Neuroscience

Normalizing EMG to Background Muscle Activation Masks Medication-Induced Reductions in Reflex Amplitudes in Parkinsonian Rigidity

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Objectives: **Exaggerated reflex responses to passive stretch and shortening contribute to parkinsonian rigidity. Studies have reported medication-induced reductions in rigidity in the absence of attenuated reflex magnitudes. The purpose of this study was to determine if normalization procedures mask medication-induced reductions in reflex responses in Parkinson's disease.**

Methods: **Twelve participants with PD performed passive wrist flexion and extension movements after a 12-hour withdrawal from dopaminergic medication and 60 minutes after medication was administered. EMG was recorded from wrist flexors and extensors. Raw EMG signals were conditioned and normalized to mean background EMG amplitudes collected 100 ms prior to the onset of passive movement by division and by subtraction.**

Results: **Raw EMG amplitudes were significantly reduced. No medication-related reductions were observed during passive flexion or extension when EMG amplitudes were normalized by division. When EMG amplitudes were normalized by subtraction, significant reductions were observed following administration of dopaminergic medication during flexion and extension. Dopaminergic medication was associated with significant reductions in rigidity work scores and significant increases in moment-angle slope plots.**

Conclusions: **These findings demonstrate that EMG normalization techniques may hinder data interpretation in studies of altered reflex responses in individuals with Parkinson's disease following the administration of dopaminergic medication.**

Rigidity | Normalization | EMG | Parkinson's disease | Reflex

Highlights

- Raw EMG indicated reductions in reflex amplitudes in ON- compared to OFF-MED states
- Normalization by division showed no medication-induced changes in reflex amplitudes
- Normalization by subtraction revealed that medication reduced reflex amplitudes

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder associated with the progressive loss of dopamine producing cells in the substantia nigra [1]. Rigidity is defined as an increased resistance to passive movement of a limb throughout a range of motion [2] and is a hallmark symptom of PD. As a hallmark symptom, rigidity is used in the diagnosis of PD and the assessment of treatment efficacy [3,4]. A unique characteristic of parkinsonian rigidity is its uniform, "lead-pipe" nature or the constant resistance throughout the entire range of motion [5-7]. This distinct feature of PD-related rigidity is the result of aberrant reflex responses to passive stretch and shortening [8-11] as well as changes in the intrinsic mechanical properties of the passive connective tissues [6,7].

Previous research has suggested that short-latency stretch reflexes are not different between individuals with PD and healthy adults, but that long-latency stretch reflex is exaggerated in individuals with PD [8,10]. Also contributing to the constant nature of parkinsonian rigidity is the shortening reaction [12]. Originally described in 1880 [13], the shortening reaction describes reflex muscle activation in response to passive muscle shortening. The interaction of these aberrant reflexes underlies the neural contribution to PD-related "lead-pipe" rigidity.

Parkinsonian rigidity has been shown to respond well to dopaminergic medication [1,3,4]. However, reported improvements in measures of rigidity are not always accompanied by concomitant reductions in reflex amplitudes [12,14,15]. A study investigating the relationship between stretch reflex amplitudes and rigidity demonstrated that dopaminergic medication was associated with reductions in rigidity, however, no consistent reduction in reflex responses to stretch were observed [12]. Another study investigating changes in PD-related rigidity in response to a contralateral activation maneuver and dopaminergic medication revealed that medication was consistently associated with reductions in the magnitude of rigidity in the contralateral active condition [15]. Though rigidity was reduced, no significant reductions in reflex EMG amplitudes were observed. In each of these studies, reflex amplitudes were normalized to background muscle activity during an electrically quiescent period prior to the onset of movement.

It has been shown that individuals with PD exhibit resting hypertonia or increased background muscle activation at rest [8]. Previous research has suggested that exaggerated reflex responses to stretch and shortening may be scaled by this resting hypertonia and that it is necessary to account for resting hypertonia when considering reflex amplitudes [8] by normalizing reflex amplitudes to background muscle activation levels. However, it has also been suggested that this common method of normalizing muscle activation amplitudes to background muscle activation may mask changes in reflex amplitudes associated with

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Table 1. Patients' clinical information

Patient	Age (yrs)	Disease Duration (yrs)	Gender	Arm tested	Rigidity (UPDRS)[a]		Medication Information[b]
					Off	On	
1	62	11	F	R	3	1	C/L 50/200 (x4); C/L/E 100 mg (x2); Pra 1.5 mg (x3)
2	67	13	F	L	3	2	C/L 25/100 (x3); R 1 mg (x3); S 5 mg (x2)
3	71	5	F	R	2	1	C/L 25/100 (x3)
4	69	3	F	R	2	2	Pra 1.5 mg (x3)
5	65	3	M	L	2	1	C/L 25/100 mg (x3)
6	59	8	M	R	2	1	C/L 25/100 (x3); R 1.0 mg (x3)
7	57	5	F	R	2	1	Az 1 mg (x1); C/L 25/100 (x3); R 3.0 mg (x3)
8	63	12	M	R	2	1	Am 100 mg (x1); C/L 25/100 (x2);
9	58	14	M	L	4	3	Am 100 mg (x2); C/L 25/100 (x3); Ct 200 mg (x3)
10	77	1	F	L	2	0	C/L 25/100 (x3)
11	67	10	M	R	2	1	Az 1.0 mg (x1); C/L 100 mg (x1); Ct 200 mg (x1)
12	63	7	F	R	2	1	Pra 1.5 mg (x3); S 1.0 mg (x1)

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

dopaminergic medications [14,15]. Therefore, the purpose of this study was to quantify the effects of currently implemented reflex normalization techniques on the interpretation of the efficacy of dopaminergic medication in reducing exaggerated reflex responses to stretch and shortening during passive wrist flexion and extension movements. It was hypothesized that the administration of dopaminergic medication would be associated with significant reductions in measures of rigidity (rigidity work scores) and significant increases in the slope of the moment-angle plots. Further, it was hypothesized that dopaminergic medication would be associated with significant reductions in raw reflex EMG amplitudes while reflex EMG signals normalized to background muscle activation (at rest) would not show significant reductions in EMG amplitude.

2. Methods

2.1 Participants

Twelve subjects with idiopathic PD (7 male, 5 female) participated in this study. Individual participant information including anthropometrics, clinical characteristics and medication profiles are presented in Table 1. Each participant was assessed for inclusion using a verbal medical history and the Motor Section (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) [16]. Participants were included in they were (1) between 40 and 80 years of age, (2) current treated using dopaminergic medication, (3) had the presence of clinical rigidity rated 2 or 3 (mild to moderate or marked) in one or both arms when dopaminergic medication was temporarily withdrawn and (4) had minimal tremor ($\leq$ 1, slight and infrequently present) in the tested arm when dopaminergic medication was temporarily withdrawn. Participants were excluded if cognitive impairments prevented them from giving informed consent, understanding experimental protocols instructions or providing adequate feedback. Participants were also excluded if they had an insufficient range of motion at the wrist (less than 50° in either flexion or extension) or a history of upper extremity impairment that would negatively affect wrist motion. The experimental protocol was approved by the University Institutional Review Board. This study was conducted in accordance with the Declaration of Helsinki and all participants provided written informed consent prior to participation in the study.

2.2 Experimental protocol

All participants had an initial clinical assessment using the Motor Section (Part III) or the UPDRS [16]. The participant was then seated in a height adjustable chair with the hand exhibiting greater rigidity according to the clinical assessment placed in a manipulandum attached to the shaft of a servomotor. The participant's shoulder and forearm were placed in neutral position with the elbow at approximately 120° of flexion and the center of wrist joint rotation aligned with the center of rotation of the servomotor. To minimize movement of the forearm (supination and pronation), the forearm was stabilized using a vacuum bag splint. Other motions of the wrist were restricted by the metacarpal restraints of the manipulandum, allowing only wrist flexion and extension to occur.

Participants were asked to remain completely relaxed during the passive wrist flexion and extension movements generated by the servomotor. Each trial began with the wrist at approximately 30° of extension. The wrist was then moved (passively) through 60° of flexion (to 30° of flexion) and returned to the initial starting position at a constant velocity of 50°/sec. Four trials were collected in each medication state (OFF- and ON-MED) followed by a 30-second period of rest to minimize fatigue and motor adaptation.

Resistance torque at the wrist was measured using a strain gauge torque transducer (TRT-200, Pacific Scientific, CA, USA) while angular position of the wrist joint was measured using emulated encoder output from the servomotor controller (SC904 series, Pacific Scientific, CA, USA). Torque and position signals were recorded at 1000 Hz and 100 Hz, respectively. To quantify reflex responses to passive muscle stretch and shortening, surface electromyography (EMG) signals were recorded from the extrinsic wrist and finger flexor and extensor muscles including: flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), flexor digitorum superficialis (FDS), extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), extensor digitorum communis (EDC). EMG signals were recorded using a 16-channel surface

Table 2. EMG measures of reflex responses to passive stretch and shortening during the passive wrist flexion and extension movements in RAW and NORM conditions in the OFF- and ON-MED states. Presented as mean (SD)

		Flexion		Extension	
Medication	Condition	Shortened	Stretched	Shortened	Stretched
OFF-MED	RAW	0.05 (0.02)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)
	DIV	4.11 (1.15)	2.95 (0.68)	3.36 (0.94)	3.18 (0.65)
	MINUS	0.03 (0.02)	0.02 (0.01)	0.03 (0.01)	0.03 (0.01)
ON-MED	RAW	0.04 (0.03)*	0.03 (0.01)*	0.04 (0.01)*	0.02 (0.01)*
	DIV	4.16 (1.20)	2.90 (0.50)	3.91 (1.18)	3.35 (0.57)
	MINUS	0.02 (0.02)*	0.02 (0.01)*	0.02 (0.01)*	0.02 (0.01)*

Note: * - denotes significant difference compared to OFF-MED state.

EMG system (Delsys, Inc., MA, USA). EMG signals were amplified (x10k) and band-pass filtered (20 – 450 Hz) before being sampled at 1000 Hz for each EMG channel. Torque, position and EMG data were captured using custom software (LabVIEW 2009, National Instruments, TX, USA).

Subjects with PD were tested in two medication states including Off- (OFF-MED) and On-medication (ON-MED). The OFF-MED condition occurred after a 12-hour withdrawal from dopaminergic medication [17] when a majority of the beneficial effects of dopamine replacement therapy was eliminated [18]. After OFF-MED testing was completed, subjects with PD self-administered their regular dose of dopaminergic medication in the laboratory. Following a 45- to 60-minute period of rest, the effect of dopaminergic medication was validated verbally by the subject. Once the efficacy of medication was established, the participants repeated the experimental protocol in the ON-MED state. EMG electrodes were not removed during the completion of all experimental testing allowing direct comparison of raw EMG amplitudes in the OFF- compared to ON-MED states.

2.3 Data analyses

To evaluate rigidity of the wrist, torque and EMG data were analyzed using custom software (MATLAB 2015, MathWorks, MA, USA). Rigidity was quantified using the rigidity work score which is calculated as the torque signal integrated with respect to joint angle [2,14,15,19]. The "lead-pipe" nature of parkinsonian rigidity was assessed using the slope of the moment-angle plot using linear regression analyses for flexion and extension movements independently [12,14,15,19,20].

EMG signals were full-wave rectified and low-pass filtered with a cutoff frequency of 30 Hz. Mean EMG amplitudes for each muscle were calculated for the flexion and extension movement periods, respectively. Rectified EMG (RAW) values were grouped by function (flexors vs. extensors), represented by the sum of the EMG amplitudes for each functional group (i.e. Flexors = FCR + FCU + FDS; Extensors = ECR + ECU+ EDC), and presented as an electrical signal (mV). Two methods of normalizing EMG were calculated. Normalization by dividing (DIV) was calculated as the quotient of the mean EMG amplitudes during each independent movement phase (flexion and extension) divided by the mean resting background EMG amplitude during the 100 ms prior to the onset of passive movement. Normalization by subtraction (MINUS) was calculated as the difference between the mean raw and background EMG amplitudes and was calculated by subtracting the mean resting background EMG amplitude during the 100 ms prior to the onset of passive movement from the raw EMG amplitudes. Normalized EMG values were grouped by function (flexors vs. extensors) and were represented by the sum of the EMG amplitudes for each functional group, similar to RAW signals. For example, the mean EMG of stretched muscles was calculated as an average of normalized mean EMG of extensors during the flexion movement and the average of normalized mean EMG of flexors during the extension movement [12,14,15]. Conversely, the mean EMG of shortened muscles was calculated as the average of normalized mean EMG signals of the flexors during flexion and the average of normalized mean EMG signals of the extensors during extension.

2.4 Statistical analyses

A series of paired samples t-tests were used to assess the effect of medication on reflex EMG amplitudes in each of the three normalization techniques (RAW, DIV, MINUS), independently. A Holm-Bonferroni adjustment was used to adjust for multiple comparisons for each dependent variable. The Holm-Bonferroni adjustment was conducted for reflex EMG amplitudes of the flexors and extensors during the passive flexion and extension movements, respectively, and are presented as shortened (flexors in flexion and extensors in extension) or stretched muscles (extensors in flexion and flexors in extension). Paired samples t-tests were also used to determine the effect of medication on mechanical measures of rigidity including rigidity work scores and slopes of the moment-angle plots. Significance was set at $p < 0.05$. All statistical analyses were conducted using PROC T-TEST in SAS University Edition (SAS Inc., Cary, NC, USA).

3. Results

3.1 Reflex Electromyography (EMG)

Table 2 presents mean reflex EMG amplitudes in the RAW, DIV and MINUS conditions when participants were tested in the OFF- and ON-MED conditions. In the RAW condition, the statistical analysis revealed significant reductions in reflex EMG amplitudes in the stretched muscles in the ON- compared to OFF-MED states during the passive flexion ($p = 0.001$) and extension movements ($p = 0.001$), respectively. In the DIV condition, no medication-induced reductions in reflex EMG amplitudes were observed in

Table 3. Measures of rigidity including rigidity torque scores and moment-angle plot slopes. Rigidity torque scores are presented for the overall movement (TOTAL) as well as flexion and extension components of the overall movement. Moment-angle plot slopes are presented for the flexion and extension components of the passive movement. Presented as mean (SD).

	Rigidity Work Score			Slope	
Medication	Total	Flexion	Extension	Flexion	Extension
OFF-MED	9.4 (3.0)	4.7 (4.2)	3.5 (3.1)	3.5 (1.4)	2.6 (1.1)
ON-MED	6.4 (3.6) *	2.2 (2.3) *	3.2 (2.7)	6.8 (3.3) *	7.0 (4.0) *
p-value	0.021	0.027	0.169	0.030	0.016

Note: * - denotes significant difference compared to OFF-MED state

the passive flexion ($p = 0.474$) or extension movement ($p = 0.235$). In the MINUS condition, dopaminergic medication was associated with significant reductions in reflex EMG amplitudes (Flexion: $p = 0.022$; Extension: $p = 0.039$). In passively shortened muscles, administration of dopaminergic medication was associated with significant reductions in reflex EMG amplitudes in the RAW and MINUS conditions during the passive flexion (RAW: $p = 0.004$; MINUS: $p = 0.013$) and extension movements (RAW: $p = 0.023$; MINUS: $p = 0.010$), respectively. However, no changes in reflex EMG amplitudes were observed in the DIV condition (Flexion: $p = 0.878$; Extension: $p = 0.700$).

3.2 Measures of rigidity

Table 3 presents rigidity data including mean rigidity work scores and moment-angle plot slopes. Medication was associated with significant reductions in rigidity work score over the entire movement cycle ($p = 0.021$). The reductions in overall rigidity work score were dominated by reduced resistance in the passive flexion movement ($p = 0.027$) while no differences were observed in rigidity work scores during the passive extension movement ($p = 0.169$). Slopes of the moment-angle plots were significantly greater in the ON- compared to OFF-MED state during the passive flexion ($p = 0.030$) and extension movements ($p = 0.016$).

4. Discussion

The purpose of this study was to investigate the effect of current methods of EMG normalization on quantifying the effect of medication on reflex responses to passive stretch and shortening in individuals with PD. The findings of this study demonstrated that dopaminergic medication was associated with reductions in RAW EMG amplitudes and EMG amplitudes normalized by subtracting baseline EMG values from the reflex amplitudes while no effect of medication was observed when reflex EMG amplitudes were divided by resting background EMG levels. The current study also presents mechanical measures of rigidity including rigidity work score and moment-angle plot slopes. These findings demonstrated that dopaminergic medication was associated with significant improvements in measures of rigidity as evidenced by smaller rigidity work scores and greater slopes of moment-angle plots. The observed improvements in rigidity measures are similar to those previously reported by research studies using similar methods [14,15].

Parkinsonian rigidity has been shown to be the result of changes in the mechanical properties of passive connective tissues [6,7,21] as well as exaggerated responses to passive stretch and shortening [10,11,22]. The unique, "lead-pipe" presentation of rigidity in PD is the result of the interaction of stretch reflexes and shortening reactions [12]. Previous research has suggested that while the short-latency stretch reflex is normal in individuals with PD [10,22], however, the long-latency stretch reflex and shortening reactions are exaggerated [11,13]. Given the importance of these reflex responses in determining the presentation of parkinsonian rigidity, accurate methods of quantifying reflex amplitudes and their responses to anti-PD treatment are needed. Previous research studies investigating PD-related rigidity have observed medication induced changes in rigidity in the absence of changes in the magnitude of reflex responses [14,15,19]. A study investigating the crossed-effect, defined as enhanced rigidity in response to a contralateral activation maneuver, reported significant increases in rigidity associated with a contralateral muscle contraction and reductions in rigidity in response to medication [15]. However, the medication-induced reductions in rigidity were observed without concurrent reductions in reflex responses to stretch and shortening. The authors suggested that a potential explanation may be that normalizing to background muscle activation in the ON-MED state functionally reduced the denominator, artificially increasing the normalized reflex amplitudes [15]. A second study investigating the effect of movement amplitude and velocity revealed similar medication-induced reductions in rigidity without systematic reductions in reflex amplitudes [14]. This study also normalized reflex responses to background muscle activation. Emerging literature suggests that methods currently used to quantify reflex responses may not adequately characterize reflex responses to anti-PD treatment.

The findings of the current study demonstrate that when EMG amplitudes are normalized by dividing the reflex amplitudes by pre-movement background EMG amplitudes, no medication effect can be observed. However, when raw EMG amplitudes (RAW) or EMG amplitudes normalized by subtracting the background signal (MINUS) were examined, medication-induced reductions in reflex amplitudes were observed. These reductions in reflex amplitudes were associated with significant improvements in mechanical measures of rigidity including reductions in rigidity work scores and increases in moment-angle plots. Previous research has demonstrated that reflex responses to stretch are sensitive to the amplitude of background muscle activation in individuals with PD [10]. This sensitivity to resting hypertonia has given rise to our current methodology of normalizing reflex responses to the EMG amplitudes preceding activity [10]. However, as demonstrated by these data, normalizing to background muscle activation by division may mask the effects of anti-PD treatment as both dopaminergic medication and deep brain stimulation have been demonstrated to reduce resting hypertonia associated with PD [23]. By reducing the magnitude of EMG associated with resting hypertonia, the value of the denominator used to normalize reflex responses decreases, artificially increasing the calculated reflex magnitude in the ON-MED condition in individuals with PD. Though normalized EMG amplitudes using subtraction would also be effected by medication-induced reductions in background EMG amplitudes, the current data demonstrate that the effect of medication was not masked. Therefore, existing literature investigating PD-related rigidity as a function of reflex responses to muscle stretch and shortening using division-based normalization techniques may not accurately represent the efficacy of anti-PD interventions and should be interpreted in light of the current findings.

The current study presents novel findings regarding current research methods that may be applicable to clinical readers of research. Though these findings identify potential methodological issues that need further consideration, the authors acknowledge several limitations to the current study. One limitation is the relatively small sample size used in this study. The recruitment of only 12 individuals with PD to participate in the study suggests that our findings may not be generalizable to the greater population and lack sufficient power to find statistically significant differences. However, the use of a repeated measures within-subject design improves the statistical power. Another potential limitation is the use of raw EMG signals to quantify medication-induced changes in reflex response following 45 to 60 minutes of rest between medication states. However, EMG electrodes were not removed nor adjusted between OFF- and ON-MED testing protocols suggesting that testing conditions were identical between the two medication states.

In conclusion, the findings of this study suggest that current normalization techniques used to quantify the amplitude of reflex responses to passive stretch and shortening may not be appropriate, may hinder interpretation of reflex activity and may mask the effects of anti-PD treatments. While the use of raw EMG signals may allow for within-subject comparison in a study using repeated measures design, other normalization methods should be considered when using a between-subjects or mixed-model analysis.

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