

Levodopa differentially modulates subcortical activity in Parkinson's disease during self-initiated internally timed movements compared to movements following a cued period.

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor impairment, and is associated with dopamine depletion within the basal ganglia (BG) [1]. Evidence from functional imaging has shown that dopaminergic therapy (e.g., levodopa) can normalize motor activity [2]; however, the action of levodopa does not mimic the normal physiology of the dopaminergic system, suggesting other mechanisms may be involved [3]. Research has shown that the BG are less involved in motor control of externally timed movements [4], in comparison to movements that are internally timed. This is further supported by the fact that PD patients find it easier to perform motor tasks that involve a cue, compared to motor tasks that do not [5]. A recent fMRI study found significantly greater activation of the prefrontal, premotor, and primary motor cortices, cerebellum, anterior cingulate and thalamus of PD patients during self-initiated movements, compared to cued movements [6]. Another fMRI study investigating internally timed movement as a continuation from an externally timed task suggests that PD patients use similar networks to perform both tasks, but PD patients may require more cerebellar involvement to compensate for BG dysfunction [7]. Furthermore, levodopa has been found to preferentially improve internally generated movements [8] by focusing brain activity to areas necessary for task performance [9]. Although previous research demonstrates that dopaminergic therapy has a differential effect on internally timed movements, the differences between self-initiated movements and internally timed movements that are initiated by a cue has not been directly investigated. Therefore, the aim of the current study was to investigate how levodopa modulates brain activity in PD patients during the performance of internally timed motor tasks, with and without a preceding cue.

METHODS

Ten patients (6 males) with mild-to-moderate PD underwent two imaging sessions, one ON medication and one OFF medication for ~12 hours. Each imaging session involved two scans of motor fMRI using a GRE-EPI sequence (TR/TE = 2000/30ms; flip angle = 65°; 64×64 matrix; 24-cm field of view; twenty-four 5-mm thick slices). All images were acquired using a 3 Tesla MR scanner (Signa VH/i; GE Healthcare, Waukesha, WI), and all visual stimuli were presented using Presentation (Neurobehavioral Systems, Albany CA) with a video projection/headcoil mounted mirror system (Avotec, Inc., Stuart, FL). Motor fMRI consisted of 15 seconds of rest followed by six 20-second blocks of button-pressing tasks. Three of the task blocks involved 10 seconds of externally timed (E) button pressing at 1 Hz, followed by 10 seconds of internally timed (I) button pressing at 1 Hz. The remaining blocks involved the same tasks in reversed order. The order of block presentation was random. Subjects were presented with a colored "X" to indicate whether the task was E (alternating between red and black at 1 Hz) or I (green), and were asked to alternate button presses using the right index and middle fingers while the colored stimuli remained on the screen. Prior to each block, five patients received a visual cue of varying duration as to which task (E or I) was to be performed first. All data analysis was performed using FSL (<http://www.fmrib.ox.ac.uk/fsl>) and the General Linear Model. Because the focus of the present study was internally-timed movements with or without a preceding cued period, we generated contrasts between the ON and OFF medication conditions for each of I1 and I2 ("1" and "2" indicate whether the task was performed first or second within each block, respectfully), as well as separate contrasts between I1 and I2 for each of the ON and OFF conditions. Anatomical images were collected for registration of fMRI data, and UPDRS (Unified Parkinson's Disease Rating Scale) scores were collected to assess the extent of disease severity. UPDRS scores and the presence of a prompt were used as covariates in the analysis of the fMRI data.

RESULTS

Mean motor related activity was consistent with previous findings, showing activation in subcortical and motor-related areas. Comparing drug conditions for I1, there was significantly greater activity in the right caudate nucleus for the ON condition, while there was significantly greater activity in the right somatosensory and left precentral gyrus (amongst other regions) for the OFF condition. The drug comparison for I2 showed a similar pattern of activity with a general increase in intensity. Higher UPDRS scores were associated with right caudate activation and lower scores were associated with cerebellar activation for I1. For I2, lower UPDRS scores were associated with activation in the left precentral and postcentral gyri. As the figure shows, examination of the differences between I1 and I2 showed differential subcortical involvement depending on whether patients were ON or OFF medication. During the ON condition, there was significantly more activity in the caudate nucleus for I1 compared to I2. During the OFF condition, there was significantly more activity in the right thalamus and right putamen for I2 compared to I1. UPDRS scores also modulated the differences between I1 and I2 within each drug condition.

DISCUSSION

The predominance of brain activity in the OFF condition suggests that levodopa has a focusing effect on cortical and subcortical activity during internally timed movements. However, the action of levodopa has a differential effect on the involvement of ipsilateral basal ganglia and thalamus depending on whether internally timed movements precede or follow a cued period. This finding suggests that there is a distinct difference between internally driven movements that are self-initiated and movements that are initiated by cue. Selective modulation by UPDRS scores indicate that disease severity and physical deficit can significantly impact how patients perform internally timed movements, regardless of whether a cue is present. These findings have the potential to influence rehabilitative strategies for helping PD patients cope with behavioral deficits, as well as provide significant information about how levodopa and future pharmacological interventions for Parkinson's disease affect brain function.

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