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Neural coupling between upper and lower limb muscles in Parkinsonian gait

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HIGHLIGHTS

- Parkinson patients had a reduced common cortical drive to upper and lower limb muscles, possibly affecting interlimb coordination.
- As a compensation mechanism, bidirectional coupling between upper and lower limb muscles was enhanced in Parkinson patients.
- These results provide neural underpinning that arm swing instructions could facilitate Parkinsonian gait.

ABSTRACT

Objective: To explore to what extent neuronal coupling between upper and lower limb muscles during gait is preserved or affected in patients with Parkinson's Disease (PD).
Methods: Electromyography recordings were obtained from the bilateral deltoideus anterior and bilateral rectus femoris and biceps femoris muscles during overground gait in 20 healthy participants (median age 69 years) and 20 PD patients (median age 68.5 years). PD patients were able to walk independently (Hoehn and Yahr scale: Stage 2–3), had an equally distributed symptom laterality (6 left side, 7 both sides and 7 right side) and no cognitive problems or tremor dominant PD. Time-dependent directional intermuscular coherence analysis was employed to compare the neural coupling between upper and lower limb muscles between healthy participants and PD patients in three different directions: zero-lag (i.e. common driver), forward (i.e. shoulders driving the legs) and reverse component (i.e. legs driving the shoulders).
Results: Compared to healthy participants, PD patients exhibited (i) reduced intermuscular zero-lag coherence in the beta/gamma frequency band during end-of-stance and (ii) enhanced forward as well as reverse directed coherence in the alpha and beta/gamma frequency bands around toe-off.
Conclusions: PD patients had a reduced common cortical drive to upper and lower limb muscles during gait, possibly contributing to disturbed interlimb coordination. Enhanced bidirectional coupling between upper and lower limb muscles on subcortical and transcortical levels in PD patients suggests a mechanism of compensation.
Significance: These findings provide support for the facilitating effect of arm swing instructions in PD gait.

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative condition, characterized by a wide spectrum of motor and non-motor behavioural symptoms. The ability to walk is often impaired in PD patients, which typically manifests as reduced gait velocity and step length, increased asymmetry and reduced automaticity (Jankovic, 2008; Nanhoe-Mahabier et al., 2011). Besides alterations in the lower limb movements, upper limb functioning is also affected in PD gait, which is characterized by a reduced and more asymmetric arm swing (Huang et al., 2013; Lewek et al., 2010; Mirelman et al., 2016). In healthy human gait, arm swing is integrated into locomotion via tight interlimb coordination. This four limb gait pattern is driven by cyclic pattern generators in the spinal cord and brain stem, which are embedded in more widely distributed networks including cortical regions. In a

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recent study by our group in healthy gait we were able to demonstrate that besides sharing these common subcortical and cortical drivers, directional coupling between the upper and lower limb muscles also occurred via subcortical and transcortical pathways, indicating that arm swing could drive and shape the leg muscle activity and to a lesser extent vice versa (Weersink et al., 2021a). The combination of neural coupling by these common drivers and directional pathways allows efficient and synchronized interlimb coordination during healthy gait. Co-occurrence of the previously described upper and lower limb alterations in PD patients would suggest that this interlimb coordination during gait may be affected by PD, which was indeed observed in two previous studies (Nanhoe-Mahabier et al., 2011; Roemmich et al., 2013). Such disturbed interlimb coordination in PD patients might result from changes in neuronal coupling between upper and lower limb muscles. On the other hand, improved lower limb gait characteristics by instructing PD patients to enhance their arm swing (Behrman et al., 1998; Weersink et al., 2020,2018) suggests a level of preserved coupling between upper and lower limbs in PD patients. In the present study, we therefore explored to what extent the neuronal interlimb coupling underlying this four-limb coordination is either preserved or affected in PD patients.

Neuronal interlimb coupling during gait can be examined using time dependent intermuscular coherence analysis, which identifies the correlation between the activity of two muscles (e.g. shoulder and leg muscle) as a function of frequency and time related to the gait cycle. Using directional coherence analysis, this total coherence can subsequently be decomposed into three components according to time-lag, distinguishing directional connections between two muscles (i.e. arms to legs or vice versa) from two muscles receiving input from a common driver. Frequently studied frequency bands in such intermuscular coherence analyses include alpha (8–15 Hz), beta (15–30 Hz) and gamma (30–60 Hz) bands, because coherence in these frequency bands is proposed to originate from distinct neural origins (Hu et al., 2018; Jensen et al., 2018; Nojima et al., 2018). As muscular alpha oscillations are generally not synchronized with cortical activity, alpha band coherence is proposed to be of subcortical origin, especially of the reticulospinal pathway that plays a pivotal role in gait control (Baker and Baker, 2003; Conway et al., 1995; Grosse and Brown, 2003; Salenius et al., 1997). Synchronization between cortical and muscle activities has especially been reported in the beta band, suggesting intermuscular beta band coherence to be primarily associated with a corticospinal drive (Conway et al., 1995; Fisher et al., 2012; Gwin and Ferris, 2012; Mima et al., 2000; Power et al., 2006). Intermuscular gamma coherence has also been proposed to result from cortically generated signals, thus reflecting the involvement in efferent motor commands (Brown et al., 1998; Clark et al., 2013; Mima et al., 2000).

In PD, degeneration of dopaminergic cells within the substantia nigra pars compacta results in impaired function of their striatal projection sites. Affected cortico-striatal loops subsequently lead to pathological changes that also occur at cortical level. Especially reduced supplementary motor area (SMA) activity in PD patients has been found to be associated with gait deficits involving both upper and lower limbs (Jahanshahi et al., 1995; Jenkins et al., 1992; Sabatini et al., 2000). Due to its strong and widespread connections with the motor field of the contralateral cortex, the SMA plays a pivotal role in bilateral interlimb coordination and is therefore a good candidate for the cortical source involved in the coupling between upper and lower limb muscles that we observed in healthy gait (Weersink et al., 2021a). These previous findings laid ground for our hypothesis that reduced SMA activity in PD patients might result in a reduced coupling between upper and lower limb muscles, which could also be responsible for their disturbed interlimb coordination. However, the facilitating effect of arm swing instructions on lower limb movements in PD gait provides an argument that neural coupling between upper and lower limbs is maintained to some extent. To explore this neural coupling between upper and lower limb muscles and its directions in PD gait, we used time dependent directional intermuscular coherence analysis. To potentially distinguish involvement of the specifically affected neural pathways, coherence values were assessed over predetermined frequency bands that are associated with distinct neural origins as was previously mentioned. Gaining more knowledge about this interlimb coupling during gait in PD patients may serve rehabilitation concepts concerning their impaired walking ability.

2. Methods

2.1. Participants

Twenty healthy participants (10 males, 10 females) with a median age of 69 (±4.75 interquartile range (IQR)) years and twenty patients with Parkinson's Disease (13 males, 7 females) with a median age of 68.5 (±12.25 IQR) years were included in the study. To minimize medication effects in PD patients, experiments were performed in their end-of-dose state. All participants were able to walk independently (for PD; Hoehn and Yahr scale: Stage 2–3), had no cognitive problems (for controls and PD range mini mental state exam (MMSE): 26–30), were right handed according to the Annett Handedness scale (Annett, 1970) and gave their written informed consent. PD patients were included if they had clinically confirmed walking difficulties and were excluded if they had tremor dominant PD. Our PD group had a median Levodopa Equivalent Dosage (LED) of 775.00 (±618.50 IQR), the diagnosis since 4.5 (±4.88 IQR) years and their symptom laterality was equally distributed (6 left side, 7 both sides and 7 right side). The study was approved by the medical ethical committee of the University Medical Center Groningen and executed in compliance with the Declaration of Helsinki (2013).

2.2. Task and data acquisition

During the experiment, all participants walked overground at their own preferred speed through a 150 m long hallway from start to finish and back wearing their own comfortable clothes and shoes. The instruction that was given was 'to walk as they would do when taking a walk in the park'. The hallway did not have any floor markings and there were no other visual or auditory cues present during the experiment that could have influenced PD gait. Turning was removed from the data before further analysis. Paired bipolar surface disc Ag-AgCl EMG electrodes that were 2 cm in diameter and self-adhesive were placed bilaterally on the rectus femoris, biceps femoris, soleus and tibialis anterior and deltoideus anterior and posterior muscles according to the Surface Electromyography for the Non-Invasive Assessment of Muscles (SENIAM) (http://www.seniam.org) recommendations. As our previous study found that neural coupling was most pronounced between shoulder muscles and upper leg muscles in healthy participants and was comparable between deltoideus anterior and posterior (Weersink et al., 2021a), we focused on analysing bilateral deltoideus anterior muscles and the rectus femoris and biceps femoris muscles. Tri-axial accelerometers (Compumedic Neuroscan, Singen, Germany) that were placed on the medial sides of both ankles and over the L3 lumbar spine segment were used to detect moment of heel strike and toe-off. A portable amplifier (Siesta, Compumedics Neuroscan, Singen, Germany) was used to record the data at a sampling rate of 512 Hz, which was subsequently synchronized with audio–video recordings. All data were

sent via WIFI to a laptop using Profusion EEG software (v. 5.0, Compumedics Neuroscan, Singen, Germany) and stored for later analysis.

2.3. Gait analysis

Time-points of left and right heel strike and toe-off were extracted using the accelerometers by an approach presented by Sejdic et al. (2015), which is also described in more detail in a previous paper of our group (Weersink et al., 2020). These time points of heel strike and toe-off were used to calculate gait characteristics and marked the different gait events in the EMG data. Stride time variability was determined by calculating stride time coefficient of variation (STCV), i.e. dividing stride time standard deviation by the average stride time, where stride time was determined by calculating the time interval between two consecutive right heel strikes. Swing time symmetry ratio reflects gait symmetry and was calculated by dividing the largest average swing time by the smaller average swing time so that all individual values were >1.0 with 1.0 denoting perfect symmetry. Gait velocity and step length were determined using Kinovea video analysis software (version 0.8.15, http://www.kinovea.org). Gait velocity was determined by dividing the length of the trajectory between two predetermined points (50.44 m) by the time it took the participants to complete this trajectory. Step length was calculated by dividing the length of this same trajectory by the number of step needed to complete it. Both gait velocity and step length were corrected for participant's height.

2.4. EMG analysis

EMG data were analysed using custom scripts in MATLAB 2018a (The Mathworks, Inc., Natick, Massachusetts, United States) based on routines available at https://www.neurospec.org. All raw EMG data were high pass (5 Hz) filtered using a finite impulse response filter and full-wave rectified. The time dependent intermuscular coherence analysis was performed using an approach introduced by Halliday et al., (1995), which calculates a normalised correlation measure that ranges from 0 to 1 between two EMG signals, e.g. upper and lower limb muscles, as a function of time and frequency. This analysis was described in more detail in (Weersink et al., 2021a) and that section is also displayed below. "A sliding window of 200 ms was used to generate periodograms for 32 offsets relative to right heel strike with an interval of 50 ms, resulting in an overall analysis window of 1600 ms. These periodograms were averaged for each offset to construct estimates of spectra, where $f_{xx}(\lambda)$ and $f_{yy}(\lambda)$ represent the autospectra of processes x and y, respectively. The cross-spectrum between x and y is denoted by $f_{yx}(\lambda)$ and is estimated in a similar manner. The coherence function between the two signals at frequency λ is defined as:

$$|R_{yx}(\lambda)|^2 = \frac{|f_{yx}(\lambda)|^2}{f_{xx}(\lambda) f_{yy(\lambda)}}$$

Subsequently, estimates of directed connectivity were computed for each offset using a non-parametric directionality (NPD) analysis, which is a framework that decomposes classical, nonparametric Fourier-based coherence estimates by direction and is described in more detail in Halliday (2015). In short, in this approach optimal whitening or minimum mean square error (MMSE) whitening is used for prewhitening of the two EMG signals. Pre-whitening refers to the process of filtering a signal before spectral analysis to make its frequency content closer to white noise. This generates two new random processes that have spectra equal to 1 at all frequencies and that have the same coherence as the two original signals. As the autospectra for these, denoted as $f^w_{xx}(\lambda), f^w_{yy}(\lambda)$, then become equal to 1, only the cross-spectrum from these pre-whitened processes is used to calculate the coherence, which is then identical to the original coherence: $\left|R^w_{yx}(\lambda)\right|^2 = \left|f^w_{yx}(\lambda)\right|^2 = |R_{yx}(\lambda)|^2$. Subsequently, an inverse Fourier transform is used to produce a time domain correlation measure from this prewhitened cross-spectrum as

$$\rho_{yx}(\tau) = \frac{1}{2\pi}\int_{-\pi}^{\pi} f^w_{yx}(\lambda)\, e^{i\lambda t} d\lambda$$

The difference with the standard approach to generate a cross-covariance estimate in the time domain is that the prewhitened time domain correlation measure $\rho_{yx}(\tau)$ only has features that occur as a result of the correlation between the signals. This allows effective removal of the confounding influence of the original signals' autocorrelation. From the resulting time domain correlation measure, three quantities are extracted according to time lag i.e. components with a negative time lag, $\tau < 0$, the value at zero time lag, $\tau = 0$, and components at positive time lags, $\tau > 0$. Three inverse Fourier transforms over these three lag ranges are then used to obtain the reverse, zero-lag and forward components of coherence, respectively, as

$$|R_{yx}(\lambda)|^2 = \left|R'_{yx;-}(\lambda)\right|^2 + \left|R'_{yx;0}(\lambda)\right|^2 + \left|R'_{yx;+}(\lambda)\right|^2$$

where the prime indicates frequency domain quantities calculated from a subset of time lags in $\rho_{yx}(\tau)$, and the symbols $-$, $+$, 0 indicate the reverse, zero lag and forward components of coherence, respectively. These three components provide a summative decomposition of the original nonparametric coherence at each frequency into reverse, zero-lag and forward components. This quantifies the directional dependence between shoulder and leg EMG signals, providing an indication of whether shoulder EMG leads or lags leg EMG. The combination of these 32 offsets was visualized in an individual heat map showing time-dependent (directed) coherence between two signals for distinct frequencies relative to right heel strike. These heatmaps were time warped to the respective individual stride time using linear interpolation and subsequently pooled to produce a group estimate. In locomotor data, the periodicity of the gait cycle dominates the low-frequency spectral components (<8 Hz) of EMG data, and therefore these frequencies were disregarded." (Weersink et al., 2021a) Consequentially, even though tremor dominant PD patients were excluded, any remaining influence of PD tremor on our results is also excluded, because PD tremor is specifically present in the 4–6 Hz frequency band (Lee et al., 2016).

2.5. Statistical analysis

Subject and gait characteristics were statistically analysed in SPSS version 23 for Windows (IBM Japan Ltd., Tokyo, Japan). Histograms and Q-Q plots were examined to determine whether data were normally or non-normally distributed. For normally distributed data, i.e. STCV and swing time symmetry ratio, mean and standard deviation were reported and an independent T test was used to statistically compare the two groups. For non-normally distributed data, i.e. age, height, weight, MMSE, gait velocity and step length, median and IQR were reported and a Mann Whitney U test was used. Gender differences between groups were assessed by a Fisher's exact test. To compare the directed intermuscular coherence between healthy participants and PD patients, a nonparametric un-paired permutation method corrected for multiple comparisons using the false discovery rate method was used. An alpha level of 0.05 was assumed for all statistical test.

3. Results

3.1. Participant characteristics

Demographic data for both groups were similar as shown in Table 1. No significant differences were found between groups regarding age (p = 0.461), sex (p = 0.523), height (p = 0.640), weight (p = 0.579) or mini mental state examination (MMSE) scores (p = 0.579).

3.2. Gait characteristics

Compared to healthy participants, PD patients showed reduced gait velocity (p = 0.038) and step length (p = 0.001) as shown in Table 2. Stride time coefficient of variation, which is indicative of stride time variability, was increased in PD patients compared to healthy participants (p = 0.001). However, healthy participants and PD patients did not differ in swing time symmetry ratio (p = 0.569). During the experiment PD patients did not exhibit freezing of gait episodes.

3.3. Intermuscular coherence

Total time-dependent coherence, representing a quantitative measure of the correlation between deltoideus anterior and rectus femoris activity in the frequency domain, summed over the forward, reverse and zero-lag directions, is visualized in the upper rows of Fig. 1. In this, forward and reverse directions mean that the deltoideus anterior EMG signal precedes or lags the rectus femoris EMG signal, respectively. In healthy controls, total coherence was most pronounced during the mid to end-of-stance phase and during the early swing phase in the beta/low gamma frequencies, for all muscle combinations. Total coherence in the alpha frequency band was present during almost the entire gait cycle, except during heel strike. Comparing total coherence between PD patients and healthy controls, revealed that PD patients exhibited a statistically significant reduction of coherence during the mid to end-of-stance phase for the gamma frequencies and increased coherence for the beta frequencies in the swing phase. These group differences were most pronounced for the total coherence between the left deltoideus anterior and bilateral rectus femoris muscles. Total coherence between biceps femoris and deltoideus anterior showed similarity with the results for the rectus femoris and deltoideus anterior, but the differences between the two groups were less pronounced (Supplementary Fig. 1). Therefore, the latter is not extensively discussed here.

The zero-lag component of coherence is considered to represent a common driver for shoulder and leg muscle activities (Fig. 1, second row). In the healthy participants, zero-lag coherence was especially present during the mid to end-of-stance phase and during the early swing phase for both alpha and beta/low gamma frequencies for all muscle combinations, although more pronounced for the left deltoideus anterior combinations in the high frequency range. Compared to healthy controls, PD patients had significantly reduced zero-lag coherence during the end-of-stance phase for the beta/low gamma frequencies (left deltoideus anterior-left rectus femoris p = 0.011, right deltoideus anterior-left rectus femoris p = 0.014, left deltoideus anterior-right rectus femoris p = 0.029 , right deltoideus anterior-right rectus femoris p = 0.027) and also during the early swing phase for the coherence between the two deltoideus anterior muscles with the right rectus femoris (p = 0.018). These group differences were most pronounced for zero-lag coherence between left deltoideus anterior and left rectus femoris muscles.

Positive and negative lag coherence, which relate to the forward directed component and reverse directed component of total coherence, respectively, are visualized in the lower two rows of Fig. 1. Here, significant forward directed coherence implies that deltoideus anterior activity leads rectus femoris activity. In healthy controls, this forward directed coherence was primarily present during the midstance and early swing phases in alpha, beta and low-gamma frequencies, and was most pronounced between the right deltoideus anterior and the left as well as the right rectus femoris. PD patients showed significantly increased forward directed coherence around toe-off for particularly the beta and lower alpha frequency bands (left deltoideus anterior – left rectus femoris p = 0.023, right deltoideus anterior – left rectus femoris p = 0.001, left deltoideus anterior – right rectus femoris p = 0.011, right deltoideus anterior – right rectus femoris p = 0.002), which was again most pronounced between left deltoideus anterior and left rectus femoris and muscles.

Significant reverse directed coherence implies that deltoideus anterior activity lags rectus femoris activity, suggesting that leg movements drive deltoideus anterior activity. In healthy controls, this reverse directed coherence was also primarily present during the midstance and early swing phases for beta/low gamma frequencies. Compared to healthy controls, PD patients exhibited significantly enhanced reverse directed coherence around toe-off for alpha and beta frequencies for especially the left deltoideus anterior combinations (left deltoideus anterior-left rectus femoris p = 0.007, right deltoideus anterior – left rectus femoris p = 0.012, left deltoideus anterior – right rectus femoris p = 0.013).

Table 1
Demographic characteristics of participants.

	Healthy participants (N = 20)	Parkinson patients (N = 20)	p-values
Age (years)	69 ± 4.75	68.5 ± 12.25	0.461
Gender (male/female)	10/10	13/7	0.523
Height (cm)	178 ± 19.25	178 ± 15.00	0.640
Weight (kg)	81.75 ± 16.50	77.5 ± 11.50	0.579
MMSE	29 ± 1.75	28.5 ± 2.75	0.183
LED		775.00 ± 618.50	
Years since diagnosis		4.50 ± 4.88	
Laterality of symptoms (left/both/right)		6/7/7	

Values are expressed as median ± interquartile range. Group differences were assessed using Mann Whitney U tests, except for gender, which was assessed using Fisher's exact test. Abbreviations: LED = Levodopa Equivalent Dosage, MMSE = Mini mental state exam.

Table 2
Spatiotemporal gait characteristics of participants.

	Healthy participants (N = 20)	Parkinson patients (N = 20)	p-values
Gait velocity (meter/second)	1.28 ± 0.36	1.18 ± 0.31	0.038
Step length (meter)	0.71 ± 0.07	0.66 ± 0.15	0.001
STCV (%)	2.873 ± 0.976	5.443 ± 2.881	0.001
Swing Time Symmetry Ratio	1.049 ± 0.047	1.064 ± 0.057	0.569

Gait velocity and step length (based on accelerometer and video recordings) are expressed as median ± interquartile range while swing time symmetry and stride time coefficient of variation (STCV) are expressed as mean ± standard deviation. Group differences in gait velocity and step length were assessed using Mann Whitney U tests and in STCV and Swing Time Symmetry using independent T tests.

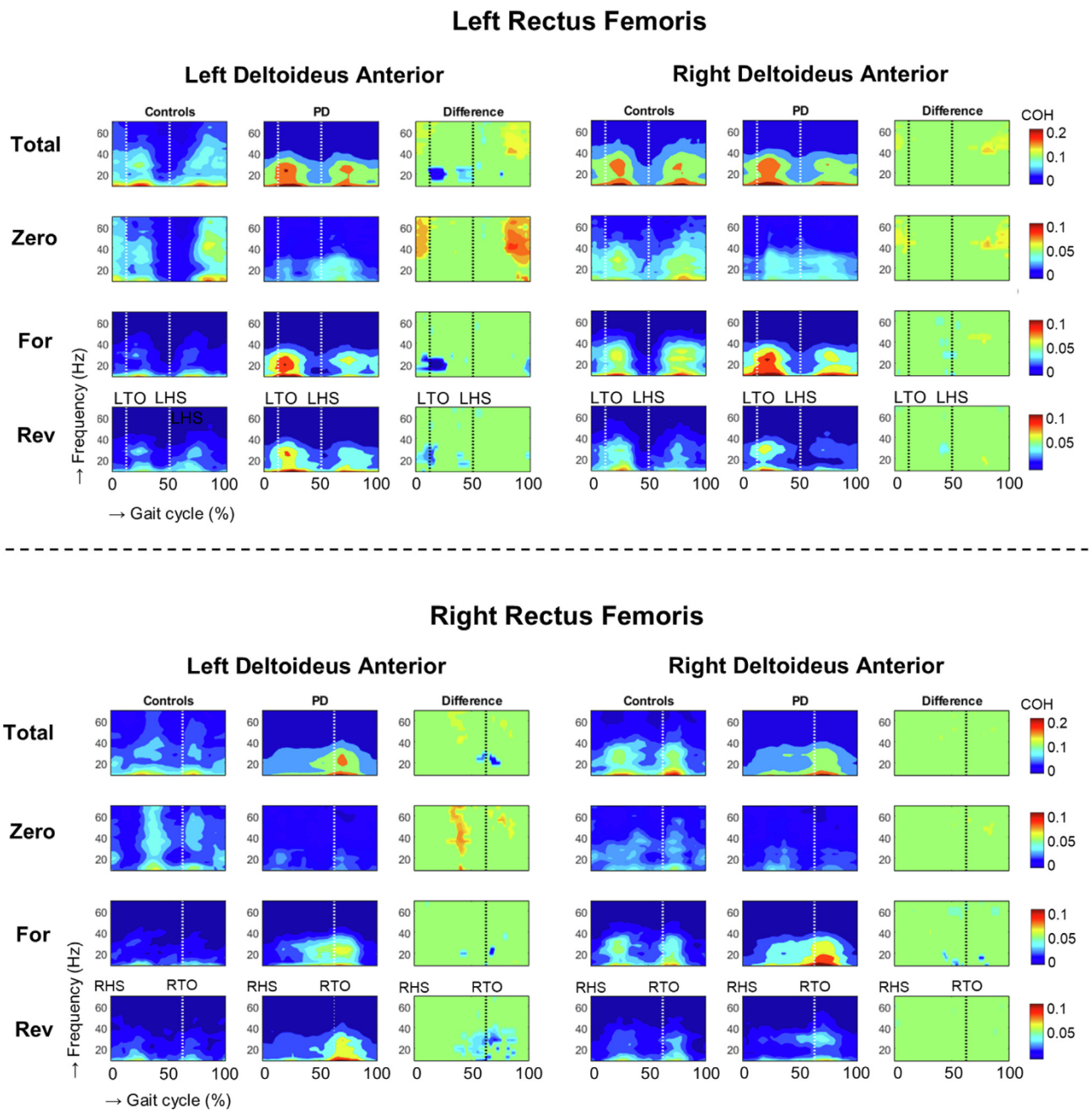

Fig. 1. Time dependent intermuscular coherence between rectus femoris and deltoideus anterior during gait. Group averaged total intermuscular coherence and the forward (for), reverse (rev) and zero-lag (zero) components of coherence between bilateral deltoideus anterior and rectus femoris muscles across the frequency spectrum (y-axis, 8–70 Hz) during one gait cycle starting at right heel strike (x-axis, gait cycle 0–100%). Magnitude of coherence is colour coded and indicated using colour bars (to the right of the figure). Vertical lines mark the occurrence of left (LTO) and right (RTO) toe-off and left (LHS) and right (RHS) heel strike averaged across all participants. Colormaps were time warped to the individual stride time. Significant differences ($p < 0.05$) between Parkinson patients (PD) and controls are depicted in the third and sixth column, with blue colours representing PD > controls and red colours representing PD < controls.

4. Discussion

In distinct phases of the gait cycle, we found reduced zero-lag coherence and enhanced forward and reverse directed coherence between deltoideus anterior and rectus femoris muscles in the beta and gamma band during PD gait compared to healthy gait. This suggests that in PD patients, the input from a common cortical driver was reduced, which particularly occurred during the second part of the stance phase. As a consequence, neuronal circuitry might be activated serving compensation (and/or correction) by adjusted shoulder muscle activity to drive and shape the leg muscle activity and vice versa, particularly around toe-off, i.e. the onset of the swing phase. Such enhanced coherence in specifically beta and gamma bands provides an argument that this altered neural coupling between upper and lower limbs has a cortical origin. These observations support the idea that neural coupling between upper and lower limb muscles is preserved in PD gait, although in an adjusted fashion, with involvement of corticospinal pathways in the altered interlimb coordination in PD patients. In addition, enhanced forward and reversed directed coherence in only the alpha band indicate an additional compensatory contribution from a subcortical origin.

Intermuscular coherence reflects synchronized motor unit activity which has previously been described for gait to occur between bilateral leg muscles (Halliday et al., 2003; Hansen et al., 2005; Jensen et al., 2019,2018) and recently also between upper and lower limb muscles (Weersink, 2021). This coherence is proposed to reflect neural coupling between the four limbs during gait, which contributes to interlimb coordination that is necessary for the production of the multi-limb gait pattern. In the present study, this time-dependent intermuscular coherence was decomposed into three components based on their time lag, allowing to make assumptions about the directionality of this coupling during successive stages of the gait cycle. The zero-lag component reflects a shared input from a common driver to the deltoideus anterior and rectus femoris muscles that can have both a subcortical and cortical origin. As intermuscular coherence in the alpha band is believed to primarily reflect coupling via subcortical interconnections (Baker and Baker, 2003; Conway et al., 1995; Salenius et al., 1997) and coherence in the beta/gamma band reflects the involvement of particularly transcortical pathways (Conway et al., 1995; Fisher et al., 2012; Mima et al., 2000; Weersink et al., 2021a), our findings indicate that the deltoideus anterior and rectus femoris muscles from healthy controls receive a shared input from both subcortical and cortical sources during mid to end-stance and early swing phase.

In PD patients, this zero-lag coherence was significantly reduced in the beta/low gamma frequencies, suggesting that these patients have a reduced common proposedly cortical driver that mostly fails at the end of stance phase and to a lesser extent at the early swing phase. A good candidate for this affected cortical source is the SMA, which plays a pivotal role in bilateral interlimb coordination and was found to exhibit reduced activity in PD patients (Jahanshahi et al., 1995; Jenkins et al., 1992; Sabatini et al., 2000). Moreover, as the SMA has also been implicated in movement initiation and temporal ordering of sequential movements (Cunnington et al., 2003; Tanji, 2001), its impaired function in driving the upper and lower limbs during the end of stance and early swing phases of the gait cycle might be the expression of reduced preparation and initiation of the swing phase in PD patients, thus resulting in gait characterised by small steps, reduced arm swing and enhanced vulnerability to freezing (Lewek et al., 2010; Nanhoe-Mahabier et al., 2011). As the reduction of zero-lag coherence in PD patients was most pronounced between the left deltoideus anterior and left rectus femoris muscles, one might question whether this could be explained by symptom laterality. However, the symptom laterality in our PD group was equally distributed and when visually comparing the individual coherence plots between left arm-leg muscles and right arm-leg muscles, we did not find a relation with symptom laterality.

Forward and reverse directed components of coherence are a reflection of the signal from one muscle leading or lagging the other, here indicating that deltoideus anterior drives the rectus femoris or vice versa. In healthy participants, we found that deltoideus anterior and rectus femoris drive each other during mid stance and early swing phase via both subcortical and transcortical pathways. Interestingly, both forward and reverse directed components were enhanced in especially the beta frequencies in PD patients compared to healthy participants, around toe off, i.e. around the onset of the swing phase. This enhanced bidirectional coupling between the deltoideus anterior and quadriceps muscles in PD patients at both subcortical (i.e. alpha) and cortical (i.e. beta/gamma) levels, might reflect a subcortical mechanism inducing muscle activity to correct suboptimal balance in the preceding final stance phase, as well as a compensation mechanism for the diminished common driver. Such subcortical compensation has also been seen in a previous study reporting enhanced anticipatory spinal neuronal activity in arm muscles of PD patients during obstacle stepping (Dietz and Michel, 2008). Although exact pathways responsible for this compensation mechanism remain speculative at this point, studies in patients with traumatic brain injury have found that the brain is able to undergo neuroanatomical and functional changes that lead to reorganization of remaining tissue (Hylin et al., 2017). As in PD patients multiple brain areas are also affected due to structural and functional changes, comparable reorganization could occur that might be responsible for the observed enhanced bidirectional coupling in PD gait. Nevertheless, our findings suggest that the directional neural interlimb coupling is preserved, and even enhanced, in PD patients, which means that also in PD patients arm movements are able to drive leg muscle activity during gait. Therefore, our findings are in line with and provides additional neural underpinning for our previous studies that demonstrated the facilitating effect of arm swing instructions on both corticomuscular and behavioural level in the same and another PD population on continuous gait (Weersink et al., 2021b) and gait initiation (Weersink et al., 2020, Weersink et al., 2018). Such arm swing instructions could be exploited for gait rehabilitation purposes in PD patients with gait impairments.

Aside from our current findings regarding interlimb coupling in PD, our study emphasizes that when examining intermuscular coherence, it is important to take directionality into account. As our zero lag coherence was reduced and directed coherence was enhanced in PD patients, summation of these components would have partially cancelled each other, which can be seen in the total coherence plots. Therefore, this summative total coherence would not have been able to detect these specific changes in directional coherence in PD patients. Therefore, future studies examining neural coupling between muscles or brain areas using coherence should consider taking these directionality components into account.

When interpreting these results, it is important to keep in mind that our interpretation that intermuscular coherence in specific frequency bands derives from either subcortical and transcortical origin remains a hypothesis. Although previous studies proposed that intermuscular coherence in the beta and gamma frequency bands derive from cortical sources because corticomuscular coherence was especially observed for these frequencies (Conway et al., 1995; Gwin and Ferris, 2012; Mima et al., 2000; Power et al., 2006), the interpretation that intermuscular alpha coherence derives from subcortical sources originates from the lack of such corticomuscular coherence and therefore remains indirect. With the current neurophysiological techniques it remains difficult to find direct evidence in humans that intermuscular alpha coherence reflects subcortical pathways. Nevertheless, our previous study, which found both alpha and beta/gamma coherence between upper and lower limb muscles, did observe time domain estimates that are consistent with conduction times of both subcortical and transcortical pathways, confirming that both pathways were involved (Weersink et al., 2021a). Another limitation of the current study is that our PD patients were, for ethical reasons, not examined in an off-state, which means that they did not take medication. We did try to minimize medication effect by examining them in their end-of-dose phase, by planning the experiment right before they were supposed to take their next medication dosage. However, for future studies it might be interesting to examine whether the observed effects are even more pronounced when PD patients are examined in an off-state. Moreover, future studies could also examine if the observed coherence effects are related to clinical behavioural parameters e.g. whether reduced zero-lag coherence is related with worse interlimb coordination.

5. Conclusion

Time dependent intermuscular coherence analysis showed that shoulder and upper leg muscles from PD patients have a reduced

common cortical driver during distinct phases of the gait cycle, which could be responsible for the disturbed interlimb coordination observed in these patients. In addition, bidirectional coupling between shoulder and upper leg muscles which was enhanced on subcortical and transcortical levels in PD patients, compared to healthy participants, may serve as a mechanism to compensate the reduction of their common cortical driving source. Overall, these findings provide additional neural underpinning for the facilitating effect of arm swing instructions in PD gait.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.11.072.

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