Levodopa-induced pattern of putamen activity in Parkinson's disease

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Introduction

- Recent research is aimed at investigating brain activity change with levodopa treatment in Parkinson's disease (PD) using functional magnetic resonance imaging (fMRI).
- Current findings are controversial in the context of the **role of the putamen**.
- While some papers report an **increase** of putamen activity with levodopa medication (Kraft 2009, Holiga 2012, 2014, Martinu 2014), other studies show a **decrease** after treatment (Kwak 2012, Maillet 2012).
- We hypothesize a differential role of the putamen **depending on the experimental context**.
- Clinical assessment and fMRI were performed after an overnight withdrawal of levodopa (at least 12 hours), and one hour after administration of 250 mg levodopa.

Methods

- 32 PD patients: equivalent akinetic/rigid type, Hoehn-Yahr stages II-III, 26 males, age 56.1±7.7 y, disease duration 12.2±2.5 y, levodopa treatment duration 9.0±3.0 y.
- MRI: 1.5-T MAGNETOM Symphony scanner (Siemens, Germany) using a birdcage head coil and T2*-weighted gradient-echo echo-planar imaging (EPI) (repetition time, TR=1 s; echo time, TE=54 ms, **500** repetitions).
- Ten oblique slices (thickness 3 mm; 1 mm slice separation; nominal in-plane resolution 3×3 mm^2) were acquired along the central sulcus, covering the primary sensorimotor cortex and the basal ganglia.
- Paradigm: Consecutive tapping (*TAP*) and rest epochs (*REST*), each lasting 10 s and recurring 25 times, resulting in 50 blocks with a total length of **500** s.
- 4 sessions per subject: *OFF/ON* levodopa medication and *LEFT/RIGHT* hand finger tapping.
- Data pre-processing and analysis was performed using SPM12.
- First-level statistics was performed for every session separately using a GLM including two experimental conditions (*TAP/REST*).
- For all patients and all sessions, both resulting parameter images were fed into a second-level analysis using a flexible factorial design including 4 factors: *SUBJECT*, *OFF/ON*, *LEFT/RIGHT*, and *TAP/REST*.
- We analyzed the interaction between the factors *OFF/ON* and *TAP/REST*.
- Using smaller models, we also analyzed *OFF/ON* differences for the *TAP* and the *REST* phase separately.
- Significant results were found with family-wise error (*FWE*) correction at the voxel-level with $p<0.05$ (using the SPM's "*FWE*-button").

Figures

1

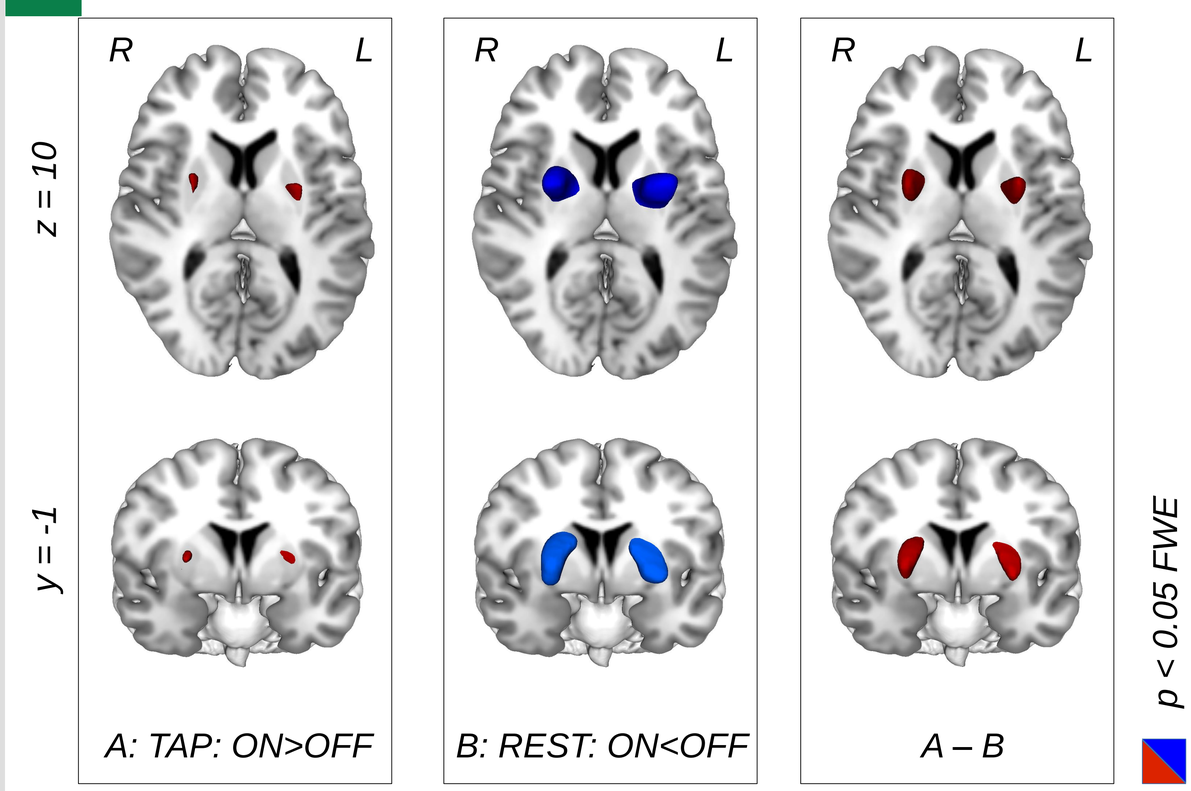

Figure 1. Cross-sectional brain slices showing the differential pattern of brain activity change with levodopa treatment in Parkinson's disease during finger tapping and rest. Using an experimental design with consecutive blocks of finger tapping (*TAP*) and rest (*REST*) in both treatment states with (*ON*) and without (*OFF*) levodopa medication, we observed a differential pattern of brain activity change in both left and right putamen. During *TAP* phases, an increased brain activity was obtained with levodopa medication (left column, color-coded in red). In contrast, during *REST* periods, putamen activity was decreased with levodopa (middle column, color-coded in blue). A significant interaction between both factors of experimental condition (*TAP/REST*) and levodopa treatment (*OFF/ON*) was observed in the left and right putamen (right column). All results were obtained with $p<0.05$ with family-wise error (*FWE*) correction at the voxel-level.

2

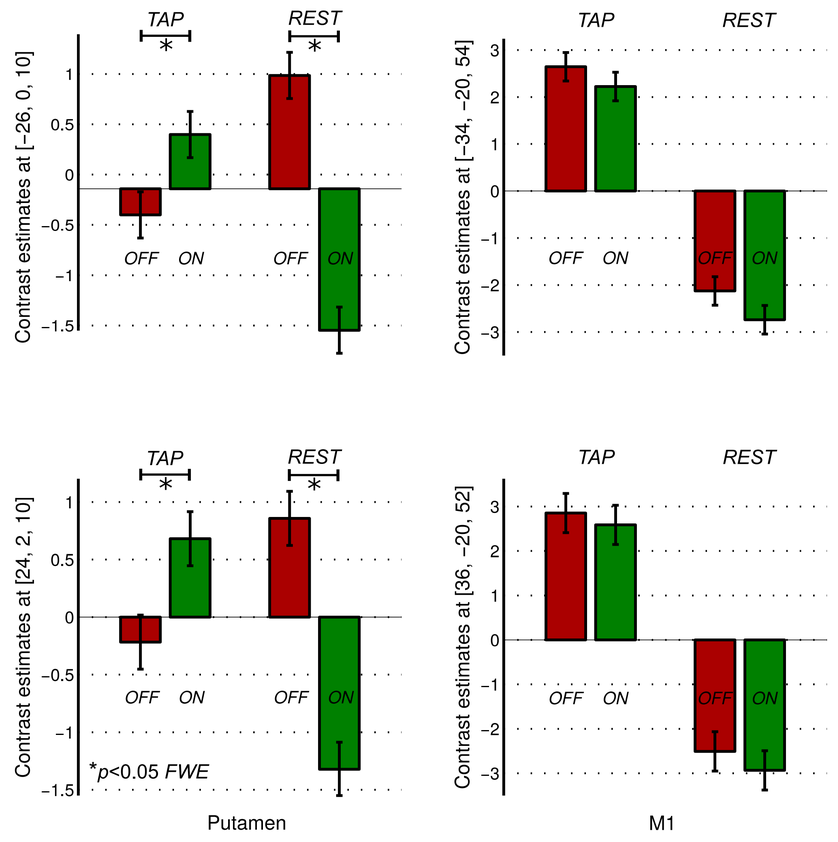

Figure 2. Contrast estimates of a factorial model containing both experimental conditions of finger tapping and rest in both treatment states without and with levodopa medication. Contrast estimates of the putamen showed a differential pattern of brain activity change after levodopa treatment during finger tapping (*TAP*) and rest (*REST*). With the *TAP* condition, we observed a putamen activity increase with levodopa treatment while we found an activity decrease during *REST* (see left column for the left and right putamen, $p<0.05$ family-wise error (*FWE*) corrected). In contrast to the differential pattern of brain activity in the left and right putamen, we did not observe any brain activity differences between the *OFF* and the *ON* state in the left or right motor cortex, neither in the *TAP* nor in the *REST* condition (see right column for the left and right motor cortex).

Results and Discussion

- In the ***TAP*** phase, we observed an **increase** of putamen activity with levodopa (Fig 1, left column, red color), while in the ***REST*** phase, we observed a **decrease** with levodopa (Fig 1, middle column, blue color).
- The interaction analysis between both factors *OFF/ON* and *TAP/REST* showed a significant effect (Fig 1, right column) reflecting the inverse pattern of levodopa-induced putamen activity change in the *TAP* and *REST*.
- Note that only the left and right putamen appeared in all analyses (see Fig 1). The inverse contrasts did not yield any significant result.
- We obtained a divergent pattern of brain activity increase and decrease with dopaminergic medication in PD patients depending on the experimental context.
- Our findings suggest a differential role of the putamen during *TAP* and *REST* depending on the state of levodopa treatment.
- Putamen at *REST* was underactive in the *ON* compared to *OFF* medication state but its activity increased with levodopa challenge with the *TAP* condition.
- This suggests a fundamental difference of involvement of resting and active motor network in PD depending on actual dopamine level in basal ganglia.

References

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