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BRIEF COMMUNICATION

Reduced activation and altered laterality in two neuroleptic-naive catatonic patients during a motor task in functional MRI

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ABSTRACT

Background. Catatonia, a symptom complex with motor, affective and cognitive symptoms seen in a variety of psychotic conditions and with organic disease, was examined using a motor task using functional magnetic resonance imaging (fMRI).

Methods. Two acute catatonic patients and two age- and sex-matched healthy controls performed sequential finger opposition (SFO) after being medicated with 2 mg of lorazepam (i.v.). Functional magnetic resonance images were collected using a gradient echo pulse sequence (EPI).

Results. Patients with catatonia showed reduced motor activation of the contralateral motor cortex during SFO of the right hand, ipsilateral activation was similar for patients and controls. There were no differences in the activation of the SMA. During left hand activation the right-handed catatonic patients showed more activation in the ipsilateral cortex, a reversal from the normal pattern of activation in which the contralateral side shows four to five times more activation than the ipsilateral side.

Conclusions. In catatonic patients there is a decreased activation in motor cortex during a motor task compared to matched medicated healthy controls. In addition activation of the non-dominant side, left-handed activity in right-handed patients, results in a total reversal of the normal pattern of lateral activation suggesting a disturbance in hemispheric localization of activity during a catatonic state.

INTRODUCTION

Catatonia is a complex behavioural syndrome showing altered motor function, with akinesia, posturing and waxy flexibility as well as psychological changes that often include intense anxieties, profound negativity and mutism. The motor phenomena involve akinesia and bizarre positions often held against gravity for long periods of time, it almost appears as if motor function is totally frozen. This syndrome can, therefore, be thought as a psychomotor disorder (Gelenberg, 1976; Northoff *et al.* 1995; Northoff, 1997) where psychological changes are transformed into motor symptoms such as akinesia and posturing. These motor alterations can be treated well with lorazapam giving an almost immediate therapeutic efficacy in many of these patients (Rosebush *et al.* 1990; Fink *et al.* 1993).

With regard to motor alterations, one may suggest specific changes in cortical motor structures in catatonia that could be investigated by carrying out functional imaging. The problem in doing this is two-fold, first the condition is rare, and it is difficult to get the patients to agree to

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any studies due to their negativity, and secondly the akinesia makes it difficult to carry out motor activation studies. In this report we were able to follow two unmedicated acutely catatonic patients who agreed to an imaging study with functional MRI (fMRI) after a single acute dose of lorazepam, which while not eliminating motor symptoms completely allowed performance of a simple motor task.

METHOD

Subjects

We investigated two acute akinetic catatonic patients (one man, 27 years of age, duration of illness was 2 months; one woman, 31 years of age, duration of illness was 6 months) who were hospitalized in acute catatonic states. Both patients were neuroleptic-naive, had not taken any other psychotropic drugs and received on admission a single dose of intravenous lorazepam (2 mg); 1 to 2 hours after injection of lorazepam the patients were studied with fMRI.

Diagnosis was made according to Lohr & Wiesniewski (1987), Rosebush *et al.* (1990) and DSM- III-R (APA, 1987). Handedness, anxiety, global psychopathology and hypo/hyperkinetic movements were evaluated in both patients with the following scales (Edinburgh (Oldfield, 1971), HAM-A (Hamilton, 1959), GAS (Endicott *et al.* 1976), SEPS (Simpson & Angus, 1970), AIMS (Guy, 1976)) at three time-points (before injection of lorazepam (1), before scanning (2), immediately after scanning (3)).

In addition, two right-handed, age- and sex-matched healthy controls without any psychiatric, neurological, medical illness or substance abuse were selected for fMRI investigation without medication and 2 hours after application of 2 mg lorazepam (i.v.). All subjects (patients after injection of lorazepam) gave written informed consent before scanning and the study was approved by the ethics committee.

Imaging procedure

Functional-MRI was performed on a Siemens Magnetom Vision 1.5 Tesla System using the standard head coil. Ten contiguous T1-weighted axial images (thickness 4 mm, gap size 0·3) were acquired up to planes parallel to the AC–PC line. Functional imaging was conducted using a Gradient Echo EPI pulse sequence with TR/TE/flip angel (1·8 ms/66 ms/90°), FOV = 20 cm, matrix 64×64 (interpolated to 128), thickness 4 mm, gap size 0·3. A series of 60 sequential multi-slice images was obtained comprising six cycles of rest and motor activation for each hand respectively. Shimming was optimized automatically with a Siemens shim adjust.

Data analysis

Data analysis was performed using custom software (Goebel, 1996) and cross-validated with AFNI (Cox, 1995). Prior to statistical analysis the time series of functional images was aligned for each slice in order to minimize the effects of head movement. For each slice the third recorded functional image was used as a reference image to which all other images of the slice time series were registered. Spatial and temporal Gaussian smoothing, removal of linear trend and nearest neighbour cluster analysis ($N = 12$) were performed. In order to evaluate statistically the differences between stimulation conditions cross-correlation analysis was applied. For the computation of correlation maps, the stimulation protocol served as a reference function reflecting the temporal sequence of stimulation and control conditions. On a pixel-by-pixel basis the signal time course was cross-correlated with the respective reference function (Bandettini *et al.* 1993). Based on the statistical estimates for the optimal threshold (Noll *et al.* 1997) pixels were included into the statistical map if the obtained correlation value was greater than 0·55, given lag values of 1 (corresponding to a 2–4 s response delay after the beginning of a stimulation condition).

The data for statistical comparisons consisted of the mean time course of all voxels. Based on this data the spatial extend of activated voxels (SE) as well as the signal change in two predefined regions of interest (ROI) (ipsi- and contra-lateral sensorimotor cortex) for each subject and condition in a given experiment was computed. Regions of interest were selected with reference to the atlas of Talairach & Tournoux (1988). Values of percentage signal change averaged across subjects were computed on the basis of the difference between the mean values of the fMRI signal in each experimental condition and the mean fMRI signal in the

fixation periods for each individual subject. Lateralization was defined as lateralization index (LI), which is computed as the difference between right and left hemispheric activation per global activation (LI = (contra-ipsi)/(contra + ipsi)). These values of activated voxels per ROI and of percentage signal change as well as LI were analysed using *post-hoc* comparisons (paired *t* test, $P < 0{\cdot}05$, ANOVA) using the stimulus condition and the diagnosis as a within-group factor.

Motor activation

The motor activation task consisted of self-paced, unrestrained and repetitive sequential finger opposition (SFO) done as quickly as possible, whereas alternative periods of rest without any movements at all served as a baseline condition. SFO was first performed with the right hand then after a brief break with the left hand. Subjects were provided with instructions and allowed to practice the task prior to scanning. During scanning their movements could be continuously observed. SFO was evaluated according to frequency (average number of finger-to-thumb movements back forth) and quality (average number of erraneous (i.e. out of sequence) finger-to-thumb movements as expressed in grades (1 = no errors, 2 = single or rare errors, 3 = multiple or some errors, 4 = several but less than 50% errors, 5 = more than 50% errors) of performance (see also Günther *et al*. 1994). Healthy controls matched their performance to that of the catatonic patients. This resulted in similar frequency and number of erraneous movements of SFO between healthy controls and catatonic patients.

RESULTS

Clinical data

According to DSM-III-R the male patient was diagnosed as catatonic schizophrenic (295.2) whereas the female patient was diagnosed as schizoaffective disorder (295.7; depressive type). All subjects were right-handed. During the scans both patients showed catalepsy but were without other catatonic symptoms. Prior to lorazepam both also exhibited akinesia, mutism, flexibilitas cerea, autism as well as catalepsy. During scanning both catatonic patients were able to initiate and execute the required movements but posturing was regularly observed during all resting periods such that the hand and the fingers were kept up against gravity without terminating the movement and returning to resting position. Psychopathology scores are shown in Table 1.

Table 1. *Psychopathology scores in catatonic patients*

	Patient 1 (male)	Patient 2 (female)
GAS		
On admission	10	10
Before fMRI	39	46
After fMRI	25	40
SEPS		
On admission	28	18
Before fMRI	6	3
After fMRI	13	6
HAM-A		
On admission	27	24
Before fMRI	4	2
After fMRI	14	6

Patients showed no hyperkinesias at all so that AIMS scores were negative throughout for both patients.

GAPS, Global Assessment Scale; SEPS, Simpson Scale for Extrapyramidal Side Effects; HAM-A, Hamilton Anxiety Scale; AIMS, Abnormal Involuntary Movement Scale.

Activation pattern in fMRI

Lorazepam results in significant reduction in the spatial extend of the activation in the predefined primary sensorimotor cortex contralateral to the activation. In the same ROI, the absolute number of voxels was significant lower in both catatonic patients in comparison to the healthy controls under lorazepam medication ($t = -7{\cdot}4$, $P = 0{\cdot}005$; see Table 2). There was no difference in the activation of SMA and ipsilateral sensorimeter cortex between the groups. There were considerable differences in left-hand activation with patients showing higher ipsilateral than contralateral activation opposed to the pattern seen in healthy controls (see Table 2 and Fig. 1). This is in contrast to the normal 4–5-fold greater activation on the contralateral side as compared to the ipsilateral side normally seen in healthy controls on the task. Compared with healthy controls, the percentage change of signal intensity showed no significant differences in the three ROI in catatonic patients.

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Table 2. *Spatial extent* (*number of activated voxels*), *mean change of signal intensity* (%) *as well as laterality index in catatonia* (*with lorazepam*) *and in healthy controls* (*without and with lorazepam*)

Activated hand	Sensorimotor cortex	Catatonic patients with lorazepam	Control without lorazepam	Control with lorazepam	Control without *v.* Control with lorazepam	Patients *v.* Control with lorazepam
Activated voxels (*spatial extend*)						
Right	Contra	704	1180	1010	Paired t test $t = 3{\cdot}3$; $P = 0{\cdot}04$ ANOVA $F = 7{\cdot}4$; $P = 0{\cdot}03$	Paired t test $t = -7{\cdot}4$; $P = 0{\cdot}005$ ANOVA $F = 35$; $P = 0{\cdot}001$
Left	—	515	1340	1030	—	—
	—	512	1030	1060	—	—
	—	311	1320	938	—	—
Right	Ipsi	62	295	286	Ipsilateral activation	—
Left	—	115	354	301	NS	NS
	—	1370	73	68	—	—
	—	335	886	518	—	—
Right	SMA	106	75	113	SMA activation	—
Left	—	32	198	159	NS	NS
	—	99	130	34	—	—
	—	144	213	214	—	—
Signal change (%)						
Right	Contra	1·54	2·04	1·91	Contralateral signal change	—
Left	—	2·30	1·71	1·63	NS	NS
	—	1·41	2·06	2·13	—	—
	—	2·23	1·77	1·60	—	—
Right	Ipsi	1·52	1·90	1·93	Ipsilateral activation	—
Left	—	1·79	1·69	1·55	NS	NS
	—	1·46	2·09	2·28	—	—
	—	2·00	1·81	1·28	—	—
Right	SMA	1·82	1·96	2·18	SMA activation	—
Left	—	1·82	1·86	1·85	NS	NS
	—	1·42	2·11	2·10	—	—
	—	2·18	2·12	1·84	—	—
Laterality index						
Right	—	+0·84	0·60	0·56	—	—
	—	+0·63	0·58	0·55	NS	NS
Left	—	−0·46	0·87	0·88	—	ANOVA $F = 5{\cdot}31$; $P = 0{\cdot}15$
	—	−0·04	0·20	0·29	NS	—
Delta LI	—	1·30	0·27	0·32	—	ANOVA $F = 4{\cdot}39$; $P = 0{\cdot}17$
	—	0·67	0·38	0·33	NS	—

DISCUSSION

The main findings of this preliminary motor activation study in catatonia are: (*i*) under medication with lorazepam there was a larger decrease in voxel activation in the contralateral primary sensorimotor cortex by catatonic patients who were still displaying posturing than health controls; (*ii*) a reversal in laterality in the spatial extent of activated voxels during left-hand movements by catatonic patients.

Catatonic and healthy subjects showed similar frequencies and qualities of movements during fMRI. Thus, the significant decrease of activation level observed in catatonics can not be explained by performance effects. In contrast to findings in schizophrenic patients on neuroleptics (Schröder *et al*. 1995) and patients with Parkinson's disease (Playfold *et al*. 1992) we could not detect specific abnormalities in SMA in our catatonic patients. These results suggest that the posturing observed in resting periods

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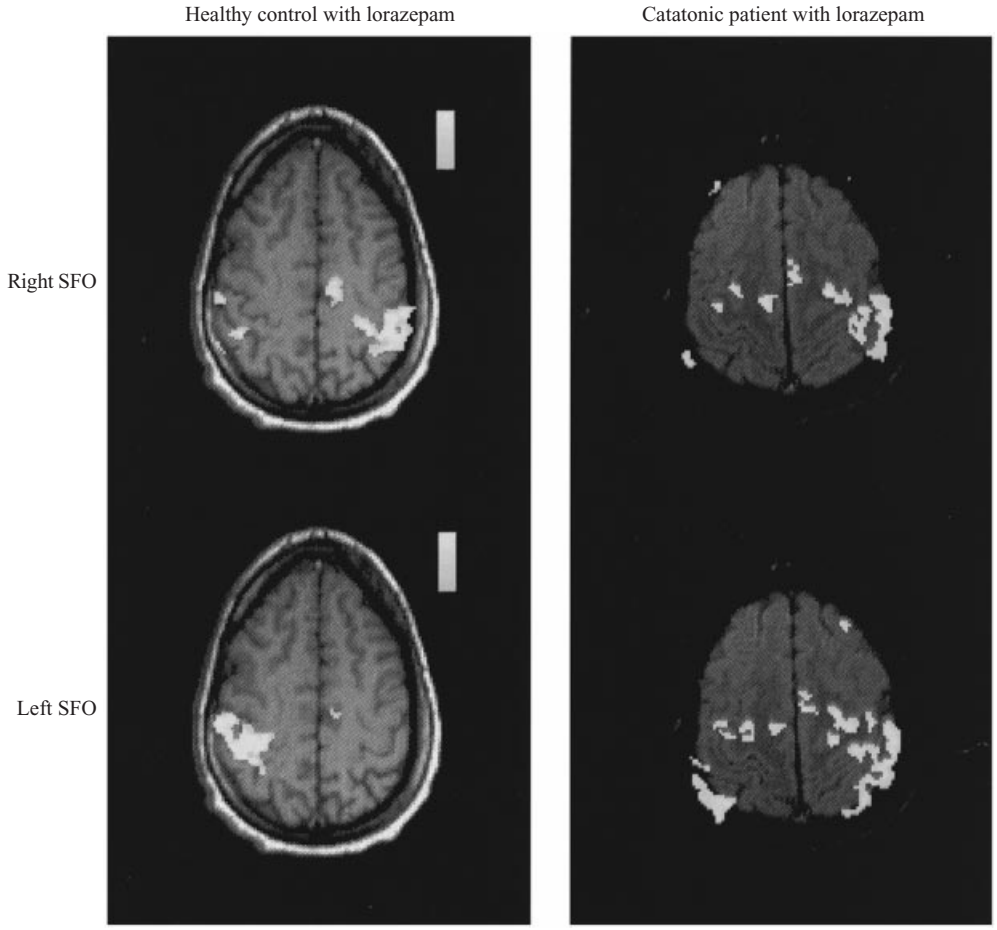

FIG. 1. fMRI activation map of SFO (right *v.* left hand; Matrix 64×64; cc $> 0{\cdot}6$). There is a considerable difference in left-hand activation with the patient (right column) showing higher ipsilateral than contralateral activation opposed to the pattern seen in the matched healthy control (left column).

may be related to functional abnormalities in primary cortical motor structures (Northoff *et al.* 1995; Northoff, 1997). Nevertheless, interpretation remains difficult due to the low number of cases and the fact that, in fMRI we measure the difference between the posturing (i.e. baseline) and the SFO (i.e. motor activation). A high basal rate of neuronal activation could account for the reduced level of fMRI activation leading to a smaller difference between baseline and motor activation due to a ceiling effect. However, activation during posturing has neither been investigated in fMRI/PET nor in EEG so that results of the present investigation should be regarded as preliminary.

A reduction in the degree of laterality was seen in a PET study of chronic schizophrenic patients using the SFO paradigm (Günther *et al.* 1994). Schröder *et al.* (1995) actually saw a reversal of laterality in a study of medicated patients using fMRI. Both of these studies investigated chronically medicated patients and did not match performance with healthy controls adding some confounds. Results of these functional studies can be compared with the pathological studies, which suggest unilateral changes on the left side (Bogerts & Lieberman, 1993), however, it is hard to see how decreasing volumes in the left temporal region could lead to increased activation of left motor cortex under left-handed stimulation. In a study of acute medication-free psychotic schizophrenic patients we have seen

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no indication of a reversal of laterality using an identical motor activation task (Braus *et al*. 1999). The most likely explanation is that this reversal is a functional consequence of the acute catatonic state, suggesting that the patients should be re-studied after remission to determine if this is a reversible phenomena. Our data point to more potential activation of the dominant (i.e. the left) hemisphere in catatonia than the non-dominant (i.e. the right) hemisphere. Such a conclusion is supported by recent findings in SPECT in a larger number of catatonic patients, which showed decrease of r-CBF in right fronto-parietal cortex (Northoff *et al*. 1997). If so, a selective shut down of right hemisphere activity is unlikely to be due to a ceiling effect since the right hemisphere is adequately and the left hemisphere appears to be increasingly activated.

In conclusion, this initial study reports decreased motor activation in an acute catatonic state with a reversal of normal laterality when the left hand is activated by catatonic patients medicated with lorazepam compared to matched medicated healthy controls. These preliminary results show no alteration in the SMA suggesting that functional abnormalities are confined to the primary motor cortex, with emphasis on the non-dominant hemisphere.

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