Neural activity changes in Supplementary Motor Area induced by dopaminergic treatment in parkinsonian patients

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Abstract

In this research we study the neural activity changes in Supplementary Motor Area in patients with Parkinson's disease using fMRI. We studied the effect of DOPA medication. The correlation with motor improvement was also tested. Statistical parametric mapping was used to detect differences in the cortical activity when is compared with both normal pattern and after DOPA supply. Patients show abnormal activation intensities in SMA, normalized after DOPA medication. Improvement in clinical outcome correlated with increase in fMRI signal, particularly with improvement of hypokinesia. The study indicates that cardinal symptoms in PD are associated with inappropriate underactivity in SMA.

Keywords: fMRI, Parkinson's disease, cortical activity, supplementary motor area

1. Introduction

Nigrostriatal dopaminergic (DA) neurons play a central role in the correct preparation and execution of the cortically started movements. Imaging techniques have been used to demonstrate that BG are involved in supporting automatic execution of movements generated at cortical motor areas, and to modify motor behaviour of routine in reply to new contexts or necessities. Previous researches in normal and parkinsonian subjects

using PET have supported the theory that the supplementary motor area (SMA) plays a crucial role in preparing and generating complex motor programmes [1]. If cortical activity in Parkinson is affected by the decrease in the positive efferent feedback arising from the basal ganglia thalamocortical motor loop, is possible to expect normalization in the activation of those areas following dopaminergic treatment, presumably correlated with the resolution of akinesia.

Recent advances in functional Magnetic Resonance Imaging (fMRI) offer the ability to study in vivo the DA system, in relation with functional activity of the prefrontal medial cortex including SMA. These areas can be activated using motor paradigms, such as self-induced motor task and changes into new contexts. Functional MRI activation represents a change in signal intensity caused by increased blood flow and oxygen use in brain areas associated with certain cognitive or sensorimotor task [2,3,4]. By measuring the fMRI response in targets of projection neurons and cortex, is possible to make inferences about local changes in neural activity. The main assumption of this approach is that the measured haemodynamic response function (HRF) is proportional to underlying neural activity.

The aim of this research was to supply evidence of the inappropriate functioning of SMA in PD and the relation with the cardinal symptoms of the disease. We investigated the changes in neural activity after dopaminergic stimulation. We have compared motor activation in normal subject and in akinetic patients with PD before and after treatment with DOPA and related these with changes in UPDRS motor scores.

2. Methods

Subjects and clinical evaluation

A total of 12 patients with PD and 4 ages matched normal subjects were studied. Unified Parkinson's Disease Rating Scale (UPDRS) motor scores were evaluated in

patients OFF and ON medications immediately before each scan.

Image acquisition and preprocessing

Imaging was carried out on a 1.5-T Siemens Magnetom Symphony scanner (Siemens, Erlangen, Germany) equipped with a fast gradient system for echoplanar imaging (EPI). A standard radiofrequency (RF) head coil was used with foam padding to comfortably restrict head motion and partially suppress scanner noise. High-resolution 3D sagittal T1-weighted images were obtained in every subject. A gradient-echo, echoplanar sequence (TR = 3000 ms, TE = 48 ms) was used to acquire 24 sagittal slices. Resolution was 2 x 2 mm in plane, and 5 mm through plane, with no skip in between planes. Each scanning run comprised 120 gradient-echo echoplanar images per slice, where rest state (i.e., no stimulus) alternated with activation, consisting in finger opposition sequential movement followed of repetitive flexion-extension movements of the hand.

To correct for head motion the first volume in a time series is used as a reference scan to which all subsequent EPI scans are realigned [5]. Each volume was spatially normalized to the space of Tailarach & Tournoux [6] and smoothed with a Gaussian kernel of 6 mm [7] before statistical analysis.

Statistical Parametric Mapping

To generate functional maps from the fMRI data set a pixel-by-pixel statistical analysis was developed using the General Linear Model [8], as implemented in SPM99 package (Wellcome Department of Cognitive Neurology, London, UK). Significant activity was based upon unpaired *t* tests performed on individual pixels producing stimulus *t* maps (task vs. control).

Statistical Comparisons

SMA borders were determined for each subject based on anatomic landmarks and Talairach's standard coordinates. The mean *t* value of the SMA was calculated for each

subject in OFF and ON medication and utilized for further statistical tests. A two-way ANOVA was then performed on the area *t* value, with post hoc evaluation using LSD test. A one-way ANOVA was performed to look for differences with normal patients.

The Pearson correlation was calculated between the signal intensity increase in the individual-subject area analysis and motor scores improvement, for each of the cardinal signs of PD and total motor score.

3. Results

SMA was activated during the task in all subjects under study. Figure 1A) shows, from left to right, the functional activation maps superimposed on a T1 weighted anatomical image from a normal subject, a patient with PD and the same patient after pharmacological treatment. These patterns were representatives of all subjects and patients, as illustrated in Figure 1B), which shows histograms of the mean (±SD) activation intensity.

When comparing between hemispheres the largest mean t value was seen in the less affected side. An ANOVA of mean t values showed a highly significant difference between hemispheres and with normal subjects ($p<0.001$).

Dopaminergic treatment significantly increased haemodynamic response in SMA ($p<0.01$) in both hemispheres, more pronounced in the less affected side (Figure 1B). An ANOVA of *t* values with post-hoc analysis with the LSD test showed a highly significant difference of the most affected hemispheres with the less affected ($p =0.002$) and with the normal pattern ($p = 0.001$), but no significant difference between the less affected side and normal activation ($p = 0.06$).

Improvement in clinical outcome correlated with increase in fMRI signal in SMA. Changes in SMA are particularly correlated with improvement of hypokinesia ($R=0.710$) and tremor ($R=0.712$) in UPDRS motor scores (Figure 2). Figures 3 shows

that activity changes are highly correlated with total motor improvement (R=0.811).

4. Discussion

Task-related activations in SMA could be identified in all normal and parkinsonian subjects. These results provide clear evidence for a role of SMA in the 'higher order' programming of movement sequences and are consisting with previous studies using PET and fMRI [9,10].

Comparing with normal activity, patients show a pattern of activation characterized by bilaterally decreased fMRI signal in SMA. This hypoactive condition is thought to reflect an affected neural metabolism by deafferentation following loss of dopamine fibers. After pharmacological stimulation with L-DOPA the pattern of activation is partially normalized. Interestingly the response is proportional for both hemispheres, suggesting that the magnitude of the changes is growing with the progression of the disease. This result is in contradiction with previous models of the basal ganglia-thalamo-cortical circuitry. One can thus speculate that this is a secondary effect to the increment of the stimulation with DOPA in others dopaminergic pathways than nigro-striatal pathway, and therefore the effect of DOPA administration is more complex than the simple inhibition of overactive striatal output.

Changes in the activation in the SMA and the clinical motor scores show a high correlation, particularly influenced by the high correlation index between the fMRI signal and hypokinesia and tremor rated with the UPDRS. These results support the idea that difficulties for planning and starting sequences of movement in patients with PD are associated with underactivity in SMA. These findings have been previously reported [1,9,10] but, as far as we know, not with a correlation analysis between the magnitude and specificity of the motor impairment and the magnitude of changes in the function of the Supplementary Motor Cortex.

5. Conclusions

The study indicates that fMRI enables quantitative evaluation of abnormal activation pattern in PD and the effect of therapeutic intervention. These results indicate that cardinal symptoms in PD are associated with inappropriate underactivity in supplementary motor area in parkinsonian condition, due to striatal dopamine depletion. This effect is partially normalized after DOPA administration.

References

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Figure 1. Functional activation in SMA: A) Statistical parametric maps superimposed on T1-weighted anatomical image. From left to right: normal pattern, patient in off medication and patient after dopaminergic supply. B) Mean (±SD) (pooled across all subjects) signal intensity in OFF and ON state vs. normal activation pattern. Normal = normal pattern, + = less affected side in patients, – = more affected side in patients.

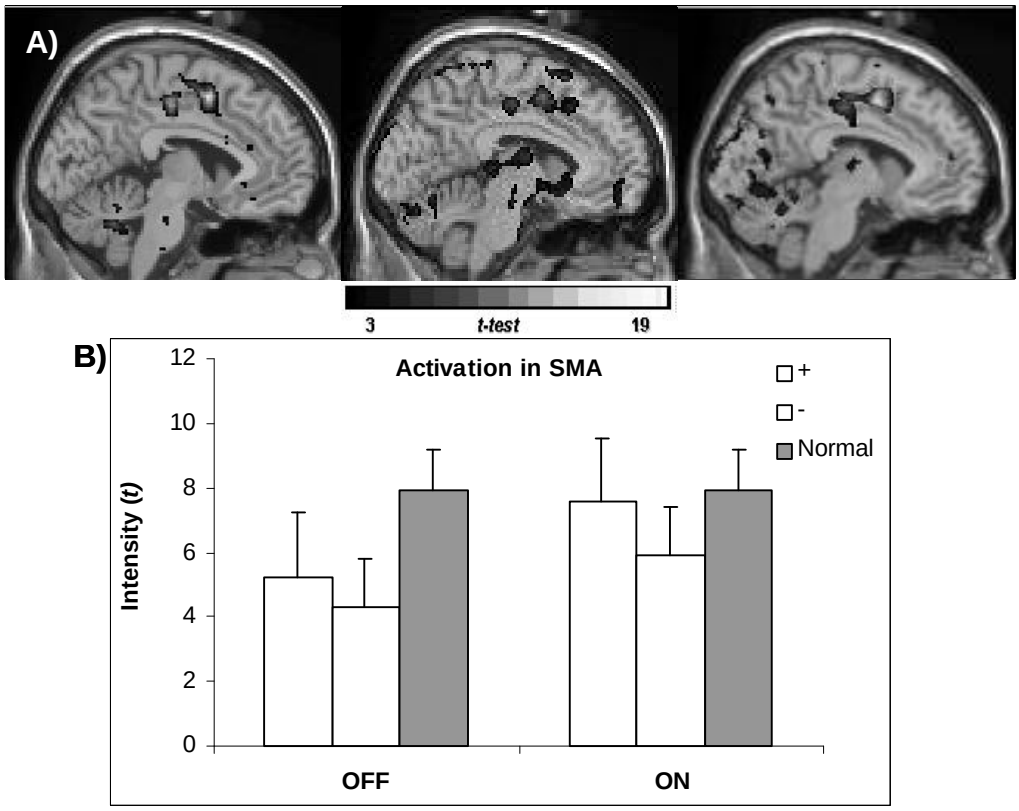

Figure 2. Correlation of percentage of fMRI signal intensity increase and the percentage of clinical motor improvement for each of the cardinal symptoms of Parkinson's disease.

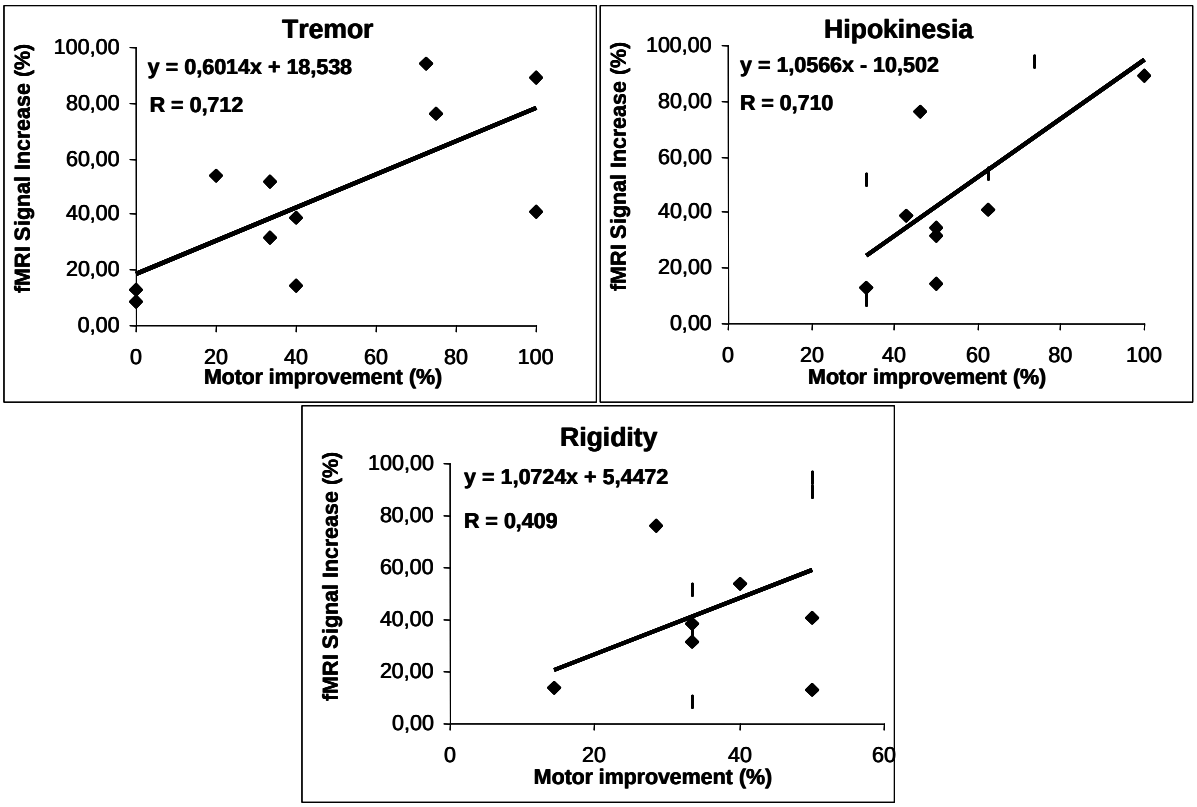

Figure 3. Correlation of percentage of fMRI signal intensity increase and total UPDRS motor score.