Neural activity changes in the 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 (SMA) in Parkinson's disease patients using fMRI and studied the effect of DOPA medication on neural activity. The correlation between the observed changes and motor improvement was also tested. Statistical parametric mapping was used to detect differences in the cortical activity when the pattern of PD patients is compared with both the normal pattern and after DOPA supply. Patients show abnormal activation intensities in rostral and caudal SMA, which is normalized after DOPA medication. The improvement in clinical outcome correlated with an 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 basal ganglia (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 and SPECT have supported the theory that the supplementary motor area (SMA) plays a crucial role in preparing and generating complex motor programmes [1]. In these studies the common finding of underactivation in Parkinson disease (PD) [2,3,4] is not unanimous. Recently, Hsu et al. [5] did not find significant cerebral blood flow (rCBF) changes in the SMA of PD patients using an independent component analysis, while Sestini et al [6] reported significant rCBF increase in the pre-supplementary motor area (pre-SMA) with deep-brain stimulation of subthalamic nucleus (STN).

Recent advances in functional Magnetic Resonance Imaging (fMRI) offer the possibility to study the DA system *in vivo*, in relation with the 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. fMRI 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 [7]. 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.

If cortical activity in PD is affected by the decrease in the positive efferent feedback arising from the basal ganglia thalamocortical motor loop, it is possible to expect normalization in

the activation of those areas following dopaminergic treatment, presumably correlated with the resolution of akinesia. Recent fMRI studies in PD patients [8,9] have confirmed reduced activity in rostral SMA, but hypoactivity [8] as well as hyperactivity [9] was reported in the caudal SMA.

This unexpected hyperactivity has been interpreted as a compensatory mechanism of a damaged motor system and it is in disagreement with the BG circuit model [10] and with a recent study using electrophysiological techniques in MPTP-treated monkey [11], which showed that SMA neurons are in a state of hypoactivity in symptomatic animals. However hyperactivity could be related to long-term dopaminergic treatment. This hypothesis is supported by imaging studies in patients with L-dopa-associated dyskinesia [1].

The aim of this research was to supply evidence of the inappropriate functioning of SMA and clarify the real state of SMA neurons in drug-naïve PD patients. We investigated the changes in neural activity after dopaminergic stimulation. To further clarify the responsibility of SMA in the cardinal symptoms of PD we have compared motor activation in normal subject and in akinetic patients before and after treatment with DOPA and independently related these with changes in akinesia, tremor, rigidity and total motor performance using UPDRS motor scores.

2. Methods

Subjects and clinical evaluation

A total of 12 right-handed patients (mean age ± SE = 51.3 ± 7.5 years, 10 male and 2 female) with early stage akinetic PD (Hoehn and Yahr stage I or II) participated in the study. Every patient was studied twice, once during the "drug-off" state and after reach the "drug-on" state. To rate the severity of patient's motor function Unified Parkinson's Disease Rating Scale (UPDRS) motor scores were evaluated immediately before being scanned. Four healthy age-matched control subjects were studied.

Motor task

Patients and controls performed an auditory-paced task, consisting in finger opposition sequential movement (5 repetitions) followed by repetitive flexion-extension movements of the hand. Each block consisted of rest state (i.e., no stimulus) alternated with activation. Subjects were instructed to keep the amplitude and frequency of the motor task constant.

Image acquisition

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 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. BOLD data were collected using a gradient-echo, echoplanar sequence (TR = 3000 ms, TE = 48 ms). Each scanning run comprised 126 volumes (9 rest-activation blocks) with 24 sagittal slices. Resolution was 2 x 2 mm in plane, and 5 mm through plane, with no skip in between planes.

Preprocessing

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 [12]. Each volume was spatially normalized to the space of Tailarach & Tournoux [13] and smoothed with a Gaussian kernel of 6 mm [14] 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 [15], as implemented in SPM2 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 determine 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

Motor activation.

Pre-SMA and SMAp were activated during the task in all subjects under study. Figure 1A) shows, from left to right, the normalized 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.

Within group comparison.

When comparing between brain hemispheres the largest mean t value was found in the hemisphere contralateral to the side of the body less clinically affected by the disease. An ANOVA of mean t values showed a highly significant difference between hemispheres ($p<0.001$).

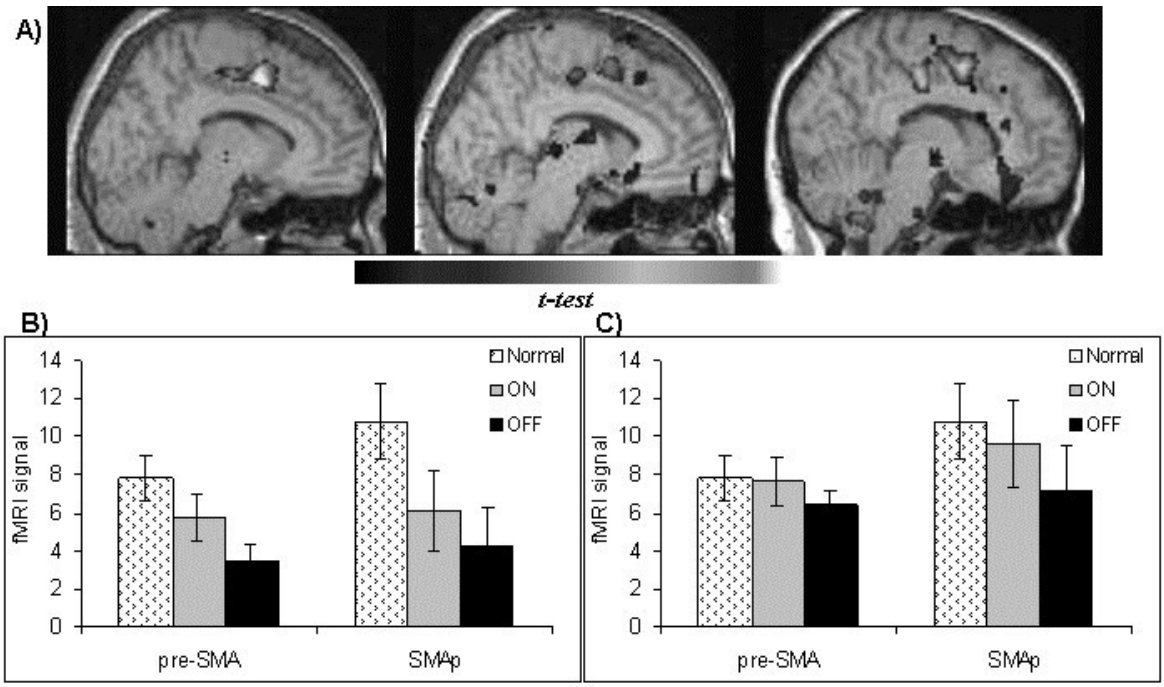

Figure 1. Functional activation in SMA: A) Statistical parametric maps superimposed on T1-weighted anatomical image. From left to right: normal pattern, patient in off medication and patient after dopaminergic supply. B) and C) Mean (±SD) (pooled across all subjects) signal intensity in OFF and ON state vs. normal activation pattern in the most affected brain hemisphere and less affected brain hemisphere respectively.

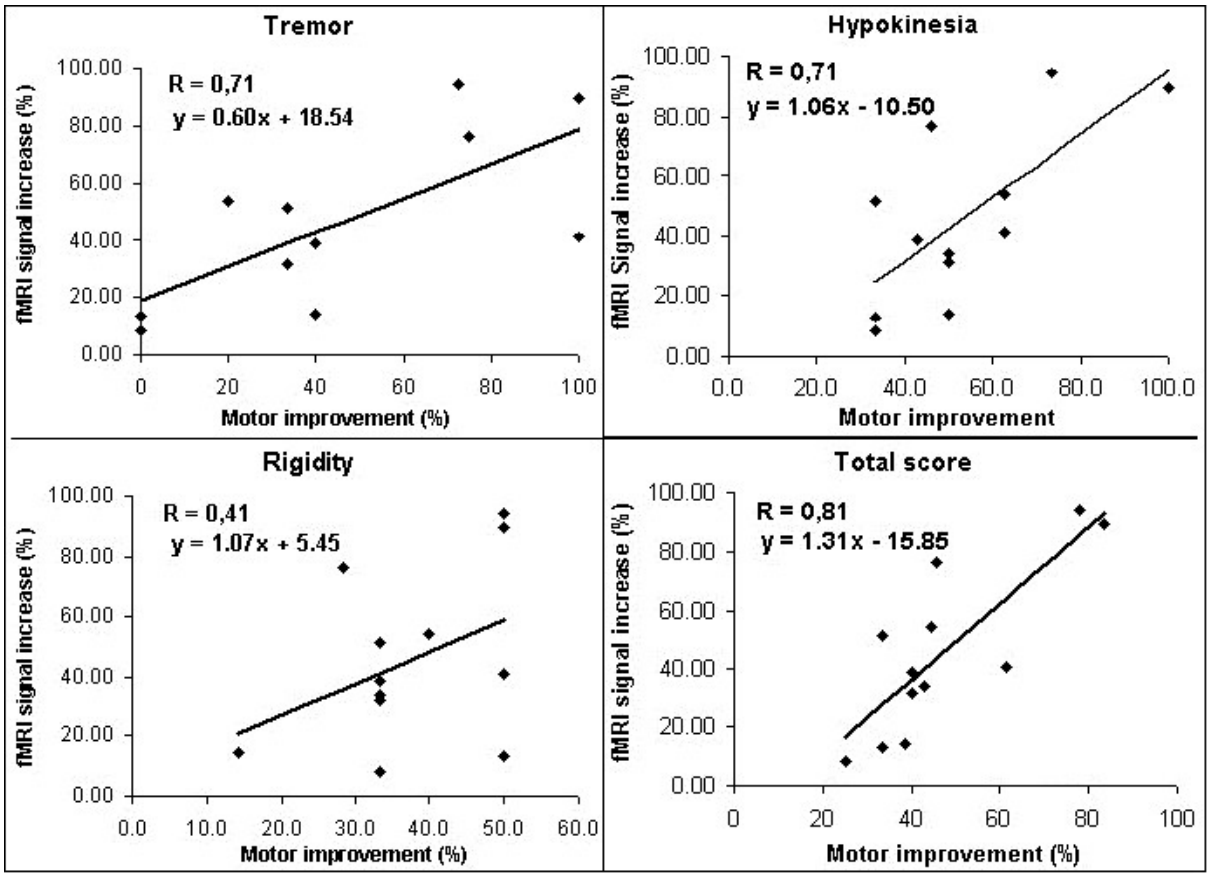

Figure 2. Correlation of percentage of fMRI signal intensity increase and the percentage of clinical motor improvement for each of the cardinal symptoms of Parkinson's disease and total UPDRS motor score.

Dopaminergic treatment significantly increased haemodynamic response in SMA ($p<0.01$) in both hemispheres, more pronounced in the less affected brain hemisphere (Figure 1B). An ANOVA with post-hoc analysis using the LSD test showed a highly significant difference between the most affected brain hemisphere and the less affected ($p =0.002$).

Between group comparison.

Comparison of PD patients with healthy controls showed a significant bilateral underactivity in pre-SMA and SMAp ($p<0.01$). On levodopa, underactivity in the brain hemisphere contralateral to the most affected hand remained ($p = 0.001$), but no significant difference between the less affected brain hemisphere and normal activation ($p = 0.06$) was found. A tendency toward normalization was detected in both hemispheres (Figure 1B).

Correlation between motor performance and activation.

Improvement in clinical outcome correlated with increase in fMRI signal in SMA. Changes in SMA are particularly correlated with improvement of hypokinesia ($R=0.710$, $p=0.01$) and tremor ($R=0.712$, $p=0.01$) in UPDRS motor scores (Figure 2 A, B and C). Figure 2D) shows that activity changes are highly correlated with total motor improvement ($R=0.811$, $p<0.01$).

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 [9,16].

When compared with the normal activity, patients show a pattern of activation characterized by bilaterally decreased fMRI signal in SMA. This hypoactive condition is thought to reflect a disturbance in neural metabolism induced by deafferentation following the 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 of the stimulation with DOPA on dopaminergic pathways, other than the nigro-striatal pathway. Based on this rationale, the effect of DOPA administration could be 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, as rated by 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 [1,9,16] 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.

fMRI has shown a wide potential to explore the neural basis for human sensory, motor and cognitive function. However the nature of the link between neural activity and haemodynamic response is currently unclear. In a recent research Logothetis et al. measured fMRI responses and neural activity simultaneously in the monkey visual cortex [17]. The results of the study indicate that local field potential (LFP) have a higher correlation with BOLD response than multiunit activity, indicating that fMRI signal reflects the activity underlying LFP rather than spiking output. However a quantitative study of the relation between BOLD response in humans V5 visual cortex with single-cell data recorded in homologous area in macaque [18] indicates a proportionality between fMRI signal and average firing rates. At a qualitative level, the similarities between our findings in SMA in normal and parkinsonian subjects and those obtained by Escola et al. [11] in the same area in MPTP-treated monkey, suggest some relation between BOLD response and single cell activity in motor circuit. A quantitative comparison is not possible because of the differences in experimental protocols. Appropriate experimental designs which bring together electrophysiological and imaging studies are crucial to understanding how BOLD fMRI and neural activity are related.

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 SMA in parkinsonian condition, due to striatal dopamine depletion. This effect is partially normalized after DOPA administration.

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