finally, temporal definition of the RP shows that motor preparation starts much later in schizophrenics than in controls, whatever the difficulty of the task.

The neural basis of Parkinson's disease is the degeneration of the nigrostriatal pathway, which affects mostly the dorsal striatum-SMA system. Impairment of this loop could explain the Parkinsonian's deficit in self-selection of movements (Touge et al. 1995; Praamstra et al. 1996). Conversely, schizophrenia can partly be considered as a glutamate-mediated disruption in the balance between dopamine afferents to the frontal cortex and the ventral striatum (Tassin et al. 1982; Carlsson 1990; Tassin 1995). This ventral loop, receiving strong inputs from limbic structures, operates in parallel with dorsal loops implicated in planning. Motor deficits revealed by the tasks of our study suggest either direct fronto-dorsal striatum loop dysfunction in schizophrenia or primary ventral loop impairment that affects dorsal loop (Groenewegen and Berendse 1995; Groenewegen et al. 1996).

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