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Effects of Parkinson disease and antiparkinson medication on central adaptations to repetitive grasping

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Abstract

Cortical activity during motor task performance is attenuated in individuals with Parkinson disease (PD) relative to age-matched adults without PD, and this activity is enhanced with antiparkinson medication. It remains unclear, however, whether the relative change in cortical activity over the duration of the task, i.e., central adaptation, is affected in individuals with PD, and if so, whether medication corrects for any unique behaviors. Movement-related cortical potentials (MRCPs) were recorded from scalp electrode sites Cz and C1 during 150 repetitive handgrip contractions at 70% of maximal voluntary contraction, in individuals with PD (n = 10) both ON and OFF of their PD medication, and neurologically normal age- and sex-matched controls (n = 10). Repetitions were divided into two Blocks (Block 1 and 2: repetitions 1 – 60 and 91 – 150, respectively), and the composite MRCP slopes were calculated during periods representing movement initiation (–2s to movement onset) and execution (movement onset to 1s). No significant interactions were noted for either comparison (PD OFF vs. control; PD OFF vs. PD ON), irrespective of electrode site (Cz or C1) or movement period (initiation or execution). Despite similar MRCP slopes and task performance, PD OFF endorsed greater perceived exertion during task performance than controls. In the present study, we observed attenuated task-related cortical activity among individuals with PD OFF relative to controls, but a similar relative adaptive response to a fatiguing task. Additionally, although antiparkinson medication enhanced cortical activity (PD OFF vs. PD ON), central adaptation was similar.

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Keywords

Movement-related cortical potential; Bereitschaftspotential; central adaptation; levodopa; Parkinson disease

Introduction

Movement-related cortical potentials (MRCPs) represent electroencephalographic (EEG)-derived cortical activity occurring around the time of movement. MRCPs afford a global measure of activity, distributed broadly although with a defined topography across the scalp, that can delineate distinct periods of motor preparation and execution (Johnston *et al.*, 2001). Prior studies employing self-paced sequential motor tasks have demonstrated reduced MRCP activity in individuals with Parkinson disease (PD) consistent with their clinical presentation (Cunnington *et al.*, 1995, Dick *et al.*, 1989, Simpson and Khuraibet, 1987). Pre-movement hypoactivity is most notable in electrodes overlying the supplementary motor area in individuals with PD (Cunnington 1996), and can be improved with levodopa administration (Dick *et al.*, 1989). Although MRCP activity, or amplitude, in individuals with PD has been well described, it is less well understood how MRCPs adapt, or compensate, during a fatiguing motor task.

Work from our lab and others has employed the repetitive hand grip contraction paradigm (100 – 200 contractions) as a method for evaluating fatigue-related changes in MRCPs. These studies have observed that fatigue produces enhanced MRCP amplitude over supplementary (SMA) and sensorimotor areas (Falvo et al. 2011; Freude and Ullsperger, 1987, Johnston *et al.*, 2001, Liu *et al.*, 2005, Schillings *et al.*, 2006). This fatigue-related increase in MRCP activity has been interpreted as a central adaptation to compensate for suboptimal force production brought about by a fatigued state (Schillings *et al.*, 2006). We recently utilized this paradigm to study the effects of aging and observed a unique central adaptation pattern whereby focal MRCP activity overlying the SMA was attenuated in older adults relative to younger adults (Falvo et al. 2011). This would suggest that the SMA and sensorimotor areas may have a finite capacity for compensating the motor effects of fatigue, perhaps necessitating recruitment of additional neural resources (i.e., cortical regions) to ensure successful task performance. It remains unclear if individuals with PD retain the capability for central adaptation relative to that of age-matched controls without PD, and whether this adaptation is affected by antiparkinson medication.

The present study has two research questions: 1) does central adaptation differ in individuals with and without PD, and 2) does antiparkinson medication affect central adaption? To address these questions, we compared MRCPs of older adults to age- and sex-matched individuals with PD, as well as compared those with PD both with and without medication. We hypothesized that central adaptation would be, 1) compromised in individuals with PD off medication in comparison to older adults, and 2) adaptation would be enhanced among individuals with PD in a fully medicated state in comparison to overnight withdrawal.

Methods

Participants

Twenty participants volunteered for this experiment and were subdivided into 'Control' (68.8 ± 4.6 ; 59 – 78), and PD (68.1 ± 8.4 ; 59 – 78) groups. Each group consisted of 10 adults (8 men and 2 women). Participants with PD (Calne *et al.*, 1992) were recruited from the Washington University Movement Disorders Center. Data from controls were previously reported (Falvo et al. 2011). Clinical demographic data are provided in Table 1.

All participants were right-handed, as determined in accordance to the Edinburgh handedness inventory (Oldfield, 1971). With the exception of PD, no participant had a history of musculoskeletal or neurological disease, were currently depressed (confirmed by the Beck Depression Inventory), or were taking any psychoactive medication for at least 6 months prior to entry into the study. Written informed consent was provided by all participants in accordance to the Declaration of Helsinki and was approved by the Washington University School of Medicine Human Research Protection Office.

All participants performed a single-session protocol, with the exception of individuals with PD. Those with PD performed the protocol twice: once after an overnight withdrawal (OFF) of their antiparkinson medication, and once in an optimally medicated state (ON), i.e. 1 – 2 hours after morning dose. Relative order of ON and OFF testing sessions was randomized, but always performed at the same time of day and separated by a minimum of 72 hours of rest.

Experimental Overview

The experimental design has been described in detail previously (Falvo et al. 2011). In brief, participants performed repetitive grasping in a seated position using an instrumented hand grip dynamometer. The dynamometer was used for determining maximum voluntary contraction (MVC) as well as for repetitive grasping using standardized instructions. Following a brief familiarization, each participant performed five sets of 30 trials or repetitions at 70% of their MVC, with approximately 2 minutes of rest between sets. Movements were self-initiated and paced with a target rate of one grip every 5-8 seconds, and participants were provided visual feedback on a monitor to ensure the target force of 70% MVC was achieved per trial and were verbally cued if pacing was inconsistent (<5s or >8s).

Data Acquisition and Analysis

Participants were fitted with an appropriately sized elastic nylon 61-channel Quick-cap, and continuous EEG data were acquired with a 70-channel NeuroScan Synamps2 amplifier system using the Scan 4.3 software (Compumedics; Charlotte, NC). This system also enabled continuous and synchronous collection of the force signal from the grip dynamometer as well as the surface electromyogram (EMG) of the flexor digitorum superficialis (FDS) in the dominant arm. FDS activity was recorded using a bipolar surface EMG arrangement, with electrodes placed 20 mm apart after vigorous cleaning and abrasion of skin. Data were recorded with a bandwidth of DC-100Hz and sampled at 1KHz.

Impedances were kept below 5 k Ω for all electrodes. Raw EMG signals were full-wave rectified and integrated for offline analysis.

Custom MATLAB programs (v7.3.0; Math Works, Inc.; Natick, MA) were used for offline data analysis. EEG signals were inspected for artifacts, high-pass filtered at 0.01 Hz (90 db) and were referred to a common average of the signals from all scalp electrode sites. Epochs for each trial (i.e. 3 s before and 1 s after force onset) were averaged separately for trials 1 – 60 (Block 1) and 91 – 150 (Block 2). Force onset was defined as a 2 SD increase in voltage from the dynamometer above resting levels. The MRCP was first analyzed as previously described by Schillings et al. (2010), by calculating the area under the curve (AUC) at discrete 0.5s time intervals occurring before (–2s to –1.5s, –1.5s to –1.0s, –1.0s to –0.5s, and –0.5s to 0s) and after (0 to 0.5s and 0.5s to 1.0s) movement onset to represent movement initiation and execution, respectively. Individual regression coefficient analyses were then used to calculate the slope or change in AUC across successive time intervals for movement initiation (–2.0s to 0s before onset) and execution (0 – 1.0s after onset). The change in slope from Block 1 to Block 2 was used to operationally define central adaptation. Since the position directly overlying the primary sensorimotor and contralateral hand motor area during finger movements show maximal amplitude in MRCPs, analyses were restricted to scalp electrodes Cz and C1 (Cunnington *et al.*, 1995). Both positions are involved in repetitive grasping and known to be affected in PD.

EMG activity of the FDS during the trials was calculated over a 2500 ms epoch (e.g. 1000 ms prior to onset to 1500 ms after onset), and then averaged across trials similar to the MRCP described above. The force signal from the dynamometer was used both for triggering purposes and to ensure participants were meeting the target level of 70% MVC. Force-time histories obtained during repetitive grasping and for MVCs were analyzed for peak and mean force.

Clinical and subjective rating scales

All participants completed the Parkinson fatigue scale (Brown *et al.*, 2005), and were also asked to subjectively rate their perceived exertion (RPE) (Borg, 1982), at rest and following completion of the repetitive contractions. The motor subsection of the Unified Parkinson Disease Rating Scale (UPDRS) was administered by a single blinded Movement Disorders Specialist to all individuals with PD, both ON and OFF their medication. This clinician/ investigator also rated the clinical disability of those with PD according to the Hoehn & Yahr (HY) scale. Participants were also asked to subjectively rate how effectively they felt their Parkinson symptoms were controlled at the time of testing on a 10-cm visual analog scale, which was administered prior to testing both ON and OFF conditions. A score of ‘0’ indicated they felt no control over their symptoms whereas a score of ‘10’ indicated they felt complete control over their symptoms. This scale was used to confirm that participants had indeed complied with instructions regarding the use of medications prior to the day of testing.

Statistical Analysis

To assess central adaptation as a function of disease and antiparkinson medication, regression coefficients were analyzed via a mixed repeated measures analysis of variance (ANOVA) with group (PD OFF vs. Control; PD OFF vs. PD ON) and time (Block 1 vs. Block 2) as between- and within-subjects factors, respectively. EMG, force and RPE data were also analyzed using a mixed ANOVA design. Baseline measures were compared via one-way ANOVA. All data are presented as mean $\pm$ SD and were analyzed using SPSS (v24; SPSS Inc., Chicago, IL). For all comparisons, a probability of $<0.05\%$ was considered to be statistically significant.

Results

Participant Characteristics

Individuals with PD had higher baseline scores on the Parkinson Fatigue scale than age-matched controls (PD: 2.3 ± 0.9 , Control: 1.38 ± 0.4 ; $p = 0.01$), but this sample was not considered fatigued according to cut-off scores (Brown *et al.*, 2005). Participants with PD reported to the laboratory after an overnight withdrawal of their medication (12.85 ± 2.7 hours). The effects of medication withdrawal were further confirmed in the form of significantly ($p = 0.05$) higher UPDRS motor scores (Average score; OFF = 28.3, ON = 25.3) as well as lower values on the 10 cm visual analog scale ($p = 0.04$; OFF = 6.5, ON = 8.5), analyzed using one-tailed t -tests (Table 1). Overall AUC of the MRCP potential for PD positive participants were attenuated in both CZ and C1. While medication does help reduce the change it does not match that of the control group. The MRCP changes during block 1 and block two are illustrated for Cz in Figure 1. Two individuals with PD while OFF medication were unable to complete the final sub-Block of 30 contractions; therefore, blocks for these participants were redefined as trials 1 - 60 (Block 1) and 61 - 90 (Block 2). Grand average waveforms are also presented in Figure 2 for electrode Cz.

PD OFF vs. Controls

Task performance was similar between groups and across blocks with regard to force production (PD OFF vs. Control; block 1: 12.8 ± 5.8 vs. 15.0 ± 6.1 kg, block 2: 12.7 ± 5.3 vs. 15.3 ± 5.4 kg), inter-grip intervals (block 1: 6.2 ± 1.6 vs. 5.7 ± 1.1 s; block 2: 6.9 ± 2.6 vs. 5.9 ± 1.2 s) and EMG activity (block 1: 46.9 ± 47.2 vs. 52.2 ± 26.6 μ V; block 2: 24.6 ± 10.7 vs. 54.3 ± 31.4 μ V). A significant interaction ($F(1, 18) = 29.8$, $p = 0.025$) for RPE was observed (block 1: 7.0 ± 1.0 vs. 6.4 ± 0.7 ; block 2: 13.7 ± 4.5 vs. 8.9 ± 1.9).

Regression coefficient slopes are reported in Table 2. No significant interactions were observed for Cz or C1 during movement initiation or execution. A main effect for block was observed only during movement initiation at Cz ($F(1,18) = 6.5$, $p = 0.016$).

Results for PD OFF are reported above; therefore, only PD ON results are reported herein. Task performance was similar between ON and OFF conditions with respect to force production (PD ON only, Block 1 vs. Block 2; 12.1 ± 6.1 vs. 11.9 ± 6.7 kg), inter-grip interval (6.6 ± 1.1 vs. 6.7 ± 1.9 kg), EMG activity (26.5 ± 15.3 vs. 41.4 ± 29.5 μ V), and RPE (7.0 ± 1.8 vs.

11.8±2.9). Only RPE demonstrated a significant main effect for block ($F(1,18) = 40.4$, $p < 0.001$).

Slopes for regression coefficient analyses are reported in Table 2. No significant interactions were observed for Cz or C1 during movement initiation or execution. A main effect for block was observed only during movement initiation at Cz ($F(1,18) = 9.0$, $p = 0.008$).

Discussion

We previously reported attenuated central adaptation during repetitive grasping in healthy aging (Falvo et al. 2011). The goal of the present study was to extend that work to determine the possible separate effects of PD and antiparkinson medication on this adaptive process. Consistent with earlier reports in PD, MRCP activity was attenuated in PD relative to age-matched controls and the administration of antiparkinson medication enhanced cortical activity (Figure 1). Contrary to our hypotheses, however, we observed similar relative central adaptation (change in slope from Block 1 to Block 2) among individuals with and without PD, and this response was unaffected by antiparkinson medication (Table 2). This pattern of attenuated cortical activity yet similar relative adaptation is noteworthy given that task performance (i.e., force production and inter-grip intervals) was similar between patients and controls irrespective of medication status. Despite similar relative adaptations and task performance, individuals with PD OFF reported a greater change in perceived exertion from Block 1 to Block 2 during the fatiguing task than age- and sex-matched controls. We interpret these findings such that individuals with PD must put forth greater effort relative to controls in order to accomplish a motor task.

To our knowledge, these are the first MRCP data to describe separate effects of PD and PD medication during a fatigue-inducing protocol. In agreement with previous studies (Cunnington *et al.*, 1995, Dick *et al.*, 1989, Simpson and Khuraibet, 1987), we found that individuals with PD have central activation impairments, showing attenuated MRCP amplitudes, and that this impairment is amplified after medication withdrawal (Figure 1). An unexpected finding, and contrary to our hypothesis, was the absence of a difference in relative adaptation between individuals with PD OFF and controls as well as ON versus OFF antiparkinson medications (Table 2). One potential explanation of these findings may be possible interference of the lateral pre-motor area during repetitive grasping. We separately examined activity in this area (C3), in the same manner as described for Cz and C1, but observed no evidence for an interaction effect and observed similar relative changes amongst groups (results not reported). An alternative explanation for our findings may reflect our use of MRCPs which may not adequately capture the spatial extent of activation (reflecting source depth). In fact, Palmer et al. previously demonstrated that individuals with PD utilize active motor reserve, whereby novel motor areas are activated to compensate for normal motor networks that are limited (Palmer *et al.*, 2009). In that study, subjects were asked to perform a sinusoidal handgrip force task at different frequencies (0.25, 0.5, and 0.75 Hz) while OFF of their antiparkinson medication. In healthy controls, activity of widespread motor networks increased monotonically with movement speed whereas those with PD recruited this ‘normal network’ to a greater extent even at the lowest frequency. Study authors suggest that although those with PD retain the ability to recruit the normal network,

they do so to a greater extent albeit with greater physiological cost (Palmer *et al.*, 2009). Further, a different PD-specific network emerged that included more involvement of the cerebellum concomitant with reduced activation of the thalamus and basal ganglia. Therefore, activation of their motor reserve (i.e. increased effort) in order to maintain normal behavioral output is secondary to a maximally recruited normal network and may likely include greater or lesser involvement of structures comprising the normal network.

In the present study, we did not find any significant medication-related effects, suggesting medication did not substantially affect central adaptive processes investigated here. Medication resulted in an approximately 10% improvement in UPDRS motor score which, although small, exceeded the minimally clinically important change (Schrage *et al.*, 2006, Shulman *et al.*, 2010). Again, it may also be possible that focusing effects of levodopa previously reported (Ng *et al.*, 2010, Palmer *et al.*, 2009) may have been beyond detection of the present study. In support, the aforementioned Palmer *et al.* study found that when individuals with PD were tested ON their medication, they did not activate their motor reserve to the same extent as when OFF medication. This was achieved by a reduction in the spatial variance of activation within regions of interest in a manner that normalized motor activity (Ng *et al.*, 2010, Palmer *et al.*, 2009). Ng and colleagues (Ng *et al.*, 2010) suggest that levodopa may exert system-level effects by refocusing the activation of cortical and subcortical structures. Even though the methods and paradigm of the present study do not allow a direct comparison, it appears plausible that focusing effects of levodopa may be realized in future MRCP studies. It should be noted that such an effect may not be specific to PD, as levodopa has also been shown to influence premotor processing when administered to neurologically normal adults (Dick *et al.*, 1987, Hasbroucq *et al.*, 2003).

Conclusion

Cortical networks governing motor function appear highly plastic, and neurodegenerative changes that occur during normal aging and with pathology underscore this plasticity. Data from the present study suggest that central adaptation is possible in individuals with PD, but may require greater effort or occur at greater physiological cost. For individuals with PD who have known central activation impairments, they may rely upon unique activation strategies in comparison to healthy older adults to successfully complete a motor task (Palmer *et al.*, 2009). Future research is needed to clarify these mechanisms in individuals with and without PD, considering amplitude as well as spatial-depth changes (Ng *et al.*, 2010, Palmer *et al.*, 2009).

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Figure 1. Area under the curve for consecutive time intervals of the MRCP at electrode Cz
 Area under the curve measurements (mean $\pm$ SE) were obtained for the periods preceding movement initiation (-2.0 to 0 s) and following movement execution (0 s to 1.0 s). Separate averages were formed based on repetitive grasping during Block 1 (trials 1-60; left) and Block 2 (trials 91-150; right). A similar pattern of results was observed from electrode C1.

Figure 2. Grand average MRCP waveform

Grand average waveforms at electrode Cz are provided for illustrative purposes for older adults (CTRL) and individuals with Parkinson disease while ‘on’ (PD ON) and ‘off’ (PD OFF) antiparkinson medication. Waveforms generated during blocks 1 and 2 are represented in black and red, respectively. *PD OFF vs. PD ON:*

Table 1

Clinical Demographics

Controls				Parkinson disease			
Participant	Age (yrs)	Sex	Age (yrs)	Sex	PD Duration	UPDRS OFF	UPDRS ON H&Y
1	61	M	59	M	9	23	12.5 2
2	52	M	52	M	3.5	15.5	12 2
3	77	F	75	F	9	30.5	23 2
4	71	M	69	M	4	31	35.5 2
5	70	M	68	M	7	28.5	27.5 2
6	78	F	78	F	4	24	21 2
7	73	M	73	M	18	40.5	35 3
8	73	M	62	M	3	18.5	15.5 2
9	78	M	78	M	5	28	34 2
10	66	M	67	M	4	43	37 2

UPDRS: Unified Parkinson Disease Rating Scale; ON: optimally medicated; OFF: off antiparkinson medication; H&Y: Hoehn & Yahr.

Table 2
Regression coefficient analysis slopes

Regression coefficient analysis slopes ($\mu\text{V}\cdot\text{ms/s}$) were calculated during movement initiation (-2.0 to 0 s) and execution (0.0 to 1.0 s) as illustrated in Figure 1.

	Block 1		Block 2	
	Initiation	Execution	Initiation	Execution
Cz				
Control	4711.7 $\pm$ 570.7	-10026.1 $\pm$ 2388.2	5106.9 $\pm$ 1093.7	-9960.5 $\pm$ 1969.2
PD OFF	2235.9 $\pm$ 591.1	-3022.3 $\pm$ 1205.5	3691.7 $\pm$ 1170.1	-3170.2 $\pm$ 1080.8
PD ON	2202.0 $\pm$ 690.8	-3625.8 $\pm$ 1893.5	3752.2 $\pm$ 1014.6	-4728.1 $\pm$ 2912.4
C1				
Control	4260.9 $\pm$ 580.5	-9580.5 $\pm$ 2442.4	4154.0 $\pm$ 951.8	-9361.2 $\pm$ 2074.7
PD OFF	1570.1 $\pm$ 656.4	-2479.2 $\pm$ 1384.1	1999.7 $\pm$ 591.2	-2733.8 $\pm$ 999.7
PD ON	1800.3 $\pm$ 666.8	-2274.4 $\pm$ 2730.8	1672.5 $\pm$ 534.0	1505.3 $\pm$ 4618.8