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Cortical and motor responses to acute forced exercise in Parkinson's disease

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ABSTRACT

Introduction: Studies in animal models of Parkinson's disease (PD) have suggested that the rate of exercise performance is important in treatment efficacy and neuroprotection. In humans with PD, lower-extremity forced-exercise (FE) produced global improvements in motor symptoms based on clinical ratings and biomechanical measures of upper extremity function.
Methods: fMRI was used to compare the underlying changes in brain activity in PD patients following the administration of anti-parkinsonian medication and following a session of FE.
Results: Nine individuals with PD completed fMRI scans under each condition: off anti-PD medication, on anti-PD medication, and off medication + FE. Unified Parkinson's Disease Rating Motor Scale scores improved by 50% in the FE condition compared to the off-medication condition. The pattern of fMRI activation after FE was similar to that seen with anti-PD medication. Direct comparison of the fMRI activation patterns showed high correlation between FE and anti-PD medication.
Conclusion: These findings suggest that medication and FE likely utilize the same pathways to produce symptomatic relief in individuals with PD.

1. Introduction

Current therapies are effective for addressing many of the symptoms of Parkinson's disease (PD), but these treatments are expensive and are often associated with a variety of side effects that may compromise the patient's quality of life. A nondrug, nonsurgical intervention to improve motor function could serve as a helpful adjunct to current PD treatments. Forced-exercise (FE) is one such option. Animal studies, using a motorized treadmill which forces the animal to exercise at a rate greater than the typical voluntary rate, have shown that forced exercise improves motor function [1,2] and has neuroprotective effects [3,4]. They suggested that forced exercise produces an endogenous increase in neurotrophic factors [3], which may improve the ability of dopaminergic neurons to produce and release dopamine [5]. This is analogous to the effect of levodopa therapy which also increases the release of dopamine in humans with PD. It is likely that contradictory results in human and animal studies are caused by differences between voluntary (human) versus forced exercise (animal).

Models of PD [6] provide a theoretical framework for understanding differences in the effectiveness of forced and voluntary exercise. Based on these model predictions, decreased motor cortical activation limits the ability of patients with PD to perform voluntary exercise at the relatively high rate used in animal studies. Therefore, patients with PD may not be able to exercise (voluntarily) at sufficiently high rates to trigger the endogenous release of the neurotrophic factors thought to underlie global improvements in motor function [3].

We demonstrated that individuals with PD who completed an 8-week lower-extremity FE intervention exhibited an improvement of nearly 35% in clinical motor ratings, whereas subjects who

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completed a voluntary-exercise intervention exhibited no improvement [7]. These changes in UPDRS-III ratings were comparable to the improvements reported following the administration of anti-PD meds [8] and deep brain stimulation [9]. Manual dexterity of patients in the FE group also improved significantly and was maintained four weeks after exercise cessation [7]. The mechanism responsible for these global improvements is unknown. However, improvements in clinical ratings and objective measures of manual dexterity suggest that FE may be altering central nervous system function in PD similar to medical or surgical therapies [10].

Functional MRI (fMRI) has documented that there is a relative decrease in activation in a supplementary motor area (SMA) in PD [11,12] and changes in activation within primary motor cortex, basal ganglia, and thalamus have also been demonstrated [13–15]. The degree and pattern of activation seen in PD have varied depending on the task utilized. FMRI studies have also shown a clear response to levodopa, specifically a normalization of activation with therapy [11,13,15]. The present study focuses on changes in fMRI activation in response to both levodopa therapy and forced exercise.

The primary aim of this study was to compare the acute effects of FE to the effects of antiparkinsonian medication on the pattern of functional magnetic resonance imaging (fMRI) activation and symptom improvement in PD. Both levodopa therapy and forced exercise are thought to increase the amount of available dopamine within the dorsolateral striatum. Given our previous findings [7], we hypothesize that FE and antiparkinsonian medication should produce similar changes in CNS function and PD symptom improvement.

2. Methods

Individuals with mild-moderate PD were recruited from neurology practices and local support groups. All study participants provided written informed consent, as required by the Cleveland Clinic Institutional Review Board.

2.1. Data collection

Data were collected over three separate sessions: when patients were off medication (OFF MEDS), on medication (ON MEDS), and off medication plus FE (OFF MEDS + FE). The order of sessions was randomized. For all sessions, subjects reported to the laboratory in the clinically defined off condition (i.e., at least 12 h since the last dose of antiparkinsonian medication). For the OFF MEDS + FE session, individuals completed the FE session one hour before clinical evaluation. For the ON MEDS session, subjects took their regular dose of medication one hour before evaluation. The total time spent in the laboratory was approximately 5 h during the OFF MEDS and ON MEDS sessions and 6 h during the OFF MEDS + FE session.

2.2. Forced-exercise intervention

The FE intervention consisted of a 1-h exercise session that included a 10-min warm-up, a 40-min forced-exercise set, and a 10-min cool down. The FE exercise intervention was based on our previously published methodology [7], in which participants exercised with an able-bodied trainer on a stationary tandem bicycle. During this 40-min forced-exercise set, the patient's voluntary efforts were augmented by the trainer's effort to achieve a pedaling rate greater than the patient could produce during voluntary pedaling. The patient, assisted by the trainer, maintained a pedaling rate between 80 and 90 revolutions per minute (rpm).

To control for differences in fitness, all patients exercised in an individualized target heart rate (THR) zone. The THR zone was calculated as 65%–80% of the patient's age-predicted maximal HR, which is 220 minus the patient's age. An exercise physiologist provided encouragement throughout the exercise session while the healthy trainer ensured that patients maintained their HR within THR by controlling the cadence and modulating the resistance. The power produced by the patient and the trainer on the tandem cycle was measured independently with two identical commercially available power meters (SRM PowerMeter; Jülich, Germany).

2.3. MRI data acquisition

Data were acquired with a 12-channel receive-only head array on a Siemens Trio 3T scanner (Siemens Medical Solutions, Erlangen, Germany). All patients were fitted with a bite bar to restrict head motion during scanning. Each of the sessions consisted of the following scans:

Scan 1: Anatomic 3D whole-brain T1: T1-weighted inversion recovery turboflash (MPRAGE); 120 axial slices; thickness, 1.2 mm; field of view (FOV), 256 mm × 256 mm; inversion time (TI), 1900; echo time (TE), 1.71; repetition time (TR), 900 ms; flip angle (FA), 8°; matrix, 256 × 128; receiver bandwidth (BW), 32 kHz

Scans 2–6: Complex finger-tapping/force-tracking motor activation study: 160 volumes of 31–4 mm thick axial slices were acquired using a pulse sequence based on the prospective motion-controlled, gradient recalled echo, echoplanar acquisition of [16] TE, 29 ms; TR, 2800 ms; FA, 80°; matrix, 128 × 128; FOV, 256 × 256 mm; BW, 250 kHz. Scan 2: TR, 2800 ms. Scans 3–6: TR, 3000 ms.

2.4. fMRI post-processing and analysis

The fMRI data from scans 2 through 6 were corrected for volumetric head motion with retrospective motion correction using 3dvolreg from AFNI [17]. The data were then passed through a spatial Hamming filter to improve functional contrast-to-noise ratio [18].

The volumetric motion parameters for the five fMRI scans (i.e. scans 2–6) were converted into an estimate of the average voxel displacement for each volume using the method of Jiang and colleagues [19]. A motion displacement threshold of 0.4 mm. This is the threshold at which, according to prior studies with a similar protocol, we can expect evidence of motion in the scan data. In addition, all five fMRI scans for each subject were qualitatively evaluated for evidence of motion by visual inspection by a trained rater of the t-maps produced for each task. We required each patient to have one good fMRI scan for all three states; otherwise, the task for that patient was not used.

The fMRI data were analyzed with a least-squares fit to a boxcar reference function, representing the activation/rest paradigm, to the time series data of each voxel [20]. The result was a whole-brain Student t map that could be thresholded to determine regions of significant involvement for the motor tasks. Activation volume was calculated by determining the number of voxels that were significantly activated above a t-score threshold of 3.5 ($P < 0.001$, one-sided, uncorrected). The percent signal change was then computed by dividing the least-squares fit amplitude by the mean signal in each voxel. A trained image analyst defined regions of interest (ROI) by assessing anatomic boundaries on Talairach-transformed T1-weighted anatomic images for each patient. The mean percent signal change (MPSC) was calculated by averaging the percent signal change across all significantly activated brain