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Interaction of Contralateral Activation Maneuver and Dopaminergic Medication on Neural and Non-Neural Contributions to Parkinsonian Rigidity

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ABSTRACT

Introduction: Rigidity is a cardinal symptom of Parkinson Disease (PD) and is defined as increased resistance to passive motion. Rigidity results from the interaction of exaggerated responses to passive stretch and shortening as well as changes to the intrinsic properties of muscle and connective tissues. A contralateral activation maneuver is used clinically to increase perceived rigidity to facilitate the diagnosis of PD. Recent research has differentiated the neural reflex and intrinsic contributions to rigidity in PD, however, little is known regarding the effect of a contralateral activation maneuver on these components of rigidity.

Methods: Fourteen patients and 14 controls performed passive wrist flexion and extension motions during recordings of joint torques and muscle activations of wrist flexors and extensors. All participants performed the experimental task with and without a contralateral activation maneuver and patients with PD repeated the protocol in Off- and On-Medication states. A system identification technique was applied to differentiate neural reflex and intrinsic mechanical components of rigidity. A mixed-model ANOVA was performed to determine the effects of group, medication and contralateral activation maneuver on the components of rigidity.

Results: The neural reflex component of rigidity was exaggerated in individuals with PD in the Off-Med state ($p<0.01$) and was reduced with the contralateral activation maneuver ($p<0.01$). Medication decreased the neural reflex component of rigidity ($p<0.01$) but had no effect on the intrinsic mechanical component of rigidity.

Conclusion: The contralateral activation maneuver alters the neural reflex component of rigidity and that medication restores function of the dopaminergic system.

INTRODUCTION

Parkinson Disease (PD) is a chronic, progressive neurodegenerative disorder characterized by motor signs including rigidity, bradykinesia, tremor, and postural instability [1]. Rigidity is a cardinal sign of PD used in clinical diagnosis and assessment of treatment efficacy [2-6] and has been shown to progress at a greater

rate than other cardinal signs of PD [7-10]. PD-related rigidity is defined as an increased resistance to passive motion throughout the entire range of motion [11] and is enhanced by contralateral activation maneuvers [12]. The protocol for the Unified Parkinson Disease Rating Scale UPDRS [13] indicates that patients should a perform a contralateral activation maneuver (i.e. hand gripping-clinching, finger tapping or fist opening-closing) if rigidity is not initially detected during passive limb motion. Rigidity can be difficult to detect without activation maneuvers in the early stages of PD. Though Parkinsonian rigidity is routinely assessed in both clinical and research settings, little is known regarding its underlying mechanisms.

Parkinsonian rigidity is the result of the interaction of exaggerated reflex responses to stretch and shortening as well as changes in the intrinsic properties of the muscle and connective tissues. The role of exaggerated reflex responses to passive stretch and shortening in PD-related rigidity have been well documented [10,11,14-16]. While the spinal stretch reflex has been suggested to be normal in individuals with PD, several studies have revealed that the long-latency stretch reflex is exaggerated underlying a greater resistance to passive motion [14,17,18]. This long-latency reflex is suggested to be a transcortical pathway resulting in longer reflex latencies compared to the short- (spinal) and medium-latency stretch reflexes [19-21]. Further, the shortening reaction is also exaggerated in individuals with PD and suggested to be responsible for the "lead-pipe" resistance detected during clinical examinations [18,22].

The characteristics of changes in the non-neural intrinsic properties of the muscle and connective tissues is less well understood. Several studies have sought to identify the nature of the changes in intrinsic properties of the muscle unit including changes in mechanical properties of muscle fibers and connective tissues in PD. These modeling studies have focused investigations on the inertial, elastic and viscous properties of the upper and lower extremity joints [23-28]. Two recent studies have used modeling techniques to differentiate the contributions of neural reflex and intrinsic components to Parkinsonian rigidity at the wrist [29,30]. Xia et al. [29] showed that individuals with PD exhibit an increased neural reflex torque compared to healthy controls and that the neural reflex torque is reduced toward that of healthy controls with the administration of dopaminergic medication. Zetterberg et al. [30] reported increased neural contributions to Parkinsonian rigidity but also reported that the neural component was increased with a contralateral activation maneuver. These findings support previous research which postulated that contralateral activation maneuver was associated with neural facilitation resulting in greater PD-related rigidity [12,20]. The efficacy of dopaminergic medication in reducing neural contributions to Parkinsonian rigidity remains unknown. Further, the interaction of dopaminergic medication and a contralateral activation maneuver has not been well elucidated. Therefore, the purpose of this study was to assess the effect of a contralateral activation maneuver on the neural and non-neural contributions to PD-related rigidity. We hypothesized that the contralateral activation maneuver would exaggerate the neural component of rigidity without changes in the non-neural component of rigidity. It was further hypothesized that administration of dopaminergic medication would decrease the effect of the contralateral activation maneuver on the neural component of rigidity to a level similar to healthy controls.

Table 1: Patients' clinical information.

Patient	Age (yrs)	Disease Duration (yrs)	Sex	Arm Tested	Rigidity (UPDRS)[a]		Medication[b]
					Off	On	
#1	48	1.5	F	L	3	1	C/L 25/100 (3x); P 1.5mg
#2	74	6.5	F	R	2	1	A 100 (x2); C/L 25/100 (3x)
#3	69	3	F	R	2	1	P1.5mg (3x)
#4	67	13	F	L	3	2	R3mg (3x); C/L/E50-200-200mg (4x); S5mg (2x)
#5	67	10	M	R	2	1	E 200 (4x); C/L 25/100 (4x)
#6	46	1	F	L	3	1	C/L 25/100 (3x); R4mg (1x)
#7	56	4.5	F	R	2	1	rasagiline1mg (1x); R3mg (3x); C/L 25/100 (3x)
#8	57	13	M	L	3	3	A 200 (3x); E 200mg (3x); C/L 25/100 (3x)
#9	63	7	F	R	2	1	rasagiline1mg (1x); P1.5mg (3x); C/L 25/100 (3x)
#10	67	4.5	M	L	2	1	C/L 25/100 (6x); DilanigoLexipo 0.5mg
#11	77	1	F	L	2	0	C/L 25/100 (3x)
#12	60	6.5	F	L	2	2	R3mg (1x); S 5mg (2x); C/L 25/100 (5x)
#13	63	12	F	R	2	1	P1.5mg (3x); C/L/E 37.5-150-200mg (4x)
#14	62	5.5	M	R	2	0	A 100mg (1x); C/L 25/100 (2x)

[a]UPDRS (unified Parkinson's disease rating scale). Rigidity: 0, absent; 1, slight; 2, mild to moderate; 3, marked; 4, severe.
[b]A, amantadine; E, entacopone; R, ropinirole; S, selegiline; P, pramipexole; C/L, carbidopa/levodopa.

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METHODS

Participants

Fourteen participants with idiopathic PD and 14 age- and sex-matched controls were recruited to participate in the current study. Participants with PD were 62.6 (± 9.1) years of age while healthy controls were 62.9 (± 8.5) years of age. Patient clinical characteristics are listed in (Table 1). The experimental protocol was approved by the university Institutional Review Board and all procedures were performed in accordance with the Helsinki Declaration. Written informed consent was obtained prior to the participation of each participant in this study.

Inclusion and Exclusion Criteria

Prior to testing, each participant was screened for inclusion using a verbal medical history and the motor section of the Unified Parkinson Disease Rating Scale [13,31]. Individuals with PD were included in the current study if they were: (1) between 40 and 80 yrs of age, (2) treated using dopaminergic medication, (3) exhibited clinical rigidity (≥2, mild to moderate or marked) in one or both arms in the Off-Med state, (4) minimal tremor (≤ 1, slight and infrequently present) in the tested arm. Subjects experiencing medication-induced dyskinesia were also included as long as dyskinesia did not interfere with the rating and testing. Participants (PD or Control) were excluded if cognitive impairments prevented them from providing informed consent, understanding instructions or providing adequate feedback.

Experimental protocol

The experimental set up is previously described in detail [29]. In summary, participants were placed in a height-adjustable seat and the arm exhibiting the greatest rigidity was placed in the dynamometer via a manipulandum with the fingers slightly flexed to minimize the stretch of finger flexors and extensors [12,29]. With the shoulder and forearm in neutral position and the elbow in mid-flexion, the ulnar aspect of the participant's wrist was aligned with the center of rotation of the dynamometer. The forearm was stabilized using a vacuum bag splint preventing extraneous motion of the forearm. Metacarpal restraints of the manipulandum isolated wrist flexion and extension. Participants were instructed to relax while the wrist was moved through a series of small-amplitude joint displacements (±2°) using a Pseudorandom Binary Sequence (PRBS). Trials were conducted with (*Active*) and without (*Passive*) a voluntary contralateral gripping contraction equal to 20% of maximal grip force. Maximal grip contraction and contralateral contraction intensity were monitored using an instrumented hand dynamometer (Vernier Software & Technology, OR, USA) and Lab View 2009 (National Instruments, TX, USA) which provided a graphic display of the contractile force. Participants viewed the graph of grip contraction and matched their force to the visual display. Surface Electromyography (EMG) signals were recorded from the extrinsic wrist flexors and extensors using a 16-channel surface EMG system (Delsys Inc., MA, USA). Specifically, EMG electrodes were placed over the muscle belly of the Flexor Carpi Radialis (FCR), Flexor Carpi Ulnaris (FCU), Flexor Digitorum Superficialis (FDS), Extensor Carpi Radialis (ECR), Extensor Carpi Ulnaris (ECU) and Extensor Digitorum Communis (EDC). Surface EMG electrode placements followed previously published recommendations [32] and were confirmed by manual muscle testing. EMG signals were amplified and band-passed filtered before being sampled at 1000 Hz for each data channel. Visual inspection of EMG and torque signals was conducted following each trial to ensure that extrinsic wrist muscles in the tested hand were quiescent. Experimental trials characterized by extrinsic muscle activation or sudden increases in torque signals were discarded and repeated. Each participant completed three successful trials in each experimental condition. All trials were followed by a period of rest to minimize the risk of fatigue.

Participants with PD were initially tested after an overnight withdrawal from anti-PD medication (Off-Med) for at least 12 hours [33], a time period associated with the loss of a majority of the beneficial effects of medication therapy [6]. After Off-Med testing was completed, participants took their regular dose of anti-PD medications(s) in the laboratory. Following a 45- to 60-minute period of rest and verbal confirmation of the efficacy of dopaminergic medication, participants repeated experimental testing in the On-Med state.

Estimation of neural reflex and intrinsic torques

A parallel-cascade system identification modeling approach was implemented to differentiate the neural reflex and intrinsic muscle mechanical contributions to rigidity. The system identification approach has been previously described in detail

[34,35] and has been used previously in individuals with neurological pathologies including PD [29]. Reflex activation dynamics, relating EMG to velocity, were estimated using a Hammerstein identification procedure [36]. The static nonlinearity emulated a half-wave rectifier (Figure 1, lower pathway). The linear Impulse Response Function (IRF), EMG_{IRF}, was characterized by a pulse-like response with a delay of approximately 50 ms, which is the reflex latency for the long-latency stretch reflexes of the forearm muscles associated with Parkinsonian rigidity [15,16]. The reflex contributions to joint torque occurred at latencies longer than 50 ms.

Neural reflex dynamics were estimated as a pathway comprising a differentiator, a static non-linearity (N) and linear dynamics ($Reflex_{IRF}$), using a Hammerstein identification method. As with the reflex EMG, the static nonlinear element is found to be very similar to a half-wave-rectifier. The static nonlinearity is normalized so that the entire gain in the pathway was assigned to $Reflex_{IRF}$. The length of the $Reflex_{IRF}$ was selected to be long enough to permit the IRF to decay to zero and hence fully describe the dynamics.

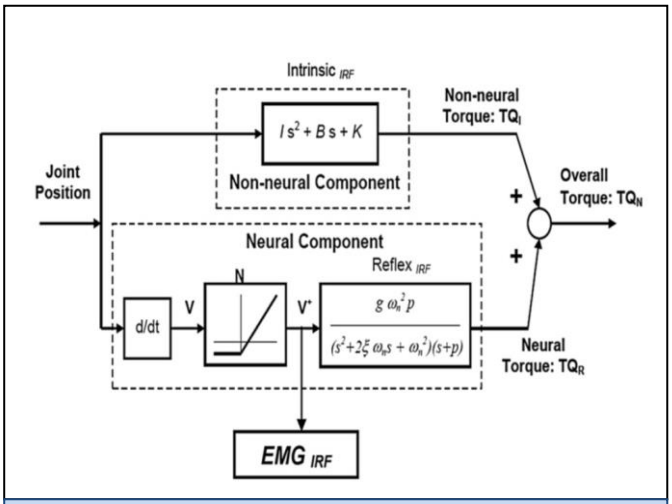

Figure 1: The parallel structure for identification of neural and intrinsic contributions to rigidity. System input: joint position (degrees); output: measured torque (Nm). Upper pathway, s: variable for Laplace domain; I: Inertia; B: viscosity; K; elasticity. Lower pathway, d/dt: differentiator; N: static nonlinear element; V: angular velocity; $V^{=}$: half wave rectified velocity; g: reflex gain; p, ω_n: first- and second-order cutoff frequencies; ξ: damping parameter.

Intrinsic dynamics were estimated in terms of a linear IRF, relating position and torque, $Intrinsic_{IRF}$ (Figure 1, upper pathway). Interference by reflex effects were prevented by constraining the length of $Intrinsic_{IRF}$ to be less than the delay associated with EMG_{IRF} (~50 ms). The dynamics arise from mechanical properties of muscle fibers.

IRFs were assessed based on the percentage of the output (torque or EMG) variance accounted for (%VAF), defined as:

$$\%VAF = 100 * \left\{ 1 - \sum_{1}^{N} \left(TQ - \hat{TQ} \right)^2 \Big/ \sum_{1}^{N} TQ^2 \right\}$$

Eq (1)

where N is the number of points, TQ is the measured torque, and $\hat{TQ}$ is the predicted torque by the IRF.

Statistical analyses

Repeated measures analyses of variance (ANOVAs) with Tukey's post-hoc comparisons were used to determine the effect of medication (Off-Med vs. On-Med) and condition (Active vs. Passive) on intrinsic and reflex torques in individuals with PD. Two repeated measures ANOVAs (group by condition) were then used to compare intrinsic and reflex torques in healthy controls to individuals with PD in the Off-Med and On-Med conditions, respectively. If a significant effect of group or condition was observed, post-hoc paired (within-subjects) or independent samples (between groups) t-tests were used to compare mean values between Passive and Active conditions in individuals with PD and healthy controls. All statistical analyses were conducted in Prism (GraphPad Software Inc., La Jolla, CA). Significance was set at $p < 0.05$.

RESULTS

Figure 2a presents recordings of the wrist joint position in the PRBS waveform and resistance torque output from a representative trial. Figure 2b compares torque responses to the PRBS pulses in the two medication states in an individual with PD as well as a healthy control participant. Figure 3 presents observation data for intrinsic and reflex torques in individuals with PD in the Off-Med and On-Med states during the Passive and Active conditions.

Table 2 presents mean intrinsic and reflex torques in individuals with PD in the Off-Med and On-Med states with and without the contralateral activation maneuver. In individuals with PD, intrinsic torques were similar in the Off-Med and On-Med states ($p = 0.149$) and no differences in intrinsic torques were observed in the Passive compared to Active conditions ($p =$

0.099). Cohen's d estimates of effects sizes of medication and condition were small (d < 0.6). Reflex torques were significantly greater in the Off-Med compared to On-Med states (p = 0.005). Further, the Passive condition was associated with greater reflex torques compared to the Active condition (p = 0.006). Cohen's d estimates of effect sizes of medication revealed a strong effect (d = 1.5) of medication in the Passive condition while a small effect of medication (d = 0.4) was observed in the Active condition. Moderate effects of condition (Active vs. Passive) were observed in the Off-Med (d = 1.2) and On-Med states (d = 0.6).

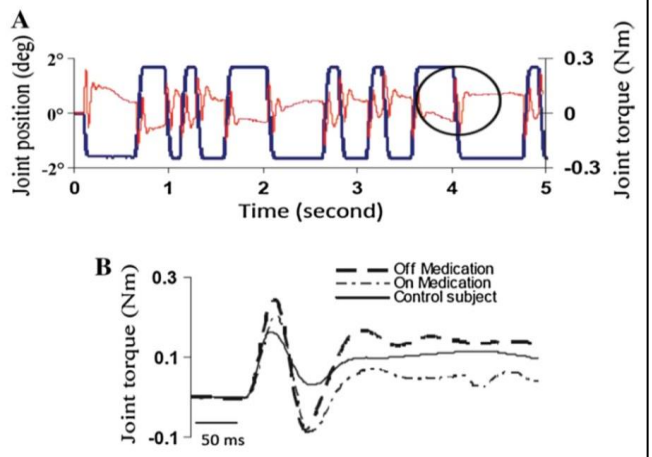

Figure 2A: Joint position (blue trace) in PRBS waveform and measured torque (red) from a PD subject in the Off-Med state. Zero degrees represents the wrist at the neutral position. B: Torque responses to a passive rotation of the joint compared between the two medication states in a subject with PD as well as with a control subject. The response is shown within the circle in panel A.

Table 2: Mean absolute torque values for individuals with PD in the On-Med and Off-Med states. Values are presented mean ± SD.

Variable	Condition	On-Med	Off-Med	Cohen's d	Int.	Med	Cond.
Intrinsic Torque	Passive	0.119 ± 0.031	0.123 ± 0.054	0.1	0.259	0.149	0.099
	Active	0.104 ± 0.026	0.117 ± 0.026	0.5			
	Cohen's d	0.5	0.2				
Reflex Torque	Passive	0.133 ± 0.013	0.165 ± 0.028	**1.5**	0.066	**0.006**	**0.005**
	Active	0.124 ± 0.016	0.133 ± 0.027	0.4			
	Cohen's d	0.6	1.2				

Note: Statistical analysis includes effects sizes (Cohen's d) and p-values from the mixed model ANOVA for the interaction of medication and condition as well as main effects of medication and condition. An effect size of 1.42 represents a strong effect of medication in the passive condition.

Table 3: Comparison of intrinsic and reflex torques in individuals with PD in the On-Med and Off-Med states with healthy controls.

PD State	Variable	Condition	Control	PD	Cohen's d	Int.	Group	Cond.
On-Med	Intrinsic Torque	Passive	0.117 ± 0.065	0.119 ± 0.031	0.03	0.331	0.448	0.066
		Active	0.109 ± 0.051	0.104 ± 0.026	0.14			
		Cohen's d	0.1	0.5				
	Reflex Torque	Passive	0.128 ± 0.065	0.133 ± 0.013	0.10	0.402	0.419	0.150
		Active	0.123 ± 0.041	0.124 ± 0.016	0.03			
		Cohen's d	0.1	0.6				
Off-Med	Intrinsic Torque	Passive		0.123 ± 0.054	0.09	0.454	0.361	0.219
		Active		0.117 ± 0.026	0.18			
		Cohen's d		0.2				
	Reflex Torque	Passive		0.165 ± 0.028	**0.73**	0.067	0.057	**0.018**
		Active		0.133 ± 0.027	0.31			
		Cohen's d		1.2				

Note: Statistical analyses include estimates of effect sizes (Cohen's d) and p-values from the ANOVA for the interaction of group and condition as well as main effects of medication and condition. An effect size of 0.73 represents a moderate effect of group in the passive condition.

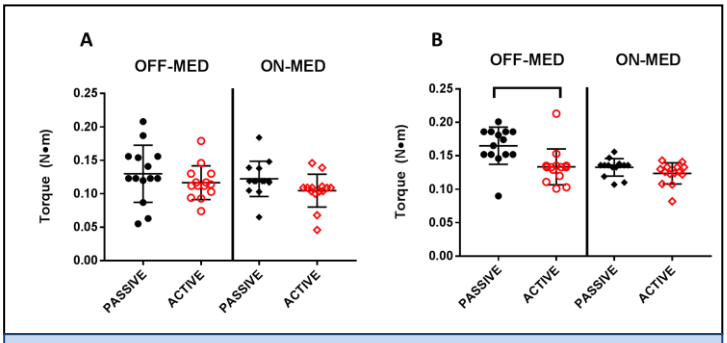

Figure 3: Individual observations for intrinsic (A) and reflex torques(B) obtained from all participants with PD in the On-Med and Off-Med states during the passive and active conditions.

Table 3 presents mean intrinsic and reflex torques in individuals with PD in the Off-Med and On-Med states in the Passive and Active conditions as well as healthy controls. No differences were observed between individuals with PD in the On-Med state and healthy controls in intrinsic or reflex torques in either the Passive or Active conditions. However, in the Off-Med state, the Passive condition was associate with greater reflex torques than the Active condition (p = 0.018). Post-hoc t-tests revealed no significant differences between the Passive and Active conditions for healthy controls (p = 0.347) while in individuals with PD in the Off-Med state the Passive condition was associated with greater reflex torques compared to the Active

condition ($p = 0.042$). Individuals with PD in the Off-Med state had greater neural torques than healthy controls ($p = 0.035$) in the Passive condition while no differences were observed in the Active condition ($p = 0.221$).

DISCUSSION

A novel finding of the current study was that the contralateral activation maneuver was associated with reductions in neural reflex contributions to Parkinsonian rigidity when individuals with PD were in the Off-Med state. These findings do not support the stated hypothesis and are in contrast to previously published data [12,30]. Administration of dopaminergic medication significantly reduced neural reflex torques to levels similar to healthy age-matched controls. These findings support the hypothesis that dopaminergic medication would be associated with reduced neural contributions to parkinsonian rigidity. Intrinsic contributions to parkinsonian rigidity were not different between the Off-Med and On-Med states nor were differences observed between individuals with PD and healthy controls.

The contralateral activation maneuver has been associated with enhancement of parkinsonian rigidity [12,13,30]. In this study individuals with PD in the Off-Med state experienced reductions in neural reflex torques with the contralateral activation maneuver. These findings are in contrast to previous research findings which reported greater rigidity [12,30] and greater neural contributions [30] to rigidity in response to the contralateral activation maneuver. Powell et al. [29] reported a two-fold increase in overall rigidity while Zetterberg et al. [43] reported a 55% increase in overall rigidity at the wrist with a contralateral activation maneuver. Zetterberg et al. [30] revealed a three-fold increase in neural reflex contributions to parkinsonian rigidity with the contralateral activation maneuver.

Exaggerated reflex responses to stretch and shortening are proposed to underlie parkinsonian rigidity [10,11,14-16,37] and represent neural reflex contributions to parkinsonian rigidity. While reflex responses to passive stretch include both spinal and supraspinal circuits, traditionally only the supraspinally mediated Long-Latency Stretch Reflex (LLSR) has been identified as a key mediator of parkinsonian rigidity [6,20,37,38]. The mechanism underlying the efficacy of the contralateral activation maneuver to increased parkinsonian rigidity is attributed to the interaction of the supraspinal LLSR and increased motor cortical excitability associated with a voluntary muscle contraction [20,39-41]. However, in the current study the contralateral activation maneuver was associated with reductions in neural reflex torques, seemingly challenging existing literature and traditional understanding of the contralateral activation maneuver in individuals with PD. It is postulated that the current findings do not conflict with previous research findings but potentially expand current understanding of a complex, multi-faceted system.

In the studies by Powell et al. [29] and Zetterberg et al. [30], the wrist was moved through large ranges of motion (50° or more) over periods of 200 ms or more. Conversely, the current study implemented small joint excursions (±2°) applied over short periods of time (~20 ms). It is possible that the passive motions implemented in the current study did not have sufficient magnitude or duration to elicit a strong LLSR response reducing facilitation of the hyper-excitable motor cortical system associated with Parkinson's disease [42]. As the spinal stretch reflex has been shown to be normal in individuals with PD [17,37,38], reductions in LLSR magnitudes would underlie decreases in neural contributions to PD-related rigidity [38].

While reduced LLSR magnitudes would contribute to the decreases in neural reflex torques, it would not fully explain the observed reductions in neural reflex torques in response to a contralateral activation maneuver. Contralateral muscle contractions increase motor cortical excitability [39] resulting in greater LLSR and perceived rigidity in individuals with PD [38,42]. However, a contralateral activation maneuver alters not only motor cortical but also spinal neuron excitability. Hortobagyi et al. [17] investigated changes in motor evoked potentials and H-reflex magnitudes in response to voluntary contraction of the contralateral homologous muscle and revealed divergent responses of the cortical and spinal circuits. While motor evoked potentials were increased with increasing muscle contraction intensity, H-reflex magnitudes were progressively reduced [39]. In the current study, the contralateral activation maneuver may have reduced spinal motor neuron excitability contributing to decreased neural reflex torques.

Anti-PD treatments seek to improve function to the neural system. The current findings demonstrate that dopaminergic

medication reduced neural reflex torques compared to the Off-Med state toward rigidity levels in healthy age-matched controls. Further, dopaminergic medication abolished differences between the passive and active conditions suggesting that restoration of neural function may alter the interaction of spinal and supraspinal circuits in response to a contralateral activation maneuver. Intrinsic contributions to PD-related rigidity remained unchanged in response to dopaminergic medication, similar to previous research findings [30].

Though the current study presents novel findings regarding the effect of a contralateral activation maneuver on parkinsonian rigidity as well as the constituent components underlying parkinsonian rigidity, the authors acknowledge several limitations. The sample size was small and may have had limited statistical power. To address the small sample size, the authors have included Cohen's d estimates of effect sizes to assess the meaningfulness of the observed differences. However, the small sample size may limit the generalizability of these findings. A second limitation includes the single contraction intensity associated with the contralateral activation maneuver. Evaluation of the changes in neural reflex torques in response to increasing intensities of the contralateral activation maneuver may have allowed for greater corroboration of the proposed mechanisms responsible for this phenomenon. However, these added conditions may have confounded these results due to participant fatigue and would have lacked direct clinical application.

CONCLUSIONS

Parkinsonian rigidity is the result of altered reflex responses to passive stretch and shortening as well as changes in the intrinsic properties of muscle. Neural contributions to rigidity are greater in individuals with PD compared to healthy controls but are normalized by administration of dopaminergic medication. Contrary to previously reported findings, the contralateral activation maneuver was associated with reductions in neural reflex contributions to rigidity, however, this finding is likely driven by differences in the methodology implemented to quantify the neural reflex and intrinsic contributions to parkinsonian rigidity. Future research should directly investigate the neurophysiological factors proposed to underlie the current observations using electrophysiological testing.

CONFLICT OF INTEREST

None

FINANCIAL DISCLOSURE

None

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