Motor Dysfunction and Sensorimotor Cortex Activation Changes in Schizophrenia: A Study with Functional Magnetic Resonance Imaging

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Recent studies demonstrate a diminished activation of the sensorimotor cortex and supplementary motor area (SMA) in schizophrenia which may be involved in the pathogenesis of neurological soft signs (NSS). Yet, the question whether a retarded motor performance may account for these changes remained to be clarified. Twelve DSM-III-R schizophrenics and 12 healthy controls were included. All subjects were right-handed. Nine patients received clozapine, two conventional neuroleptics, and one was drug-free. Functional magnetic resonance imaging (fMRI) was obtained in a resting condition and during pronation/supination at three speed levels (low, medium, and high) with motor performance recorded simultaneously using a pronation/supination device. While measures of motor retardation (i.e., repetition rate and amplitude of the movements) did not differ between patients and controls, the variability of performance was significantly (P < 0.05) increased in the patients’ group. In addition, patients with schizophrenia showed a significantly (P < 0.05) decreased activation of the sensorimotor cortices. Similar, although nonsignificant (P = 0.09) activation changes were observed in the SMA. Activation differences were more pronounced at a slow speed and in the drug-free patient. These results confirm a diminished sensorimotor cortex and SMA activation and indicate that variability of performance rather than retarded performance per se may correspond to these changes. © 1999 Academic Press.

Key Words: neurological soft signs; schizophrenia; functional magnetic resonance imaging; sensorimotor cortex; supplementary motor area.

INTRODUCTION

Minor motor and sensory disturbances or neurological soft signs (NSS) are frequently found in schizophrenia (Schröder et al., 1992). While NSS address different aspects of sensory and motor dysfunction, recent studies (Jahn et al., 1995; Jahn, 1996) demonstrate that motor NSS, such as an impaired finger-to-thumb opposition or pronation/supination, are of particular clinical significance in differentiating patients with schizophrenia from healthy controls. Positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) studies demonstrated a diminished activation of the sensorimotor cortices and supplementary motor area (SMA) in schizophrenia which may be involved in the pathogenesis of NSS (Günther et al., 1994; Schröder et al., 1995). However, studies in healthy volunteers (Dettmers et al., 1995; Jenkins et al., 1994; Rao et al., 1996; Sabatini et al., 1993; Sadato et al., 1996) found these activation measures to increase with movement rate and force. Since motor function is altered in schizophrenia, these studies underline the importance of rigorous control of motor performance in neuroimaging studies of the motor system.

More recently, Jahn et al. (1995) developed a device to investigate repetitive pronation/supination, which is generally considered to be a typical NSS (for review see Jahn, 1996), for subtle kinematic changes. Using this pronation/supination (PS) device, Jahn and coworkers (1995) demonstrated that motor performance in schizophrenia is characterized by an increased intraindividual variability of kinematic indices such as peak velocity and peak acceleration. The respective coefficients of variability (CV) were highly correlated with NSS scores but not with extrapyramidal side effects. In contrast, measures of retarded motor performance, i.e., frequency and mean amplitude of repetitive movements, showed only minor, nonsignificant reductions and were not correlated with NSS scores. In interpret-
ing their results, Jahn and coworkers (1995) suggest that NSS in schizophrenia correspond to an impaired fine motor coordination and that the analysis of CV provide a sensitive and valid measure of this deficit. In the present fMRI-study we investigated sensorimotor cortex and SMA activation at three different speed levels while controlling motor performance using a PS device adopted to the fMRI environment. The aims of our study were: (1) to investigate sensorimotor cortex and SMA activation with respect to motor performance; and (2) to address the question whether a decreased activation of the respective areas in schizophrenia refers to an increased variability of performance rather than to motor retardation.

METHODS

Patients and healthy controls. Twelve patients (4 F, 8 M) with a DSM-III-R (APA, 1987) schizophrenia and 12 healthy volunteers (6 F, 6 M) were included. The mean age was 28 ± 9 and 27 ± 3 years, respectively (df = 1, F(1,20) = 0.5, P = not significant). All but one drug-free patient were investigated when being in a stable condition after remission of the acute illness. Nine patients received 150–600 mg clozapine (mean dose: 290 ± 140 mg/day), two conventional neuroleptics (flupentixol 12 mg/day and benperidol 16 mg/day in combination with biperiden 4 mg/day, respectively), and one patient was drug-free. None of the patients showed extrapyramidal side-effects nor signs of tardive dyskinesia on clinical examination. Psychopathological symptoms and NSS were assessed on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) and the Heidelberg NSS-scale (Schröder et al., 1992), respectively. The mean BPRS-score of patients was 32 ± 8.2. Ratings were performed on the same day as the fMRI study. All subjects were right-handed as measured on the respective subtest of the Tübinger Luria Christiansen Scale (Hamster et al., 1985). Particular care was taken to exclude subjects with a history of neurological disorders, tardive dyskinesia, or substance abuse. This was done by clinical examination (including a complete neurological status), laboratory testing, and evaluation of a complete set of T1-weighted 3D MRI.

Experimental procedure. After written consent, fMRI were performed on a 1.5 Tesla MRI system (Magnetom SP 4000, Siemens, Erlangen/Germany), using a standard head-coil and optimized T2*-weighted FLASH-sequences (TR/TE/ = 85 ms/60 ms/40, TH = 3 mm, FOV = 200 mm, NEX = 1, MAT = 28 × 128, TA = 12 s/image; Schad et al., 1993). To prevent head motion additional foam pads were placed inside the head coil. Ears were plugged with wax. For slice selection, a sagittal scout scan and a set of 16 contiguous T1-weighted images parallel to the AC–PC line were acquired. Of these images, a 3-mm slice approximately 2 cm above the corpus callosum covering the pre- and postcentral gyri and the SMA was chosen for functional evaluation. To optimize field homogeneity, interactive magnet shimming with all first order coils was performed on the selected slice. A detailed description of the image technique used is given by Baudendistel et al. (1996).

Scans were obtained in a resting condition and during pronation/supination at three speed levels (verbal instructions: "slow," "medium speed," "as fast as possible"). Speed levels were given in a standardized order ("slow," "medium," "fast" speed level). Under each right and left hand pronation/supination, 60 fMRI images were acquired, alternating five images (corresponding to a time period of 1 min) in resting condition and under pronation/supination. Verbal instruction was kept constant for two consecutive activation tasks. Pronation/supination was not practiced prior to the fMRI study except brief periods during the clinical NSS examination. Motor performance was simultaneously recorded using a PS-device (Jahn et al., 1995) adapted to the fMRI environment (Baudendistel et al., 1996). The device consists of an U-shaped handgrip attached to the rotation axis of a precision potentiometer. Rotational movement of the grip results in a position-dependent output voltage, corresponding to the actual rotation angle. Data were sampled at a frequency of 100 Hz and analyzed off-line using the CS software package (MedCom, Munich/Germany; Mai and Marquardt, 1994). The CS package provides extended evaluation procedures such as filtering the stored movement data by use of nonparametric kernel estimates and subsequent kinematic analyses of velocity and acceleration profiles of the movement trajectories (Marquardt and Mai, 1994).

Data analysis. Image analysis was performed on a VAXstation 3100 (DEC). A cine mode was used to detect significant inplane head motion during the acquisition. Particular care was taken to identify any signs of head motion in the z-direction such as slight motion artifacts in the frontal and occipital cortex. Subjects presenting with any significant motion artifacts were excluded from further evaluation. For each performance rate Student's t parametric maps of activation versus baseline images were calculated. Regions of interest (comprising the left and right sensorimotor cortices and the SMA, respectively) were defined using a grid overlay method. For exact localization of the activation changes the fMRI were superimposed on corresponding T1-weighted images. Activation strength (mean t value of significant pixels, with P < 0.005) was calculated for each region of interest (Fig. 1). Further methodological details are described by Baudendistel et al. (1995).

Kinematic analysis of motor performance focused on three indices: (i) the repetition rate or frequency (Hz) of the movement, (ii) the mean amplitude (rotation angle),
and (iii) the intraindividual variability (%) of performance. The latter was defined as the coefficient of variation (CV = SD/M × 100) of the peak angular velocity. In recent studies on various kinematic variables (Jahn, 1996) these measures proved to be valid and reliable indices of central and independent features of simple repetitive movements.

Consecutively, three-way analyses of variance (ANOVA) were calculated for each of the fMRI and performance measures, with independent groups (patients, healthy volunteers) and repeated measures for speed ("slow," "medium speed," and "as fast as possible"), and hemisphere (right, left sensorimotor cortex/fMRI variables) or "hand" (right, left hand/kinematic variables). A two-way ANOVA was calculated for the SMA since the respective measures were obtained across both hemispheres. Complete fMRI data were obtained in all patients and 10 controls; complete kinematic data sets in each 8 patients and controls, respectively.

RESULTS

Group means and standard deviations of motor performance indices are given in Table 1.

While the repetition rate increased at higher speed levels ($F(2, 13) = 21.2; P < 0.005$), no other main or interaction effects on the frequency and mean amplitude of the movements were significant ($0.01 \leq F \leq 2.3$; not significant). Motor variability (CV of peak angular velocity) was significantly increased in the schizophrenic patients as compared to the healthy controls ($F(1, 14) = 5.8; P < 0.05$). The "group × speed" interaction on motor variability did not reach definite significance ($F(2, 13) = 3.7; P = 0.05$). No other main or interaction effect on motor variability emerged ($0.02 \leq F \leq 2.6$; not significant).

Sensorimotor cortex activation (Table 2) increased significantly with elevated speed under both contralateral (main effect speed: $F(2, 40) = 15.4, P < 0.005$) and ipsilateral pronation/supination (main effect speed: $F(2, 40) = 5.0, P < 0.05$).

A significant main effect "speed" was also found for the SMA ($F(2, 40) = 14.3, P < 0.005$/Table 3). When compared with the healthy controls, patients with schizophrenia were characterized by significantly decreased activation values in the sensorimotor cortices under both contralateral (main effect group: $F(1, 20) = 5.7, P < 0.05$) and ipsilateral pronation/supination (main effect group: $F(1, 20) = 4.6, P < 0.05$),
### TABLE 1

Group Means (M) and Standard Deviations (SD) of the Three Kinematic Variables Measured under Pronation/Supination at Three Speed Levels

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th></th>
<th>Schizophrenic patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slow</td>
<td>Medium</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Freq. M</td>
<td>0.4</td>
<td>0.4</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Freq. SD</td>
<td>0.2</td>
<td>0.3</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Ampl. M</td>
<td>121.9</td>
<td>124.7</td>
<td>129.7</td>
<td>123.6</td>
</tr>
<tr>
<td>Ampl. SD</td>
<td>38.0</td>
<td>98.5</td>
<td>48.5</td>
<td>31.0</td>
</tr>
<tr>
<td>CV M</td>
<td>17.6</td>
<td>15.2</td>
<td>13.7</td>
<td>15.5</td>
</tr>
<tr>
<td>CV SD</td>
<td>5.7</td>
<td>1.9</td>
<td>2.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Note. Legend: Freq., frequency (Hz); Ampl., mean amplitude (°); CV, coefficient of variation of peak angular velocity (%).

but not in the SMA (main effect group: $F(1, 20) = 3.2, P = 0.09$). These differences were more pronounced in the drug-free patient who showed activation values well below the group means. Repeated analyses after exclusion of this patient revealed consistent results.

None of the clinical measures (daily clozapine dosage, severity of illness/totall BPRS-score, NSS-scores) was significantly correlated with any of the activation measures. When compared with the healthy controls, the schizophrenic patients presented with significantly increased total NSS-scores ( NSS cont. = 4.1 ± 3.6, NSS schiz. = 21.1 ± 9.2; $F(1, 20) = 30.0, P < 0.005$).

### DISCUSSION

Our study provides two major findings: (1) an indication that activation of the motor cortices increases with motor speed; and (2) further evidence that sensorimotor cortex and SMA activation is reduced in schizophrenia.

Activation of the sensorimotor cortices and the SMA under pronation/supination was found to increase with the repetition rate of movements. This effect applied for both patients with schizophrenia and healthy controls. A similar speed effect was reported by Sabatini et al. (1993) who investigated 24 right handed healthy volunteers during finger-to-thumb opposition using SPECT with 133-Xenon as a tracer. Twelve subjects executed the task with their right and left hand consecutively with a fast frequency and large amplitude, while the other 12 subjects performed the task with their right hand only at a slow frequency and small amplitude. Regarding the sensorimotor cortices, the rCBF varied according to the task's performance with fast and large movements producing a greater activation. An effect of performance on rCBF changes under finger-to-thumb

### TABLE 2

Group Means (M) and Standard Deviation (SD) of Activation Measures (Mean t Value) in the Sensorimotor Cortices under Contra- and Ipsilateral Pronation/Supination in Patients and Healthy Controls

<table>
<thead>
<tr>
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<th>Schizophrenic patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slow</td>
<td>Medium</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td></td>
<td>Contr</td>
<td>Ipsi</td>
<td>Contr</td>
<td>Ipsi</td>
</tr>
<tr>
<td>Right Sensomotor Cortex M</td>
<td>4.06</td>
<td>3.67</td>
<td>4.14</td>
<td>3.97</td>
</tr>
<tr>
<td>Right Sensomotor Cortex SD</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Left Sensomotor Cortex M</td>
<td>3.96</td>
<td>3.79</td>
<td>4.22</td>
<td>3.81</td>
</tr>
<tr>
<td>Left Sensomotor Cortex SD</td>
<td>0.3</td>
<td>0.3</td>
<td>0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Note. Legend: sensomotor cortex, sensorimotor cortex; contr., contralateral; ipsi., ipsilateral.
opposition was also observed in PET (Seitz et al., 1990) and fMRI (Rao et al., 1996) studies in nine and five healthy volunteers, respectively. These observations parallel the findings of Fox et al. (1985) and Wise et al. (1991) who found a proportional relation between stimulus repetition and cortical activation in the primary visual and auditory cortex. While Sabatini et al. (1993) did not confirm such a proportional relation between task performance and activation for the SMA, the present results indicate that a performance effect also applies for the SMA. Obviously methodological differences, in particular the higher spatial and temporal resolution capacity of the fMRI and the comparison between three instead of two different speed levels in the present study may account for this discrepancy.

When compared with the healthy controls the schizophrenic patients showed a significantly decreased activation in the sensorimotor cortices under both contra and ipsilateral pronation/supination. Using PET with [15O]deoxyglucose as a tracer, Günther and coworkers (1994) investigated 13 patients with schizophrenia and 14 healthy controls in a baseline condition and during a complex motor sequence task. When compared with the healthy controls, the schizophrenic patients showed different activation patterns with a reduced activation in the contralateral sensorimotor cortex and the SMA. Further evidence suggesting sensorimotor cortex changes in schizophrenia comes from a fMRI study on 10 schizophrenic patients and 7 healthy volunteers (Schröder et al., 1995). Subjects were investigated in a resting condition and during finger-to-thumb opposition using similar methods for fMRI acquisition and image analysis as in the present study. Again, activation values in the sensorimotor cortices and the SMA were lower in the patients with schizophrenia than in the healthy controls. A reduced activation of the SMA was also reported by Mattay et al. (1997) who investigated 8 patients with schizophrenia and 7 healthy controls using fMRI. In addition, a decreased sensorimotor cortex activation in schizophrenia was also described by Spence et al. (1997). While these studies agree in suggesting changes of the sensorimotor cortex and SMA activation in schizophrenia, another recent fMRI study (Buckley et al., 1997) did not describe any significant activation differences in the primary motor cortex in nine patients with schizophrenia. The fMRI technique employed by Buckley and colleagues differed in two important aspects, i.e., a low number of images obtained and a low significance level ($P < 0.05$) for calculating $t$ test maps, from the studies cited above. Moreover, Buckley et al. (1997) practised the movement prior to the fMRI examination. This may have well led to a reduced activation in the healthy volunteers since a recent study found activation of the sensorimotor cortices to decrease with motor learning (Shadmehr and Holcomb, 1997). Others investigated sensorimotor cortex activation with respect to task complexity (Shibasaki et al., 1993). These studies found higher activations with increasing task complexity corresponding to the effects of motor learning described by Shadmehr and Holcomb (1997).

The potential impact of performance differences on these findings was not particularly addressed. However, as demonstrated by the present study, patients with schizophrenia show a diminished activation of the sensorimotor cortices at an increased variability of motor performance but do not differ significantly from healthy controls with respect to the frequency and amplitude of the pronation/supination movements. Obviously, the present comparison of kinematic data in each 8 schizophrenic patients and healthy controls is only of limited statistical power. However, a recent clinical study (Jahn et al., 1995) in each 25 patients with schizophrenia and healthy controls yielded a similar pattern of motor changes in schizophrenia with an increased variability of motor performance but only minor changes of frequency and amplitude. Hence, retarded motor performance per se is not likely to account for the activation changes in schizophrenia.

With respect to the SMA, patients with schizophrenia showed a pronounced although nonsignificant activation deficit. This finding is at variance with previous studies (Mattay et al., 1997; Schröder et al., 1995), which demonstrated a significantly reduced activation in this brain region. Obviously, methodological differences, such as sample effects may account for this

![Table 3](table3.png)

**TABLE 3**

GroupMeans (M) and Standard Deviation (SD) of Activation Measures (Mean t Value) in the Supplementary Motor Area (SMA) Under Right and Left Pronation/Supination in Patients and Healthy Controls

<table>
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<th>Healthy controls</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td><strong>SMA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>3.74</td>
<td>3.90</td>
</tr>
<tr>
<td>SD</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Note:**
- The table above shows the group means (M) and standard deviations (SD) of activation measures (mean t value) in the supplementary motor area (SMA) under right and left pronation/supination in patients and healthy controls.
- The mean t values are calculated for different speed levels (slow, medium, fast) for both healthy controls and schizophrenic patients.
- The right and left hemispheres are indicated for each group.
discrepancy. Since SMA functioning is extremely task dependent (Deecke, 1996), differences in the motor tasks used may provide an alternative explanation: the finger-to-thumb opposition task given in the studies cited above may involve greater demands on typical SMA functions such as planning and temporal structuring (Friberg and Roland, 1988; Tanji and Shima, 1996) when compared with pronation/supination in the present study.

Based on the present findings, one may hypothesize that increased motor variability in schizophrenia may refer to a reduced activation of the SMA and of the sensorimotor cortices. Following Günther et al. (1994), the reduced activation of motor areas in schizophrenia may correspond to a limited capacity to produce focal cerebral responses. The activation found in the schizophrenic patients do not appear to be affected by age and severity of illness, nor clozapine dosage. Moreover, the activation changes were more pronounced in the neuroleptic-free patient than in those patients receiving neuroleptic medication. That NSS are not the consequence of neuroleptic treatment is demonstrated by a number of recent clinical studies (Schröder et al., 1998; for review: Jahn, 1996). The limited temporal and spatial resolution capacity of the fMRI technique used have to be considered as another potential confounding variable. In addition, some cerebral sites important for motor functioning, in particular the basal ganglia and the cerebellum, were not investigated. Hence, future studies using 3D EPI fMRI and pixel-based image analysis are warranted to differentiate between the various cerebral sites involved. However, the study supports previous reports of a diminished sensorimotor cortex and SMA activation in schizophrenia and indicates that these changes may correspond to an increased motor variability but not motor retardation in the disease.

ACKNOWLEDGMENT

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REFERENCES