Compensatory Mechanisms during Motor Sequence Learning in Parkinson's Disease. A fMRI Study.

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Introduction
Parkinson's disease (PD) is known to cause difficulties in movement performance. These impairments have been associated primarily to basal ganglia dysfunction. In early stages of motor learning, subcortical regions have been described as crucial structures in the acquisition of novel sequences. Therefore, the study of the learning process in PD patients could reveal distinct neural patterns as a result of striatal dysfunction. In this study we aimed to elucidate compensatory mechanisms in PD patients compared to a control group in the early learning phase and differences between the most affected and less affected hand in the performance of an automatic movement.

Materials and Methods
Nine PD patients (8 M) with predominant right side affectation (mean age 62 ± 10 years) and right handed were studied. All the patients were medicated (UPDRS 4-17) and without dementia. Eighteen healthy subjects (13 M) (61.3 ± 7.13), right handed, were recruited. Subjects gave written informed consent before entering the scanner. Volunteers were required to learn different sequential finger movements (novel sequence) with the right, left and both hands in separate sessions. The control task consisted on an ordered finger sequence (little, ring, middle, index, little, ring, middle, index) which was interleaved in the presentation. A series of 300 volumes was acquired using a T2*-weighted EPI sequence (49 slices, slide thickness= 3mm, no gap, TR= 3000 ms, TE= 30 ms, resolution= 3x3 mm^2, FOV= 192x192, BW= 2230 Hz/pixel). Anatomical image acquisition (1 mm isotropic) was done using a T1-weighted MPRAGE sequence. The studies were performed on a 3.0 T Siemens TRIO using an 8-channel head array. Images were preprocessed in the standard way. Statistical analyses were performed at two levels using SPM5. At the first level, individual task-related activation was evaluated using the general linear model, creating the contrasts needed for the second level analysis ((novel sequence-control sequence) and (right control task–left control task)). At the second level, two different analyses were done. First, a flexible factorial analysis with three factors: subject, group (healthy subject or PD patient) and task (novel sequence – control sequence for right, left and bimanual task) was set up in order to evaluate differences between the PD and control groups. In a later step, a random-effects model was done for the comparison between right and left hand execution of the control sequence in PD patients. Behavioral data corresponding to the number of correct movements per trial in the novel and control sequence was evaluated for every type of motor task and for every group. Differences in behavior between the PD and control groups were assessed using two sample t-tests and differences among the three types of motor task in the PD group were evaluated using one-way ANOVAs for repeated measures. Post hoc comparisons were assessed using Bonferroni correction.

Results and Discussion
An overall increase in cortical, cerebellar and striatal activity was detected as the positive effect of group (PD > Control) (Figure 1). Cortical activation clusters were located in bilateral parietal, occipital and frontal areas, right middle and inferior temporal gyrus, and SMA, posterior cingulate and precuneus in the middle line. Cerebellar activity appeared bilaterally in Crus1, Crus2, VI, VII, VIII, IX and X. Striatal activation increase was found unilaterally in right putamen. Differences in behavior (number of correct movements) between the PD group and the control group were observed for every type of motor task (right, left and bimanual) in the novel sequence (Right Hand: p=0.007; Left Hand: p=0.042; Bimanual: p=0.023). For the control sequence, there were differences in behavior for the bimanual task (p=0.007) and a trend of significance for the right hand task (p=0.05). Therefore, changes observed in the positive effect of the group could be due to differences in the stage of the learning process between the two groups also. However, the increase in activity in the right putamen, contralateral to the most affected brain hemisphere, suggests a mechanism of compensation at the subcortical level. Moreover, several studies support the hyperactivity of certain brain areas to compensate the striatal deficit in Parkinson's disease (1, 2, 3). In a second analysis, we aimed to compare in the PD group (all right side affected), activation patterns in the performance of the control sequence executed with one hand with respect to the other hand (Figure 2). No differences in behavior between the right and left hand in the control sequence were observed in the PD group (p=0.288). We found contralateral cortical and ipsilateral cerebellar motor related regions significant in both comparisons. Performance with the affected hand recruited extra areas located in parietal, occipital and temporal lobe, as well as cerebellar areas in the left hemisphere (Crus1), in the left thalamus, putamen, pallidum and in the bilateral caudate nucleus. The lateralization index was of -0.0841 for the activation map which showed increased activity in the right hand task compared to the left hand task and of 0.584 for the opposite contrast. This indicates that the affected hand required more bilateral recruitment of brain areas compared to the left hand performance. In PD, the basal ganglia corresponding to the most affected hemisphere were extra recruited in the execution of simple movements with the most impaired hand in order to obtain the same results in behavior than with the opposite hand. Further studies in a group of left side affected PD patients would be necessary to discriminate whether the contralateral recruitment of the basal ganglia is a compensatory mechanism caused by the striatal deficit or due to dexterity.

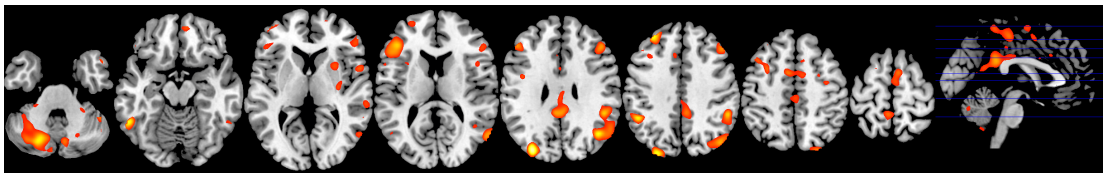

Figure 1. SPM {t} map showing positive effect of PD group in a flexible factorial analysis with three factors: subject, group (PD, control) and task (novel-control sequence) (p<0.001, FDR corrected, k>30)

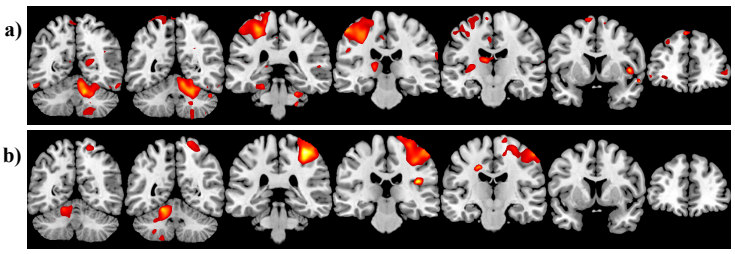

Figure 2. (a) Activation map corresponding to regions more activated in the control task executed with the right hand compared to the one executed with the left hand. (b) Areas more activated in the control task executed with the left hand compared to the right hand task. (p<0.005, unc., k>30).

Conclusions
Compensatory mechanisms in movement learning were described in a population of PD patients. The patients differed from the control group in the increased magnitude of the BOLD signal in areas involved in early learning, together with the putamen contralateral to the most affected hemisphere. The behavioral results of the affected and non affected hand were similar for the control task in the PD group. However, the affected right hand performance recruited more significantly contralateral basal ganglia territories than the left unaffected hand.

Bibliography
1. Ceballos-Baumann J Neurol 2003; 250 Suppl 1: I15-23. 2. Doyon Curr Opin Neurol 2008; 21(4): 478-83. 3. Wu et al. Brain 2005; 128(Pt 10): 2250-9.
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