Annals of Biomedical Engineering, Vol. 42, No. 9, September 2014 (© 2014) pp. 1901–1912
DOI: 10.1007/s10439-014-1036-2

Neuromuscular Complexity During Gait is not Responsive to Medication in Persons with Parkinson's Disease

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(*Received 22 January 2014; accepted 19 May 2014; published online 28 May 2014*)

Associate Editor Thurmon E. Lockhart oversaw the review of this article.

Abstract—The purpose of this study was to investigate the effects of dopaminergic therapy on neuromuscular complexity during gait and on the relationship between neuromuscular complexity and gait speed in persons with Parkinson's disease (PD). Nine persons with PD walked at self-selected speed for 5 min after having withdrawn from dopaminergic medication for at least 12 h and while optimally-medicated. Electromyographic recordings were taken from eight leg muscles bilaterally. Non-negative matrix factorization was applied to reduce the dimensionality of the electromyographic signals into motor modules. We assessed neuromuscular complexity by investigating the number, structure, and timing of the modules. We also investigated the influence of dopaminergic medication on the relationships between neuromuscular complexity and gait speed. Though gait speed increased significantly after medication intake, medication did not affect neuromuscular complexity. Neuromuscular complexity was significantly associated with gait speed only while the participants were medicated. Thus, the supraspinal structures that govern neuromuscular complexity during gait do not appear to be solely dopaminergically-influenced in PD. The lack of dopaminergic influence on neuromuscular complexity may explain why persons with PD exhibit gait slowness even while medicated, and an intervention that restores neuromuscular complexity may result in gait speed improvement in PD.

Keywords—Motor modules, Muscle, Lower extremity, Electromyography, Dopamine, Levodopa, Non-negative matrix factorization, Decomposition.

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INTRODUCTION

Human locomotion requires precise coordination of a large number of descending muscle activation signals to produce an efficient gait pattern. The dimensionality of this seemingly complex control system can be reduced by considering individual muscle activation patterns as components of motor modules.[19] Motor modules may allow for more efficient motor control by the central nervous system, as several studies spanning both gait and postural control tasks have demonstrated that activation of a relatively small number of motor modules can represent activity across a much larger number of muscles with a high degree of accuracy.[2,18,19,25,36–38]

Analyses of motor modules reveal the neuromuscular complexity of walking by quantifying how accurately physiological muscle activation patterns can be approximated by computational reconstruction. These analyses hold advantages over traditional analyses of muscle activation patterns in that they are entirely objective and provide quantitative data about the coordination of muscle patterns through computational reconstruction of electromyography (EMG) signals rather than subjective inspection. For instance, neuromuscular complexity can be quantified by determining the number of modules necessary for the reconstruction to account for a predefined threshold (typically, 90 or 95%) of variability in the physiological EMG signal. Alternatively, neuromuscular complexity can be quantified using the opposite approach by calculating the percentage of variability in the physiological EMG signal that is accounted for by a predefined number of modules. Herein, we quantify neuromuscular complexity using both methods. In

both approaches, neuromuscular complexity is thought to be simplified if the EMG pattern is more "easily" reconstructed by the computational analysis; that is, we consider neuromuscular complexity to be simplified if fewer modules are needed to account for a predefined amount of variability in the EMG signal or if a certain number of predefined modules account for more of the variability in the EMG signal.

Motor module analyses have recently revealed simplification of neuromuscular complexity in multiple populations characterized by gait difficulty, including persons post-stroke[10] and with Parkinson's disease (PD).[28] That is, these populations generally require fewer modules to reconstruct physiological EMG signals measured during gait when compared to healthy adults. The simplification of neuromuscular complexity during gait observed in these populations has recently become a topic of considerable interest, as investigators have described robust relationships between simplified neuromuscular complexity and several clinically-observable gait deficits (e.g., decreased gait speed, reduced propulsion, and gait asymmetry) in persons post-stroke and with PD.[1,10,28] Recent evidence suggests that neuromuscular complexity can be altered with locomotor training in persons post-stroke and, importantly, these changes in EMG patterns led to significant improvement in gait speed and symmetry.[31] Indeed, the clinical impact of investigations of neuromuscular complexity is increasing in clarity.

Despite these findings, the neural mechanisms that underlie neuromuscular complexity during gait are currently unknown. Investigations of animal movements have suggested that motor modules may be controlled largely through brainstem and spinal mechanisms.[8,14,29] A recent study of feline postural responses suggested that neuromuscular complexity is unlikely to be controlled within the spinal cord alone, noting marked changes in the number and structure of the modules after spinal transection.[9] Taken with findings demonstrating that neuromuscular complexity during human gait is affected by supraspinal pathologies such as stroke and PD,[10,28] it seems likely that motor modules are influenced by higher neural structures.

Though the specific neural structures that govern these modules are currently unclear, they appear to play a role in the gait dysfunction observed in persons with PD.[28] Gait deficits in PD have long been an important topic in PD research and remain among the strongest predictors of reduced quality of life within this population.[13] Of these, a significant reduction in gait velocity is perhaps the most prominent.[21] As PD results in dopaminergic degeneration of the basal ganglia, dopaminergic therapy has been the "gold standard" treatment for motor symptoms of PD since the 1960s.[4,11] However, not all parkinsonian gait features are dopaminergically-responsive. Previous studies described modest improvements in stride length and gait speed after dopaminergic intake,[5,22] though these parameters remain impaired relative to controls.[23] Precisely why gait speed is impaired in PD even after dopaminergic intake remains unclear, though we have recently observed that gait speed is strongly related to neuromuscular complexity in optimally-medicated persons with PD.[28] A better understanding of whether dopaminergic medication influences neuromuscular complexity during gait could provide important insight into the mechanisms underlying gait dysfunction in PD as well as the role of dopaminergic systems on modular control of human gait.

The primary purpose of this study was to compare the number, structure, and timing of lower extremity motor modules during gait when persons with PD are withdrawn from dopaminergic therapy (OFF meds) and when optimally-medicated (ON meds).The secondary purpose was to investigate relationships between neuromuscular complexity and gait speed in each medicated state. Based on our previous findings demonstrating associations between gait speed and neuromuscular complexity in PD,[28] we hypothesized that (1) persons with PD would exhibit further simplification of neuromuscular complexity during gait when OFF meds accompanied by disruptions in motor module timing and (2) neuromuscular complexity would be associated with walking speed in each medicated state. If true, these hypotheses would suggest that dopaminergic systems influence neuromuscular complexity during gait in humans, though probably not exclusively.

METHODS

Participants

Nine persons with mild-to-moderate PD participated (2 females, 65.7 ± 7.3 years, 174.2 ± 10.0 cm, 76.7 ± 9.4 kg, disease duration: 49.5 ± 18.6 months, OFF meds Unified Parkinson's Disease Rating Scale (UPDRS) Motor score: 41 ± 10, ON meds UPDRS Motor score: 37 ± 7). Diagnosis of idiopathic PD was confirmed by a movement disorders specialist at the University of Florida's Center for Movement Disorders and Neurorestoration. All participants were being treated with stable doses of orally-administered carbidopa/levodopa therapy. Four participants were also taking a dopamine agonist. All participants provided written informed consent before participating in the study as approved by the University Institutional Review Board.

Protocol

Participants arrived at the laboratory after having withdrawn from taking any anti-parkinsonian medication for at least 12 h.[5] Thirty-five passive reflective markers were attached to lower and upper body bony landmarks in accordance with the Vicon Plug-in-Gait marker set (Vicon Nexus, Oxford, UK). Bipolar surface electrodes were placed bilaterally over the soleus (SOL), medial gastrocnemius (GAS), tibialis anterior (TA), vastus medialis (VM), rectus femoris (RF), semimembranosus (SM), biceps femoris (BF), and the gluteus medius (GM). Surface EMG signals were recorded with a telemetric EMG system (1200 Hz; Konigsburg Instruments, Pasadena, CA). Kinematic data were collected using a seven-camera motion capture system (120 Hz; Vicon Nexus, Oxford, UK) while participants walked on an instrumented split-belt treadmill (Bertec Corporation, Columbus, OH) and overground. The EMG and kinematic data were time-synchronized and collected simultaneously.

All participants first performed ten overground gait trials at a self-selected comfortable pace (OFF meds OG) and then walked on the treadmill for 1 min at 1.0 m/s (OFF meds Fast) after a 2-min warm up at 0.5 m/s to accommodate to walking on the treadmill. They then walked on the treadmill at their preferred walking speed (OFF meds Pref) for 5 min while holding onto the handrails and wearing a harness that provided safety against falls but did not support body weight. Preferred walking speed during treadmill walking was determined using a technique outlined by Dingwell and Marin.[12] OFF meds OG was included to allow us to observe the effects of dopaminergic medication on gait speed in the participants' unconstrained, everyday walking environment as well as to investigate potential differences in neuromuscular complexity between treadmill and overground walking in PD. OFF meds Fast was included to investigate potential effects of treadmill speed on neuromuscular complexity in PD.

After completing the OFF meds sessions of testing, all participants took their daily medication and waited for 1 h before walking on the treadmill at the same speed they had previously selected while OFF meds(ON meds Pref). The reflective markers and EMG electrodes were left on the participants during the break so as not to alter their positioning. Participants also performed ten overground gait trials at a self-selected comfortable pace while ON meds (though EMG data was not collected here). They completed the motor portion (Section III) of the UPDRS while being video-recorded prior to treadmill walking while both OFF and ON meds. The UPDRS videos were later scored by a movement disorders-trained neurologist who was blinded to the medicated state of each participant.

Muscle Synergy Analysis

We analyzed the data using methodology similar to previous research on neuromuscular complexity during gait in PD.[28] The raw EMG signals were high-pass filtered (35 Hz) with a zero lag fourth-order Butterworth filter, demeaned, rectified, and then low-pass filtered (7 Hz) with a zero lag fourth-order Butterworth filter.[10,28] After processing, we normalized the amplitude of each EMG signal to its peak value during the trial and time-normalized each signal to 100% of the gait cycle. For each individual leg (nine participants—18 total legs), the processed physiological EMG signals (EMG_0) for all muscles were combined into a matrix containing eight rows (one row for each muscle being recorded) and one column for each EMG_0 data point. Thus, the total number of columns for a given subject and leg was 101 (the number of data points after temporal normalization to 100% of the gait cycle) multiplied by the total number of gait cycles collected (therefore, the number of gait cycles collected for each participant depended on the participant's cadence).

Our muscle synergy analysis was conducted using the non-negative matrix factorization (NNMF) algorithm in MATLAB (Mathworks, Natick, MA) altered to implement the methodology previously described by Ting and Chvatal.[35] For each subject, we applied our NNMF algorithm to the matrices containing the EMG_0 data across all gait cycles from OFF meds Pref, OFF meds Fast, OFF meds OG, and ON meds Pref separately. The number of modules, n, was initially specified. The NNMF algorithm subsequently decomposed the EMG_0 signals into n motor modules, where each module was defined by a linear system in which a single muscle weighting vector was scaled by a corresponding time-varying activation profile. The muscle weighting vectors were contained within an $8 \times n$ matrix that identified the relative contributions of each of the 8 individual muscles to each of the n modules(each weighting vector was scaled such that the maximum value in the vector was equal to 1). The activation profiles were organized in an $n \times 101$ matrix that represented the firing patterns of the n modules across the 101 points of the temporally-normalized gait cycle. Reconstructed EMG signals (EMG_r) were then generated by multiplying the $8 \times n$ matrix of muscle weightings by the $n \times 101$ matrix of activation timing profiles on a cycle-by-cycle basis. Each gait cycle was analyzed separately with the assumption that muscle weightings were fixed for that cycle while activation profiles were allowed to vary across gait cycles.[35] The NNMF algorithm minimized the sum of

squares of the errors (Σ $(EMG_0 - EMG_r)^2$) by adjusting each module's muscle weighting vector and activation profile given our a priori restrictions on the number of modules included in the analysis.

The NNMF analyses were performed by iteratively increasing n from one to six modules. The accuracy of our EMG reconstructions by the NNMF at each iterative reconstruction assuming n modules was quantified by calculating the percent variability accounted for $(\%VAF = 1 - (EMG_0 - EMG_r)^2 / EMG_0^2)$ for all muscles analyzed together.[36] For a specified number of modules, a higher %VAF is indicative of less neuromuscular complexity, as the EMG_r explained a higher amount of the variability in EMG_0. We considered a reconstruction to be acceptably accurate if the total %VAF across all reconstructions collectively reached 95%.[18,19] To be clear, this meant that not all muscles were required to reach 95% VAF individually, but rather it was necessary that the reconstruction of the entire eight-muscle system (EMG_r) meet this threshold. However, in addition to calculating the total %VAF for the entire reconstruction collectively, we also calculated %VAF for individual muscle signals to investigate the accuracy of individual muscle signal reconstructions, though no minimum %VAF was required for these individual reconstructions when considering whether or not a given configuration reached our overall 95% VAF threshold.[36]

The structure of the motor modules was organized based on the dominant contributors to their respective muscle weighting vectors. The dominant contributor to each module was defined as the muscle contributing the largest individual weight to the module's muscle weighting vector. For example, module one was defined by SOL as the dominant contributor since SOL exhibited the largest weight within this module; module two was defined by TA as the dominant contributor, etc. Once the structure of the motor modules was organized for each participant, the amplitude and timing of the modules' activation profile peaks were calculated. All parameters were calculated for each leg individually and thus we assumed every leg to be independent in the statistical analyses (i.e., each participant contributed two legs).[10,28]

Overground Gait Analysis

Overground gait data was collected over ten consecutive passes along a 12-meter walkway (this resulted in 10–20 strides per participant, depending on the participant's stride length and cadence, as some of the walkway was outside the view of the cameras). Stride length was calculated as the anterior-posterior displacement of the ankle marker between consecutive heel-strikes of the same limb. Stride time was calculated as the time interval between these consecutive heel-strikes. Step length was calculated as the anterior-posterior displacement of the ankle markers between limbs at heel-strike. Step time was calculated as the time interval from heel-strike to the subsequent heel-strike of the contralateral limb. Walking speed was calculated as stride length divided by stride time.

Statistical Analysis

All variables were first tested for normality using Shapiro–Wilk tests. To confirm that the dopaminergic medication resulted in the expected improvement in PD motor symptoms and overground spatiotemporal gait parameters, we performed paired samples t-tests comparing UPDRS motor scores, overground walking speed, stride length, stride time, step length, and step time between medicated states. A Pearson's Chi Squared test analyzed differences between ON meds Pref and OFF meds Pref in the proportions of PD participants accessing varying numbers of modules at 95% VAF. As a large majority of the legs (15 of the 18 legs studied) reached 95% VAF with four modules during both ON meds Pref and OFF meds Pref, our subsequent analyses were focused on the structure and timing of the four-module configuration. To be clear, this meant that the four-module configurations were included in the analyses even for the three legs that required five modules to reach 95% VAF. To investigate whether dopaminergic medication affected neuromuscular complexity during comfortable treadmill walking, we performed paired samples t-tests to compare 1) the total %VAF by one through six modules, and 2) the %VAF for individual muscles by four modules between medicated states. To investigate whether dopaminergic medication affected the muscle weighting vectors and/or activation profiles (i.e., the characteristics of the modules), we performed paired samples t-tests to compare the amplitude of the individual contribution of each muscle to the muscle weighting vectors for four modules as well as the amplitude and timing of activation profile peaks for four modules between medicated states.

It was possible that the results here were influenced by our decision to maintain a consistent treadmill speed between the OFF meds Pref and ON meds Pref testing sessions (i.e., the participants were walking slower than their preferred speed during ON meds Pref), though manipulation of walking speed does not affect neuromuscular complexity in healthy adults.[19] To investigate whether neuromuscular complexity was affected by changes in treadmill speed, we performed a paired samples t test to compare the total %VAF by four modules between OFF meds Pref and OFF meds

Fast and a χ^2 test to analyze differences in the proportions of PD participants accessing varying numbers of modules at 95% VAF during OFF meds Pref and OFF meds Fast.

We also aimed to investigate whether gait deficits in PD were related to simplified neuromuscular complexity while OFF and ON meds, as we have previously shown this to be the case while ON meds.[28] We investigated relationships between neuromuscular complexity (in terms of total %VAF by four modules) during comfortable treadmill walking and spatiotemporal overground gait parameters by performing two-tailed Pearson's correlations between the following pairs of variables:

(1) The OFF meds Pref total %VAF by four modules vs. OFF meds overground spatiotemporal gait parameters.
(2) The ON meds Pref total %VAF by four modules vs. ON meds overground spatiotemporals gait parameters.
(3) The change in total %VAF by four modules from OFF meds Pref to ON meds Pref vs. OFF meds-ON meds change in overground spatiotemporal gait parameters.

We investigated relationships between neuromuscular complexity during treadmill walking and spatiotemporal parameters of overground walking rather than treadmill-to-treadmill or overground-to-overground relationships for two reasons. First, we deemed it important to have a large, reliable dataset (on the order of >100 strides) from which to assess neuromuscular complexity, hence inclusion of the treadmill rather than overground data. Second, we chose to relate neuromuscular complexity to overground gait parameters rather than treadmill parameters because the self-selected comfortable treadmill speed was influenced not only by motor deficits of PD, but also the participants' comfort with the treadmill and concern about selecting a speed that could be comfortably maintained for five consecutive minutes.

It was possible that neuromuscular complexity during treadmill walking was not representative of neuromuscular complexity during overground walking in PD, thus rendering the correlational analyses described above inappropriate. To examine whether neuromuscular complexity differed between treadmill and overground walking, we performed a paired samples t tests to compare the total %VAF by four modules between OFF meds Pref and OFF meds OG and a χ^2 test to analyze differences in the proportions of PD participants accessing varying numbers of modules at 95% VAF during OFF meds Pref and OFF meds OG. Importantly, we also performed two-tailed Pearson's correlations to investigate relationships between neuromuscular complexity (in terms of total %VAF by four modules) during OFF meds Pref and OFF meds Fast as well as during OFF meds Pref and OFF meds OG. We concluded that, even if neuromuscular complexity differed between treadmill and overground walking, the analyses relating neuromuscular complexity on the treadmill to spatiotemporal parameters of overground walking would remain valid as long as neuromuscular complexity during treadmill walking was associated with neuromuscular complexity during overground walking.

We also performed an additional two-tailed Pearson's correlation to investigate whether age impacted neuromuscular complexity by comparing the OFF meds Pref and ON meds Pref total %VAF by four modules vs. age. All levels of significance were set at $p < 0.05$.

RESULTS

Effects of Dopaminergic Therapy on Spatiotemporal Gait Parameters and Neuromuscular Complexity

We first confirmed that the administration of dopaminergic medication significantly improved global PD-related motor impairment as measured by the motor portion of the UPDRS ($p = 0.04$). Regarding the gait response to medication, we observed a significant increase in self-selected overground walking speed from OFF meds to ON meds ($p = 0.01$; Fig. 1a). This improvement is considered a moderate-to-large clinically important difference.[16] We also observed significant increases in stride length and step length as well as significant decreases in stride time and step time from OFF meds to ON meds (Table 1).

We quantified neuromuscular complexity using two metrics: the total %VAF by the modules (i.e., how accurately the NNMF algorithm reconstructed the physiological EMG signals assuming a given number of modules– a higher number thus indicates simpler control) and the number of modules required to reach 95% VAF (i.e., the number of modules required for the NNMF algorithm to reconstruct the physiological EMG signals with a specific degree of accuracy—here, a smaller number indicates simpler control).[28] The analyses did not detect a significant difference in the total %VAF for any number of modules or a difference in the proportion of legs requiring four or five modules to reach 95% VAF (all participants reached 95% VAF with four or five modules) between OFF meds Pref and ON meds Pref (both $p > 0.05$, Figs. 1b and 1c, respectively). There were also no significant differences between medicated states in the %VAF for reconstructions of individual muscle EMG signals (mean %VAF ± standard deviation, OFF meds vs.

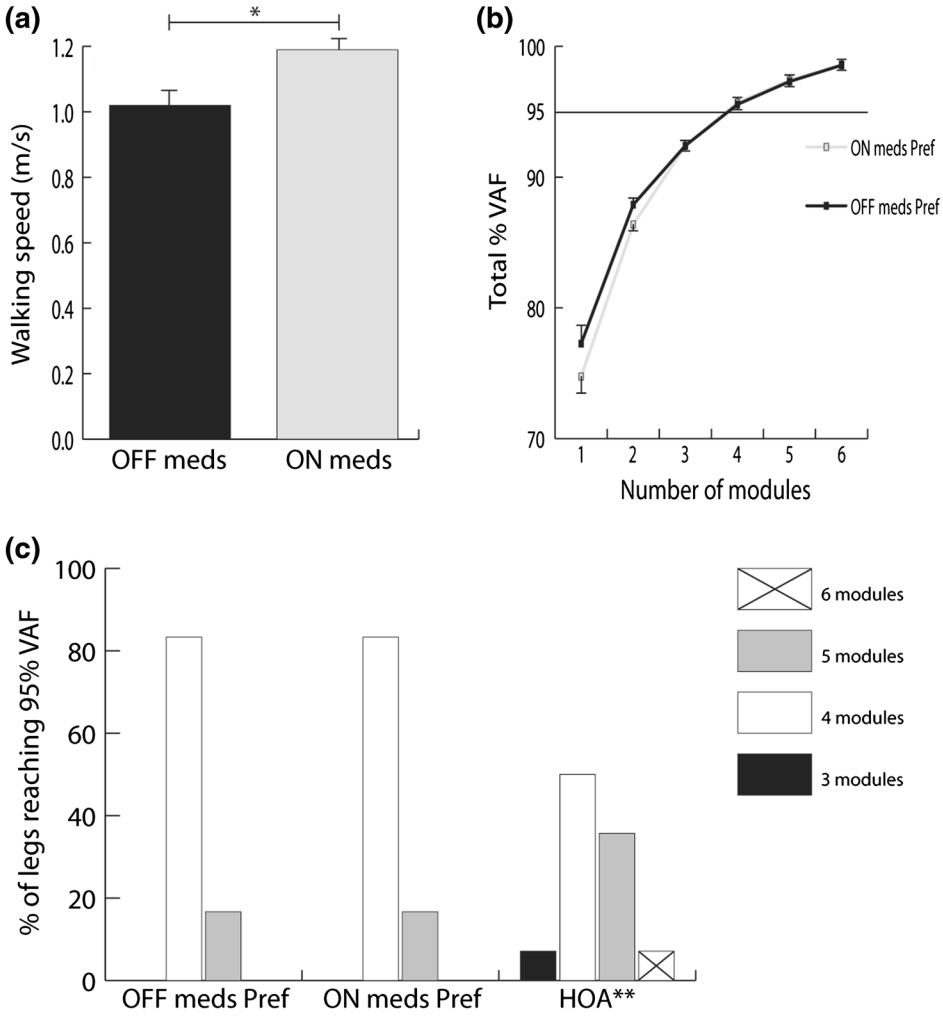


FIGURE 1. (a) Overground gait speed for the participants with PD when OFF (black) and ON (gray) meds. (b) Total percent variability accounted for (%VAF) with one to six modules assumed during OFF meds Pref (black) and ON meds Pref (gray). (c) The percentage of legs that reach 95% total VAF at three (black), four (white), five (light gray), and six (dark gray) modules for persons with PD during OFF meds Pref and ON meds Pref as well as healthy older adults (HOA). *$p < 0.05$, **Data from Ref. 28, included for reference. Error bars indicate standard error.

TABLE 1. Spatiotemporal gait parameters during overground gait in the medicated and unmedicated states.

	Stride length (m)	Step length (m)	Stride time (s)	Step time (s)
OFF meds	1.19 ± 0.16	0.57 ± 0.08	1.18 ± 0.13	0.59 ± 0.07
ON meds	1.32 ± 0.16	0.63 ± 0.07	1.11 ± 0.11	0.55 ± 0.06
Change	0.13 ± 0.11**	0.06 ± 0.05**	−0.07 ± 0.07*	−0.04 ± 0.04*

OFF meds—after 12-h medication withdrawal, ON meds—1 h after taking medication, *$p < 0.05$, **$p < 0.01$.

ON meds: SOL: 96.2 ± 1.9% vs. 96.2 ± 2.2%, GAS: 95.2 ± 1.9% vs. 94.5 ± 2.9%, TA: 96.1 ± 3.6% vs. 95.4 ± 5.0%, VM: 93.4 ± 2.2% vs. 93.3 ± 2.6%, SM: 94.9 ± 2.6% vs. 95.4 ± 2.0%, BF: 95.1 ± 2.2% vs. 95.6 ± 2.2%, RF: 95.6 ± 2.0% vs. 94.7 ± 2.8%, GM: 93.9 ± 2.2% vs. 94.0 ± 2.2%; all $p > 0.05$)between OFF meds Pref and ON meds Pref.

We also did not observe any differences in the structure of the modules (i.e., the individual contributions from each muscle to the muscle weighting vectors)in the four-module configuration (Fig. 2) between OFF meds Pref and ON meds Pref. However, the participants did show a significant increase in the magnitude of the first peak of the activation profile of

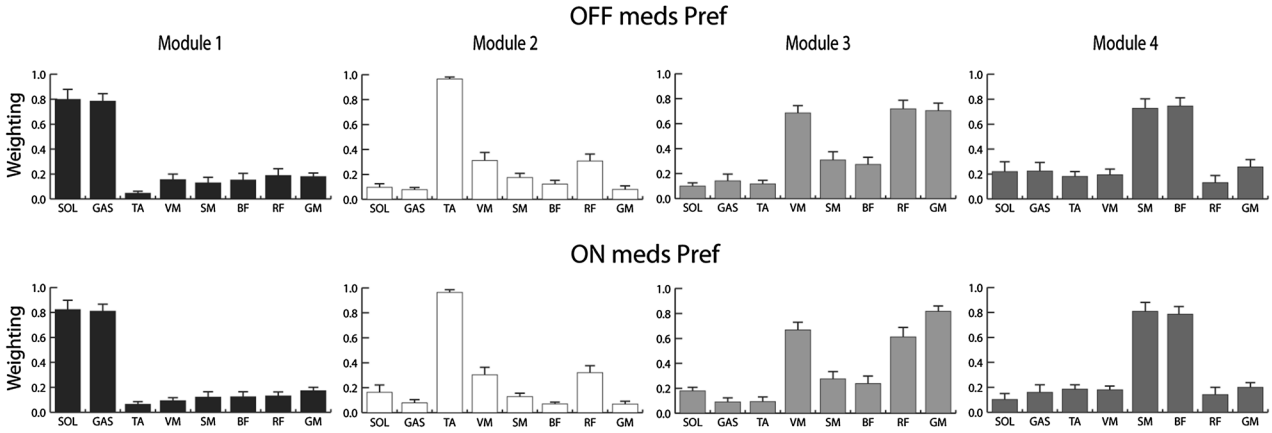


FIGURE 2. Mean contributions of each of the eight lower extremity muscles to the muscle weighting vectors with four modules assumed during OFF meds Pref (top) and ON meds Pref (bottom).The structure of the motor modules was organized based on the dominant contributors to their respective muscle weighting vectors. Error bars indicate standard error.

the third module during ON meds Pref compared to OFF meds Pref ($p = 0.02$; Fig. 3). We did not observe differences between ON meds Pref and OFF meds Pref in the timing or amplitude of any other module's activation profiles when assuming four modules.

Effects of Treadmill Speed on Neuromuscular Complexity

We did not observe a significant difference when comparing the total %VAF by four modules during OFF meds Pref (mean treadmill speed ± standard deviation: 0.86 ± 0.14 m/s) to the total %VAF by four modules during OFF meds Fast ($p > 0.05$; Fig. 4a) or the percentage of legs requiring four or five modules to reach 95% VAF ($p > 0.05$; Fig. 4b). Consistent with previous findings in young adults,[19] neuromuscular complexity was not affected by treadmill speed in persons with PD.

Relationships Between Total %VAF and Spatiotemporal Gait Parameters

Consistent with previous findings,[28] we observed significant negative associations between the total %VAF at the four-module configuration of ON meds Pref and overground walking speed when the participants were ON meds when the legs were analyzed individually (i.e., each participant has two total %VAF values – one for each leg - at a single walking speed; $r = -0.53$, Cohen's $d = -1.25$, $p = 0.02$, Fig. 5a) and when the total %VAF was averaged between legs for each participant (i.e., each participant has one total %VAF value at a single walking speed; $r = -0.79$, $d = 2.56$, $p = 0.01$, Fig. 5b). These associations resulted from a non-significant positive relationship between total %VAF and stride time ($r = 0.36$, $d = 0.77$, $p = 0.14$) and non-significant negative relationship between total %VAF and stride length ($r = -0.31$, $d = -0.65$, $p = 0.21$). Interestingly, we did not observe a significant association between total %VAF during OFF meds Pref and overground walking speed when the participants were OFF meds ($r = -0.25$, $d = -0.52$, $p = 0.31$, Fig. 5c). Further, the changes in the total %VAF between OFF meds Pref and ON meds Pref at the four-module configuration were not significantly associated with changes in overground walking speed between medicated states. We did not observe significant associations between total %VAF and any other spatiotemporal gait parameters in either medicated state, nor did we observe significant associations between age and total %VAF in either medicated state ($r = -0.28$ and -0.30, $d = -0.59$ and $d = -0.63$, $p = 0.26$ and $p = 0.23$ for OFF meds Pref total %VAF and ON meds Pref total %VAF vs. age, respectively; ON meds Pref total %VAF vs. age shown in Fig. 5d).

Differences in Neuromuscular Complexity Between Treadmill and Overground Walking in Persons with PD

We did observe a significant difference when comparing the total %VAF by four modules during OFF meds Pref to the total %VAF by four modules during OFF meds OG ($p < 0.001$; Fig. 4a) and the percentage of legs requiring four or five modules to reach 95% VAF ($p < 0.01$; Fig. 4b). Our previous data showed that neuromuscular complexity is simplified in persons with PD relative to healthy older adults[28] during treadmill walking; these findings expand upon this data to demonstrate that neuromuscular complexity is further simplified in overground as compared to treadmill walking within this population.

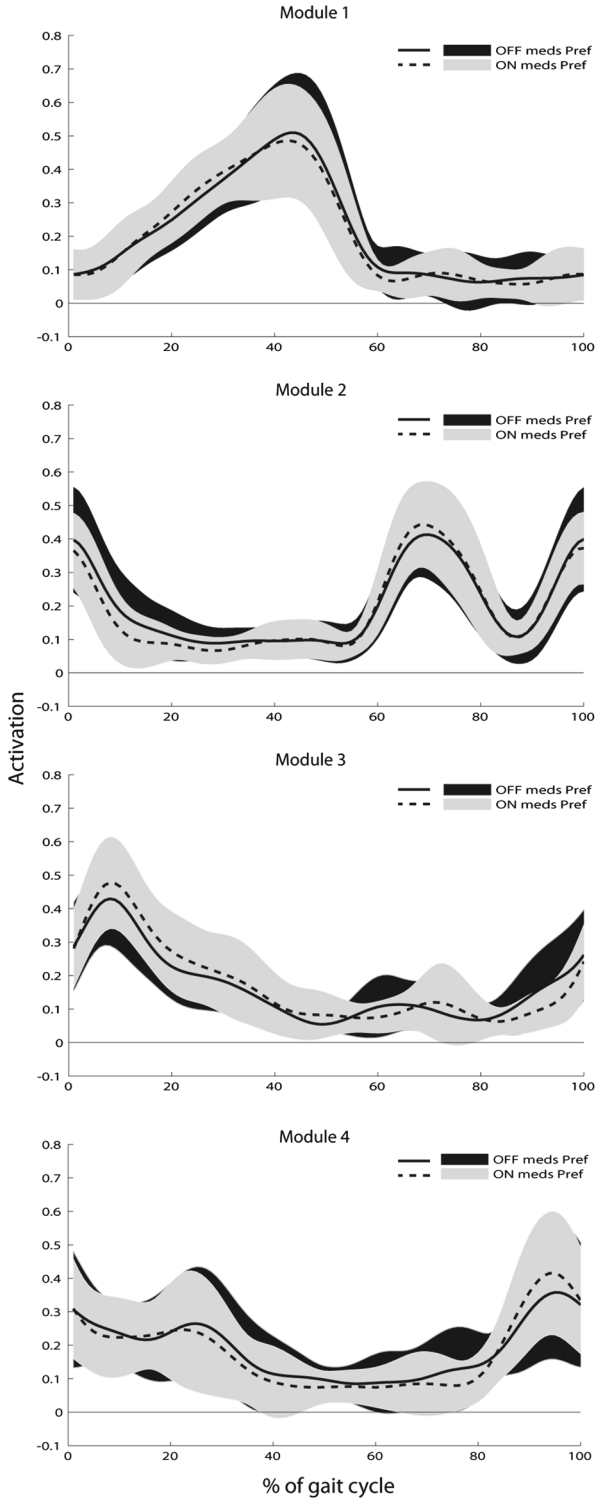


FIGURE 3. Ensemble activation profiles (normalized to 100% of the gait cycle) for each of the four modules during OFF meds Pref (dashed line, gray) and ON meds Pref (solid line, black). Lines indicate the group mean while shading indicates standard deviation. *Peak value is significantly different between medicated states ($p < 0.05$).

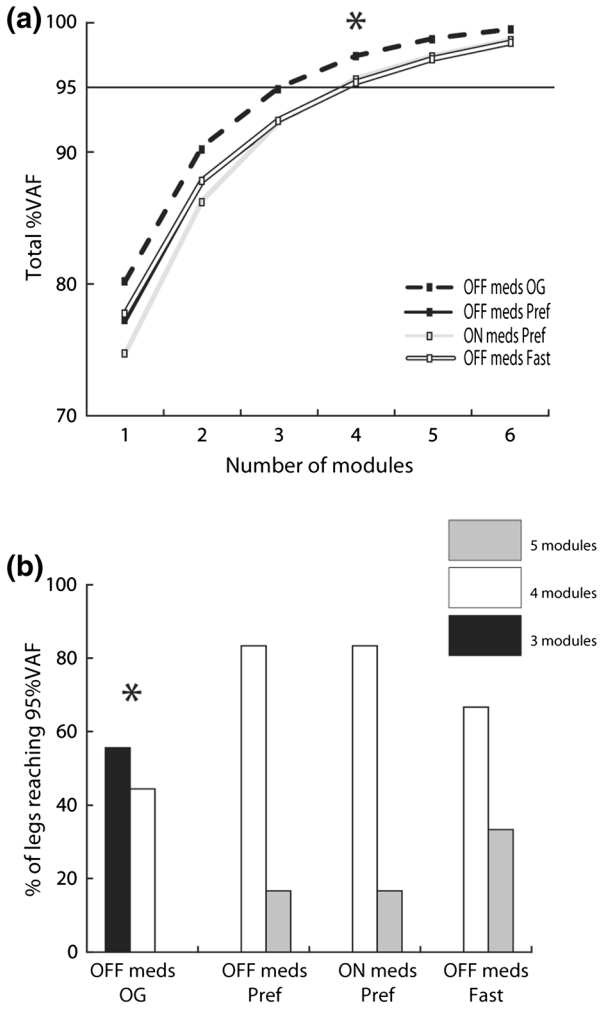
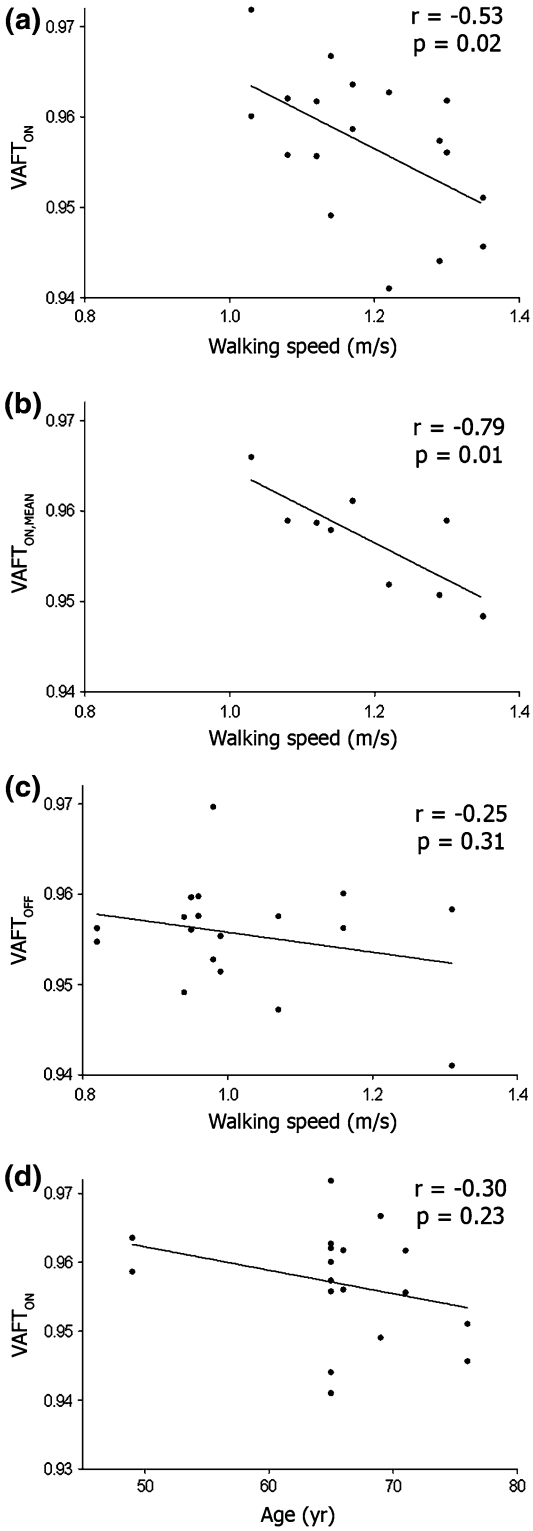


FIGURE 4. (a) Total percent variability accounted for (%VAF) with one to six modules assumed during OFF meds OG (black dashed), OFF meds Pref (black solid), ON meds Pref (gray), and OFF meds Fast (white). (b) The percentage of legs that reach 95% total VAF at three (black), four (white), and five (gray) modules for persons with PD during OFF meds OG, OFF meds Pref, ON meds Pref, and OFF meds Fast. *OFF meds OG is different than all other conditions with $p < 0.05$. Error bars omitted in Fig. 4a to preserve figure clarity among the four conditions.

Relationships Between Total %VAF Across Multiple Walking Tasks

Because neuromuscular complexity differed between overground and treadmill walking in our sample of participants with PD, we also investigated whether neuromuscular complexity was related between the three OFF meds walking conditions (OFF meds Pref, OFF meds Fast, and OFF meds OG). For instance, if a participant demonstrated simplified complexity during treadmill walking, would we expect that he/she would



◀FIGURE 5. Associations (assuming four modules) between (a) ON meds walking speed and ON meds Pref total %VAF with each leg treated independently, (b) ON meds walking speed and ON meds Pref total %VAF with each participant's legs averaged to one %VAF value, (c) OFF meds walking speed and OFF meds Pref total %VAF with each leg treated independently, and (d) age and ON meds Pref total %VAF with each leg treated independently. Associations shown in (a) and (b) are statistically-significant ($p < 0.05$) while those shown in (c) and (d) are not ($p > 0.05$).

also demonstrate simplified complexity during overground walking? Indeed, we observed significant relationships between total %VAF by four modules during OFF meds Pref and both total %VAF by four modules during OFF meds Fast ($r = 0.56$, $d = 1.35$, $p = 0.02$) and total %VAF by four modules during OFF meds OG ($r = 0.53$, $d = 1.25$, $p = 0.02$).

DISCUSSION

Even while ON meds, persons with PD exhibit simplified neuromuscular complexity during gait such that fewer motor modules are generally needed to reconstruct accurately lower extremity EMG signals compared to healthy adults.[28] In this study, we demonstrated that simplified neuromuscular complexity during gait in persons with PD is largely non-responsive to dopaminergic therapy. Contrary to our hypotheses, the number, structure, and timing of the modules observed during walking were almost completely unaffected by dopaminergic medication(only the activation profile of the third module was altered by dopaminergic medication, and even then, the change was small). Our findings also suggest that the simplification of neuromuscular complexity during gait in PD cannot be treated by dopaminergic therapy alone and is related to walking speed decrements within this population. It appears that, in this sample, dopaminergic pathways (which include dopaminergic connections intrinsic to the basal ganglia and midbrain and their downstream connections to the cortex and spinal cord, for example) have little influence on neuromuscular complexity during gait.

Our results demonstrating an association between walking speed and neuromuscular complexity only while persons with PD are ON meds further the notion that dopaminergic medication affects only some neural substrates that influence locomotion.[5,22,23] First, let us entertain potential contentions to these findings. It could be argued that our results may be influenced by the differences in self-selected walking speed between medicated states. However, Ivanenko *et al.*[19] previously demonstrated that, beyond changes in the timing of muscular activation patterns necessary to alter the pacing of the legs, walking speed does not affect neuromuscular complexity in healthy adults (i.e., %VAF remains similar assuming the same number of modules across several walking speeds). We were able to replicate these findings in persons with PD in the present study. Thus, we can be reasonably certain that these

results stem from the neurological deficits underlying the walking speed decrements in PD rather than simply a decrease in walking speed independent of neurologic insult. Moreover, one may suggest that the clinical significance of these findings is limited due to the seemingly small range in %VAF values across the participants during comfortable treadmill walking (as the lowest %VAF is slightly greater than 0.94 and the highest is slightly greater than 0.97; Fig. 4a). However, to provide perspective as to the magnitude of this difference, a %VAF difference of 0.03 (or 3%) appears to be roughly twice the average difference in %VAF between a control limb and a paretic limb in the post-stroke study previously conducted by Clark *et al.* (see Fig. 3 in Ref. 10). Thus, the relationships we report do not appear to be statistical artifacts (as they have been reported now in two independent samples of persons with PD[28]), but rather are demonstrative of an important association between the neural structures governing neuromuscular complexity and gait speed in persons with PD.

This study also demonstrated that neuromuscular complexity during treadmill walking is significantly associated with neuromuscular complexity during overground walking in persons with PD. This is an important finding because it suggests that we can investigate neuromuscular complexity during unconstrained overground gait with lab-based treadmill studies that allow for collection of a much larger number of continuous strides. It should be noted that we did observe simpler neuromuscular complexity during overground gait compared to treadmill walking in PD. It is possible that neuromuscular control of gait becomes more complex during treadmill walking in PD because the treadmill improves PD gait by providing an external cue[34]; however, the mechanisms underlying the difference between neuromuscular complexity during treadmill and overground gait in PD should be further explored.

In the unmedicated PD state, it is likely that several neural processes with locomotor influence are dysfunctional (see reference 3 for review). Some of these processes are dopaminergically-responsive and thus, after dopaminergic intake, gait speed is partially (though not wholly) restored. Our findings reveal that the processes influencing neuromuscular complexity are not among these dopaminergically-responsive processes, but rather it appears that simplified neuromuscular complexity may be a contributing factor to the gait speed decrement observed in PD even after dopaminergic intake. Thus, an intervention that affects neuromuscular complexity may lead to significant walking speed improvement within this population. A recent study suggested that manual body weight-supported treadmill training altered several characteristics of neuromuscular complexity during gait in persons post-stroke, including the number and timing of the motor modules.[31] Interestingly, the restoration of neuromuscular complexity led to marked improvement in several measures of global gait function.[31] These findings are exciting in that they demonstrate the potential for at least partial restoration of neuromuscular complexity following a behavioral intervention. However, the neuropathology underlying stroke is very different from that of PD; thus, the neural changes that resulted from the locomotor training intervention (if indeed the improvements resulted from changes in the central nervous system) may or may not be relevant to gait rehabilitation in PD.

As the neural targets for neuromuscular complexity restoration during gait in PD remain unclear, a better understanding of these mechanisms could have profound impact on gait rehabilitation in PD. We previously speculated that disruptions in dopaminergic pathways intrinsic to the basal ganglia as well as connections between the basal ganglia and the pedunculopontine nucleus (PPN), a cholinergic nucleus located in the brainstem, may simplify neuromuscular complexity during gait in PD.[28] As our results now suggest that it is unlikely that dopaminergic pathways influence neuromuscular complexity, it seems that brainstem structures may play a significant role. Indeed, previous studies have suggested that motor modules in other species are influenced by supraspinal structures. Chvatal *et al.*[9] recently investigated postural responses in spinal cats, reporting disruptions in directional balance control and a reduction in modules after spinalization. Further, Roh *et al.*[29] demonstrated that an intact brainstem is necessary to produce a full repertoire of behavioral movements in the frog, as the movements and modules were disrupted when the brainstem was transected. It seems likely that the brainstem has significant influence on the neuromuscular control of human gait, though the role of the brainstem in human locomotion remains under investigation.

While the role of brainstem structures (specifically, the PPN) on locomotor control is not entirely understood in humans, it is well-established that PD results in degeneration of cholinergic neurons within the PPN.[7,17] Inearly PD[27] or even the absence of dopaminergic deficits,[20] the loss of these cholinergic neurons is related to gait dysfunction.[15,26] Further, decreased thalamic cholinergic innervations from the PPN has been strongly linked to decreased gait speed, increased falls, and postural instability in PD while dopaminergic degeneration alone appears to have a comparatively lesser effect.[6,7,24] Though this evidence highlights the brainstem as a likely contributor to gait function (and potentially, the control of neuromuscular

complexity during gait), it is possible that function of the PPN may rely in part upon dopaminergic projections.[30,32] Thus, given that we did not observe any effect of dopaminergic medication on neuromuscular complexity in this sample of persons with PD, the specific role of the brainstem on neuromuscular complexity during gait remains intriguing.

The activation profile of the third module was the lone characteristic of any module to be affected by dopaminergic medication. Thus, while it is unlikely that this lone change in the third module played an exclusive role in improving gait speed in the participants in this study, we feel it is important to discuss. The first peak of the third module was approximately 14% higher in amplitude, on average, when ON meds as compared to OFF meds. This module is characterized predominantly by knee extensor musculature (VM and RF), demonstrating a large peak of activity during early stance and a smaller peak around push-off as the leg transitions from stance to swing (similar to the first module described in reference 25). Therefore, we suggest that this increase likely serves to stabilize the knee during weight transfer in order to decelerate the center of mass in the sagittal plane.[25]

Our study is not without limitations. A relatively small sample of only nine participants (18 legs) were studied; however, considering the striking similarities between the modules ON meds Pref and OFF meds Pref and the fact that the number of modules required to achieve 95% VAF was unchanged between medicated states for all 18 legs, our findings appear quite robust. As we were primarily interested in the effects of dopaminergic therapy on the modules contributing to forward progression, our analysis was limited to include only musculature which contribute predominantly to movements in the sagittal plane. Our investigation was limited to persons with mild-to-moderate PD. Thus, the participants in this study generally exhibited only a mild improvement in the UPDRS motor score after dopaminergic intake (approximately 11%, on average), which would be considered a minimal-to-moderate improvement.[33] However, the subjectively-measured gross motor response to dopaminergic medication is less relevant to the current study than the objectively-measured gait response, which we observed to be moderate-to-large.[16] Investigation of destabilizing locomotor tasks (e.g., turning, obstacle avoidance, perturbed walking) and more severely impaired participants may further our understanding of neuromuscular complexity during gait in PD. Additionally, future research should explore interventions that can alter neuromuscular complexity during gait in PD. The current results suggest that treadmill-based interventions may show greater potential for increasing complexity than over-ground walking.

CONCLUSION

Neuromuscular complexity during gait is minimally affected by dopaminergic therapy in persons with PD, as the number, structure, and timing of the modules were largely similar between the medicated states. Thus, it appears that neuromuscular complexity during gait is not a dopaminergically-influenced process in humans. We also observed that the total %VAF by the modules is associated with walking speed in persons with PD when ON meds but not OFF meds, suggesting that simplified neuromuscular complexity and dopaminergic dysfunction are likely independent contributors to gait slowness in PD. The neural mechanisms underlying simplified neuromuscular complexity in PD remain puzzling, though it appears that interventions which restore neuromuscular complexity during gait may possess significant potential to improve gait speed in persons with PD.

ACKNOWLEDGMENTS

This work was supported in part by NIH grants 1R21AG033284-01A2 and UF National Parkinson's Foundation Center of Excellence. We would also like to thank Dr. Umer Akbar and Dr. Nawaz Hack for their assistance in scoring the UPDRS videos.

CONFLICT OF INTEREST

The authors declare that there are no relevant conflicts of interest.

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