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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.

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Author Contributions

AF coordinated the study, collected data, oversaw FE sessions and participated in manuscript preparation. AT designed, programmed and implemented the force tracking equipment and assisted with data collection. EB designed, programmed and implemented the finger tapping equipment, processed imaging data and assisted in manuscript preparation. AR oversaw FE sessions and assisted with data collection and manuscript preparation. MF and AA recruited and screened PD patients and performed clinical evaluations. ML designed scanning protocols, analyzed imaging data and participated in manuscript preparation. JLA and MP conceived of the project and managed all aspects of the project including data collection and analysis and were responsible for manuscript preparation.

Keywords

Parkinson's disease; forced exercise; aerobic exercise; fMRI

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 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 hours during the OFF MEDS and ON MEDS sessions and 6 hours during the OFF MEDS + FE session.

2.2 Forced-exercise intervention

The FE intervention consisted of a 1-hour exercise session that included a 10-minute warm-up, a 40-minute forced-exercise set, and a 10-minute 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-minute 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% to 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), 1,900; 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, 2,800 ms; FA, 80° ; matrix, 128 × 128; FOV, 256 × 256mm; BW, 250 kHz. Scan 2: TR, 2,800 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 0.4mm. 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 voxels inside the relevant ROI. ROIs were chosen from regions that were known to be in the motor circuit [21] and that showed considerable activation during motor tasks. The following ROIs were drawn separately on the right and left sides: primary motor cortex, supplementary motor cortex, thalamus, globus pallidus, and putamen.

2.5 Effect of exercise and medication

For the force tracking tasks (sine and constant force tracking with MAH and LAH) *Pct* was computed from ROIs on the contralateral side from the hand used for the task. For the bilateral tapping task, *Pct* was computed by averaging the mean percent signal change on both sides. The difference in *Pct* between the ON MEDS and OFF MEDS states was defined as the effect of medication (ΔP_{med}), and the difference between the OFF MEDS + FE and OFF MEDS states was defined as the effect of exercise (ΔP_{ex}).

2.6 Clinical evaluation

Before fMRI at each session, PD symptoms were clinically evaluated with the Unified Parkinson's Disease Rating Scale Motor (UPDRS-III) Exam. This exam was administered by a movement disorders neurologist who was blinded to the study condition.

2.7 Statistical analysis

Data were analyzed with a one-way analysis of variance (ANOVA) with condition (3 levels: OFF MEDS, ON MEDS, OFF MEDS + FE) as fixed factor. Post-hoc pair-wise comparisons were performed using Tukey test, when required. Correlation analysis was run on calculated differences between UPDRS Motor III scores in each condition. SPSS Version 22 was used for analysis.

2.8 Motor Tasks during fMRI

The relationship between motor performance and brain activation patterns was assessed with fMRI while patients performed upper-extremity motor tasks. Participants completed a bilateral finger tapping task and force-tracking tasks where they tracked a constant or sine wave target force profile with their more affected hand (MAH) and less affected hand (LAH). Patients used a precision pinch grip (i.e., thumb and index finger only) when performing the force tracking tasks and were instructed to do their best on all of the motor tasks. Details of these tasks are described in Beall [22].

3. Results

A total of 6 male and 3 female patients (mean age, 61 ± 10 y; range, 44–79 y) with mild to moderate Parkinson's disease (PD) participated in this study (Table 1). Subjects had been diagnosed with PD for 1 to 6 years (3.4 ± 1.8 y) before participation, and all were taking anti-parkinsonian drugs with an average Levodopa equivalent daily dose (LEDD) of 485 ± 2.2 mg across patients (range 160–900mg) [23]. All participants were able to finish this forced-exercise intervention without any adverse events. The pedaling rate was maintained at 84.5 ± 2.7 rpm during the exercise set. Average power and heart rate during the exercise sessions were 46.9 ± 34.5 watts and 120.4 ± 18.5 bpm, respectively.

3.1 Imaging

For each of the three conditions (OFF MEDS, ON MEDS, and OFF MEDS + FE), patients underwent an anatomic 3D whole-brain scan and five additional scans assessing motor activation. A complex bilateral finger-tapping task was used to monitor brain activity during fMRI. Motor tasks included a complex bilateral finger-tapping task, a constant force-

tracking task with the more affected hand (MAH) and less affected hand (LAH) and a sine wave force tracking with MAH and LAH. Because of motion corruption, data from only three motor tasks from each of the patients, on average, could be included in the study. Only tasks where patients had a good MRI scan for all three conditions were used in analysis. Because of this smaller sample size and the potential decrease in statistical significance, we could not analyze data by individual tasks. All available motor tasks were, therefore, assessed together.

The effects of medication and FE were first compared by plotting the difference in mean percent signal change between the OFF MEDS and ON MEDS states (ΔP_{med}) versus the different in mean percent signal change between the OFF MEDS and OFF MEDS + FE states (ΔP_{ex}) for 5 regions of interest (ROIs) that were defined by an image analyst. In all 5 regions, the correlation was significant at the 2s significance level. Figure 1 shows the activation and percent signal change during the bilateral tapping task on slices through the subcortical and cortical motor regions in all 3 states. Specifically, analysis focused on the supplementary motor area, primary motor cortex, globus pallidus, putamen, and thalamus [11, 13]. Correlation analysis was published previously [10, 22], but there were strong correlations in all five areas described above indicating a similar change in MRI response between FE and PD medicated conditions.

3.2 Clinical evaluation

A movement disorders specialist, who was blinded to the patient's condition, performed clinical evaluation using the Unified Parkinson's Disease Rating Motor Scale (UPDRS-III) in the OFF MEDS, ON MEDS and OFF MEDS + FE conditions (Table 2). All but one of the patients showed improvements in UPDRS-III scores in the ON MEDS condition when compared to OFF MEDS and all nine patients exhibited improvements in UPDRS-III scores OFF MEDS + FE, compared to OFF MEDS. Overall, medication improved UPDRS-III ratings by 37% while UPDRS-III ratings improved by 48% in the OFF MEDS + FE relative to OFF MEDS (Table 2).

Analysis of variance (ANOVA) indicated significant difference in UPDRS Motor III scores among the conditions (ON MEDS, OFF MEDS, OFF MEDS + FE) ($F_{2,23} = 14.78$; $P < 0.001$, Fig. 2A). Post-hoc Tukey testing demonstrated that UPDRS-III ratings were significantly ($P < 0.001$) improved when comparing ON MEDS to OFF MEDS (P= .002) and when comparing OFF MEDS to OFF MEDS + FE (P< .001). There was no statistical difference between the ON MEDS and OFF MEDS + FE condition (P = .43).

The effects of anti-PD meds and FE were calculated as the difference between the ON MEDS and OFF MEDS states and the difference between the OFF MEDS + FE and the OFF MEDS states, respectively. A correlation analysis was completed between the relative effects of ON MEDS and OFF MEDS + FE to one another and was statistically significant ($R = 0.7714$; $P = 0.025$), with a 2σ significance level (Fig. 2B).

4. Discussion

These data indicate that forced-exercise and anti-parkinsonian medication produce similar levels of improvement in PD symptoms and that both interventions result in similar fMRI patterns of activation. The current results demonstrated correlations in areas of activation and degree of activation when medication and forced exercise were compared while the patients were performing upper extremity motor tasks. Clinical evaluations indicated that both FE and medication produced significant improvements in PD symptoms. All of the study participants experienced symptomatic relief after forced exercise without any reported side effects. These results suggest that forced-exercise may be a useful noninvasive adjunct to medication for PD patients.

However, much is still unknown about the changes in brain function and motor function in patients with PD. Response to exercise (forced exercise in particular) in patients with PD has not been studied extensively using imaging techniques. In an fMRI study of healthy older adults, Colcombe found that a 6-month aerobic exercise intervention resulted in increased gray and white matter volume, particularly in the prefrontal and temporal cortices [24]. In addition, a 4-month intervention of exercise training resulted in increased cerebral blood flow and greater connectivity in the hippocampus compared to a control group [25]. In a study using transcranial magnetic stimulation (TMS), high-intensity exercise increased the cortical silent period (CSP) when compared to zero-intensity or low-intensity exercise [26]. Increased CSP suggests cortical inhibitory processes may decrease corticomotor excitability in patients with PD. Surgical and pharmacological interventions in the treatment of PD have also demonstrated increased CSP, suggesting that the effect of high-intensity exercise is comparable to these interventions in corticomotor excitability and can lead to improved motor performance [27].

Previous fMRI studies in Parkinson’s disease have shown extensive changes in the pattern of activation involving the supplementary motor area, primary motor cortex, basal ganglia and thalamus. The results of these tests have varied somewhat depending on the task performed as well as this stage of disease. Levodopa therapy provides a precursor of dopamine within the substantia nigra allowing for a net increase in dopamine release in the dorsolateral striatum. In general, levodopa therapy has produced patterns of activation which typically show a normalization and or return to an activation pattern seen more commonly in control subjects. [11, 13, 28] These findings may reflect both direct motor effects, as well as the potential effects of attention.

The similarity between forced exercise and medication in the pattern and degree of brain activation on fMRI suggests that there may be a common underlying mechanism of action within the brain which results in symptomatic relief. In PD, decreased production in dopamine leads to increased activation of inhibitory pathways (GABAergic) on the basal ganglia-thalamic-cortical loop which includes thalamus, putamen, globus pallidus, primary motor cortex and supplementary motor cortex. [29] This preliminary data, as well as the results of previous studies [22], suggest that both therapies may result in a net increase in dopamine release within the dorsolateral striatum which could alter these inhibitory influences and increase activation of these areas. [27, 30]

There are several limitations to this study including a small sample size, no post-intervention follow-up and a variable subject population. Clearly, the relatively small subject numbers require additional work to confirm these results. Post-intervention follow-up imaging would have allowed for us to determine how long the effects of a single FE session last, but future studies will address the timing of these improvements. The subject pool was broad in disease duration (1–6 years) and in OFF UPDRS Motor III scores (23–58). However, a strength of this study is that we used individuals as their own control when compared among the three conditions (ON MEDS, OFF MEDS, OFF MEDS + FE). To our knowledge, this is the first study to demonstrate acute changes on fMRI in response to forced exercise in patients with PD that are similar to the medicated state.

5. Conclusions

The current study investigated only the acute effects of exercise on PD; we concede that the sustained effects are of greater interest. Nevertheless, these acute effects are important as they provide initial insight into potential mechanisms underlying the promising effects of forced-exercise on PD symptoms. We are currently conducting a long-term forced-exercise intervention with PD patients and these patients are undergoing baseline and end of treatment imaging studies. The fMRI data indicated FE and medication produced similar increases in the magnitude and extent of activation in cortical and subcortical motor areas. Similar clinical response and fMRI between FE and medication conditions suggest both utilize similar pathways to improve symptoms in patients with PD.

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Highlights

1. Following an acute bout of forced-exercise while off anti-parkinsonian medication, Parkinson's disease patients exhibited a fMRI pattern of activation that was similar to patterns under anti-parkinsonian medication.
2. The similarity between forced exercise and medication in the pattern and degree of brain activation on fMRI suggests that there may be a common underlying mechanism of action within the brain which results in symptomatic relief.
3. While promising, the long-term effects of forced-exercise is necessary to better understand the role of any mode of exercise on PD motor and non-motor function.

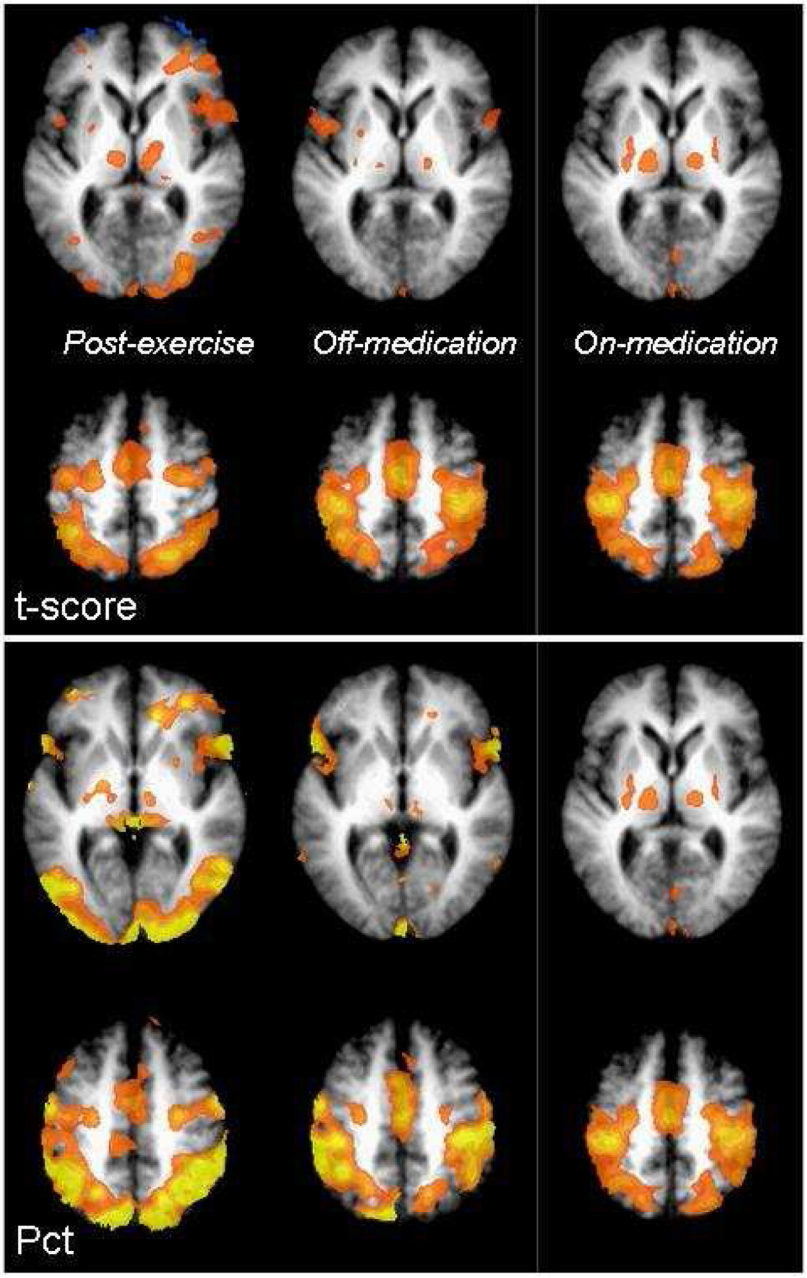

Figure 1.

Bilateral tapping task activation t-score and mean percent signal change (Pct) in each of the 3 states, averaged across patients and shown on Talairach-averaged anatomy. Activation t-score (**top**) was thresholded at 3.5 sigma. Pct (**bottom**) was masked by activation thresholded at 2 sigma.

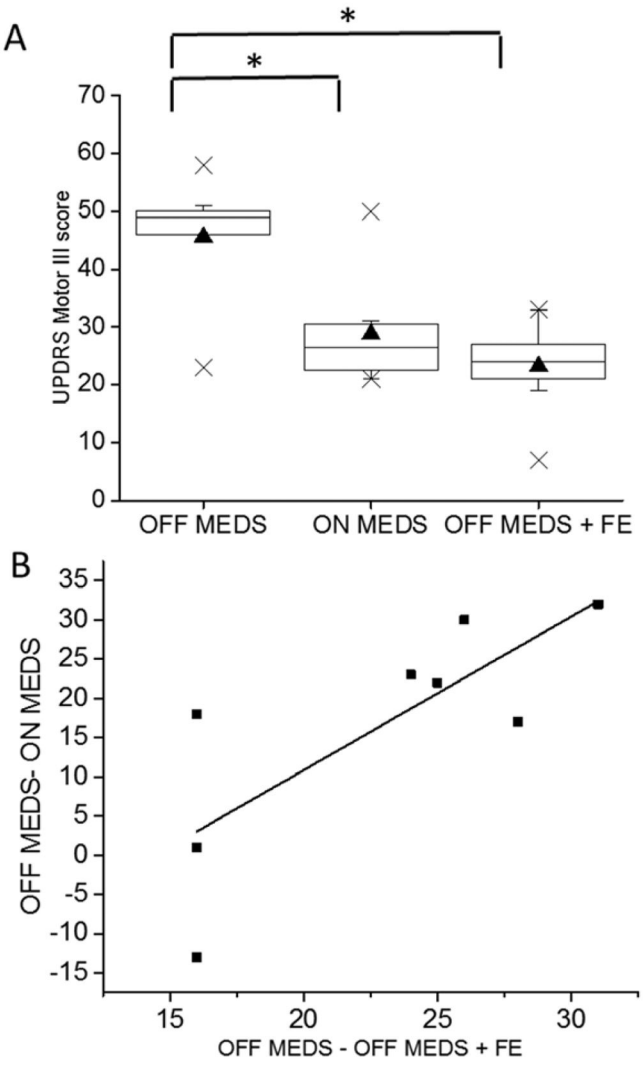

Figure 2.

(a) UPDRS-III motor scores during OFF MEDS, ON MEDS, and OFF MEDS + FE conditions. Scores significantly improved in ON MEDS and OFF MEDS + FE states compared to OFF MEDS state. Box and whisker plots show the median (band in the box), the 25th and 75th percentiles (box boundaries), the 1th and 99th percentiles (X), and the mean (triangle). *= P< 0.01(**b**) Correlation between OFF MEDS + FE state and ON MEDS state in UPDRS-III Motor Scores.

Table 1

Subject demographics, medication and FE performance.

Gender	Age (years)	PD duration (years)	LEDD (mg)	Avg. cadence (rpm)	Avg. Power (W)	Avg. heart rate (bpm)
M	57	2	900	84	73	108
M	79	1	300	83	18	90
M	65	5	225	79	95	138
F	44	2	550	85	1	136
M	61	5	550	89	98	133
F	51	5	500	85	35	135
F	61	6	650	86	33	133
M	69	3	532	86	21	97
M	62	2	160	85	49	115
Mean	**61.0**	**3.4**	**485.2**	**84.5**	**46.9**	**120.4**
SD	**10.06**	**1.8**	**228.5**	**2.7**	**34.5**	**18.5**

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Table 2

Subject clinical evaluation, UPDRS Motor III scores

Gender	UPDRS Off meds	UPDRS On meds	UPDRS Off meds + FE	UPDRS % improvement Off meds to On meds	UPDRS % improvement Off meds to Off meds + FE
M	49	31	33	36.7	32.6
M	50	-	31	-	38.0
M	58	26	27	55.2	53.4
F	49	27	24	44.9	51.0
M	46	23	22	50.0	52.2
F	23	22	7	4.3	69.6
F	51	21	25	58.8	50.9
M	47	30	19	36.2	59.6
M	37	50	21	−35.1	43.2
Mean	**45.6**	**28.7**	**23.2**	**31.4**	**50.1**
SD	**10.1**	**9.3**	**7.6**	**31.7**	**11.1**