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Enhanced arm swing improves Parkinsonian gait with EEG power modulations resembling healthy gait

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ABSTRACT

Background: The supplementary motor area (SMA) is implicated in stereotypic multi-limb movements such as walking with arm swing. Gait difficulties in Parkinson's Disease (PD) include reduced arm swing, which is associated with reduced SMA activity.
Objective: To test whether enhanced arm swing improves Parkinsonian gait and explore the role of the SMA in such an improvement.
Methods: Cortical activity and gait characteristics were assessed by ambulant EEG, accelerometers and video recordings in 27 PD patients with self-reported gait difficulties and 35 healthy participants when walking normally. Within these two groups, 19 PD patients additionally walked with enhanced arm swing and 30 healthy participants walked without arm swing. Power changes across the EEG frequency spectrum were assessed by Event Related Spectral Perturbation analysis of recordings from Fz over the putative SMA and gait analysis was performed.
Results: Baseline PD gait, characterized by reduced arm swing among other features, exhibited reduced within-step Event Related Desynchronization (ERD)/Synchronization (ERS) alternation (Fz; 20–50Hz), accompanied by a reduced step length and walking speed. All became similar to normal gait when patients walked with enhanced arm swing. When healthy controls walked without arm swing, their alternating ERD-ERS pattern decreased, mimicking baseline PD gait.
Conclusion: Enhanced arm swing may serve as a driving force to overcome impaired gait control in PD patients by restoring reduced ERD-ERS alternation over the putative SMA. Accompanied by increased step length and walking speed, this provides a neural underpinning of arm swing as an effective rehabilitation concept for improving Parkinsonian gait.

1. Introduction

Parkinson's Disease (PD) is characterized by a wide spectrum of motor and non-motor symptoms. As the disease progresses, most PD patients experience gait disturbances, characterized by small shuffling steps, disturbed gait initiation and reduced or absent arm swing. The four limb movement pattern in gait is driven by cyclic pattern generators in the spinal cord and brain stem, embedded in more widely distributed networks including cortical regions such as the supplementary motor area (SMA). Due to transcallosal connectivity, the SMA plays a pivotal role in coordinating bilateral limb movements during gait [1–3]. Reduced SMA activity is commonly found in PD patients and is associated with disturbed gait and reduced arm swing [4,5]. The association between SMA activity and arm swing gained further support by our previous finding that walking of healthy participants without arm swing was accompanied by impaired step-related mediofrontal activity [1]. Pacing the movement pattern in gait fits the central role of the SMA in movement initiation [6,7]. The relation between impaired gait initiation in PD and altered SMA activity [8,9] was recently elaborated by our observation that the instruction of enhanced arm swing improved gait initiation in PD patients, accompanied by functionally normalized SMA activity [8]. For steady state gait, behavioral studies have claimed that enhancing arm swing increases walking speed and step length in PD patients [10,11]. These findings laid ground for the present study, testing whether enhanced arm swing during continuous gait might similarly serve as an SMA-mediated driving force to overcome impaired gait control in PD.

SMA activity during overground walking can be studied by ambulant

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electroencephalography (EEG). Analysis of event related spectral perturbations (ERSP) in the EEG enables the assessment of average dynamic changes in power across the frequency spectrum as a function of time relative to gait-related events. Alpha (7–12 Hz) and beta (12–30 Hz) oscillatory activity are thought to play a predominant role in modulation of motor activity, with a power decrease (event related desynchronization (ERD)) prior and during movement followed by a post-movement inhibitory power increase (event related synchronization (ERS)) [12,13]. During walking with arm swing, an intra-stride ERD-ERS pattern over the sensorimotor cortex is present [1,14,15], while especially cyclic low-gamma band modulations appeared to be associated with the contribution of arm swing to this four-limb movement pattern [1,14,16].

In the present study, we explored the effect of enhanced arm swing during continuous PD gait on both EEG power changes and gait characteristics. Ambulant 32-channel EEG was obtained in healthy controls walking both normally and without arm swing and in PD patients walking normally and with enhanced arm swing. We focused on cortical activity recorded from the Fz electrode, located over the mediofrontal cortex and thus including the SMA. It was hypothesized that (i) PD patients exhibit a less pronounced within-step alternating ERD-ERS pattern over the putative SMA and that (ii) this ERD-ERS pattern is changed to that observed in healthy gait when patients walk with enhanced arm swing. Moreover, (iii) such normalized EEG pattern accompanies improved gait.

2. Methods

2.1. Participants

Thirty-five healthy participants (17 males, median age 67 ± 9 years) and 27 PD patients with self-reported gait difficulties (17 males, median age 65 ± 11 years) were included in the study. PD patients were assessed in their end-of-dose state to minimize medication effects. All participants could walk independently (for PD; Hoehn and Yahr scale: Stage 2–3), had no significant cognitive problems (Mini Mental State Examination (MMSE) $\geq$ 26), were right handed according to the Annett Handedness scale and gave written informed consent. The study was executed according to the Declaration of Helsinki (2013) and was approved by the medical ethical committee of the University Medical Center Groningen.

2.2. Task and experimental set-up

Participants were instructed to walk overground at their own comfortable speed through a straight hallway of 150 m from start to finish and back. Data of 30 healthy participants and 19 PD patients were collected in two sessions, while 5 healthy and 8 PD subjects were only assessed in the first session. The first (baseline) condition for both groups was normal walking, i.e. to walk as they would do when taking a walk in the park. In the second session, healthy participants walked the same trajectory without arm swing (arms kept straight and aligned with the trunk), while PD patients walked with enhanced arm swing, which implied deliberately enlarging the amplitude of their arm swing. Normal gait was always scheduled first to avoid participants becoming highly aware of their arm swing thereby potentially influencing natural gait. Data collection of this study was divided in two different time periods; the study design of the first period (healthy controls n = 5, PD n = 8) only concerned a single session without a second session of adjusted arm swing. However, the initial data were included to provide a more reliable average of ERSP plots for future comparison purposes.

The experimental set-up was described previously [1] and is briefly summarized here. Overground ambulant EEG was recorded using a cap with 32 active monopolar Ag-AgCl electrodes (EasyCap, Herrsching, Germany) located according to the international 10–20 system. To allow detection of heel strike and toe-off during the gait cycle, tri-axial accelerometers (Compumedics Neuroscan, Singen, Germany) were placed over the L3 segment of the lumbar spine and on the medial side of both ankles, using Velcro straps. EEG and synchronized accelerometer signals were recorded at 512 Hz sampling rate using a portable amplifier (Siesta, Compumedics Neuroscan, Singen, Germany), synchronized with video recordings of all sessions and sent via WIFI to Profusion EEG software (v. 5.0, Compumedics Neuroscan, Singen, Germany) for later analysis.

2.3. Gait analysis

The time-points of heel strike and toe off were determined by an approach introduced by Sejdic [17]. These time-points were used to calculate swing time and stride time and served as a marker for EEG analysis. Stride time coefficient of variation (STCV) was calculated by dividing stride time standard deviation by mean stride time for each participant. As an index of gait symmetry, individual swing time symmetry ratio was calculated by dividing the largest average swing time by the smaller average swing time, where 1.0 denotes perfect symmetry. Step length and walking speed were determined using video recordings. Walking speed was determined by the time it took to cover a predetermined 50.44 m of the 150 m trajectory during outward and backward journey, whereas step length was calculated by dividing the length of this same trajectory by the number of steps needed to complete it. Both walking speed and step length were corrected for participant's height.

2.4. EEG data pre-processing and analysis

Pre-processing and further EEG analyses were performed in MATLAB 2015a (The Mathworks, Inc., Natick, Massachusetts, USA) using EEGLAB 14_1_2b (sccn.ucsd.edu/eeglab). EEG recordings from each task were down sampled to 256 Hz to speed up computations. All data were pre-processed as described previously [1] and are briefly summarized here. EEG data was high pass filtered (1 Hz) and powerline noise was regressed out. Channels exhibiting substantial artefacts were removed using the following criteria: channels (1) with magnitude <30 or >10.000 μV; (2) with kurtosis >5 standard deviations from the mean; (3) uncorrelated with neighbouring channels ($r < 0.04$) for more than 1% of the total time; (4) with a standard deviation at least three times higher than other channels. Next, data was re-referenced to the average of the remaining channels and transformed into temporally independent components (ICs) using infomax independent component analysis [18]. ICs were classified as electrocortical sources, muscle sources or movement artefacts based on their power spectra, event related spectral perturbations and locations of their equivalent current dipoles [19,20], which is further specified in our previous study [1]. Afterwards, the complete dataset was split into epochs from 1000 ms before until 2000 ms after each right heel strike.

ERSPs were calculated for these epochs using the gain model [21] in EEGLAB. Event related spectral power changes were analyzed by the ERSP index:

$$ERSP(f,t) = \frac{1}{n}\sum_{k=1}^{n}(F_k(f,t))^2$$

where for n trials, $F_k(f,t)$ is the spectral power estimate of trial k at frequency f and time t. ERSP plots show mean time-frequency points across the input epochs, where higher or lower spectral power differs from mean power during the 1000 ms pre-stimulus baseline period, i.e. the mean of an entire gait cycle. Time points for gait events were aligned by time-warping single trial spectrograms for each subject to individual mean time intervals between right heel strikes using linear interpolation. Finally, the grand average mean ERSP plots for Fz for all conditions were generated.

2.5. Scalp maps

To provide additional insight in the spatial distribution of the most prominent ERD and ERS phenomena at Fz, 32 channel ERSP scalp distribution maps were made for all conditions. For these scalp maps, 5% time intervals of the gait cycle were selected within the most prominent ERD and ERS phenomena at Fz, i.e. during the double support phase after right and left heel strike (0–5% and 50–55%) and during the early left and right swing phase (20–25% and 70–75%) in the high beta/low gamma (20–50 Hz) frequencies.

2.6. Statistical analysis

Statistical analysis of subject and gait characteristics was performed in SPSS version 23 (IBM Japan Ltd., Tokyo, Japan). For non-normally distributed independent data (age, height, weight and MMSE), Kruskal Wallis tests were used to compare conditions. Gender ratios were compared between groups using Fisher's exact test. To compare normally distributed independent data, i.e. swing symmetry and STCV between groups and levodopa equivalent dosage and years since diagnosis between PD conditions, independent t-tests were used. To compare non-normally distributed independent data, i.e. step length and walking speed between groups, Mann Whitney U tests were used. To compare paired normally distributed values, i.e. swing symmetry and STCV for PD walking normally and with enhanced arm swing and for healthy controls walking normally and without arm swing, paired t-tests were used. To test for differences in step length and walking speed between the two PD conditions and between the two healthy control conditions, a sign test was used.

Statistical analyses of ERSP data were performed using EEGLAB 14_1_2b in MATLAB 2015a. Significance of pooled ERSP differences from baseline average gait cycle log spectrum was determined using the permutation method [21]. Significant ERSP differences between conditions were identified with a nonparametric permutation method corrected for multiple comparisons using the false discovery rate method. Paired statistics were used to test for differences between walking conditions within groups. Unpaired statistics were used to compare groups. For all statistical tests an alpha level of 0.05 was assumed.

3. Results

3.1. Subject characteristics

Demographic data for all groups were similar (Table 1). The groups did not significantly differ regarding age ($p = 0.745$), sex ($p = 0.307$), height ($p = 0.081$), weight ($p = 0.684$), MMSE score ($p = 0.081$), levodopa equivalent dosage ($p = 0.475$) and years since diagnosis ($p = 0.599$).

Table 1
Demographic characteristics of participants.

	HC all (N = 35)	HC norm + no swing (N = 30)	PD all (N = 27)	PD norm + swing (N = 19)
Age (yr)	67 ± 9	67.5 ± 9	65 ± 11	68 ± 11
Gender (m)	17/35	13/30	17/10	13/19
Height (cm)	172 ± 17	171.5 ± 16.5	178 ± 12.25	178 ± 14
Weight (kg)	80 ± 15	73.5 ± 14.50	78 ± 14.50	78 ± 13
MMSE	29 ± 1	29 ± 1	29 ± 2	28 ± 3
LED			569 ± 680	750 ± 600
Yrs since diagnosis			5.75 ± 6.13	4.5 ± 5.50

Values are expressed as median ± interquartile range, except for levodopa equivalent dosage (LED) and years since diagnosis that are expressed as mean ± standard deviation. No significant differences between groups were found.
Abbreviations: HC all = all healthy controls walking normally, HC norm + no swing = healthy controls walking both normally and without arm swing, PD all = all Parkinson patients walking normally, PD norm + swing = Parkinson patients walking both normally and with enhanced arm swing.

3.2. Gait characteristics

In the baseline condition of 'natural' gait along the outward and backward trajectories, PD patients showed reduced walking speed ($p = 0.004$, effect size $d = 0.78$; $p = 0.007$, $d = 0.76$) and step length ($p < 0.001$, $d = 1.11$; $p < 0.001$, $d = 1.03$) compared to healthy controls during both outward and backward trajectories, respectively (Table 2). STCV was increased in PD patients, compared to healthy controls ($p < 0.001$, $d = 0.52$). When PD patients walked with enhanced arm swing walking speed ($p < 0.001$, $d = 0.69$) and step length ($p < 0.001$, $d = 0.79$) increased and normalized towards healthy control values. This resulted in an 11.5% decrease in STCV, although this was not significant. With enhanced arm swing, PD walking speed and step length did not differ between outward and backward trajectories (Sign test, $p = 0.147$ and $p = 0.092$, respectively). Vice versa, walking without arm swing in healthy controls resulted in reduced ($p = 0.001$, $d = 0.11$) step length, only during the backward trajectory compared to walking naturally. Symmetry of swing phases did not differ between groups.

3.3. Event related spectral perturbations at Fz

In healthy controls during normal gait, recordings at Fz showed a pattern of well-demarcated ERD-ERS alternation within each step (Fig. 1). A strong ERD emerged in the high beta/low gamma (20–50 Hz) frequency bands during double support phase, followed by a transition to ERS in early swing phase. In the alpha/beta (8–20 Hz) frequency band, this ERD started around toe-off until mid-swing phase and transitioned to ERS in the final part of the swing phase until the beginning of the double support phase. This ERD-ERS alternation was less pronounced in PD patients, leaving only high beta/low gamma ERD from the end of the swing phase until the double support phase. High beta/low gamma ERS during swing phase ($p = 0.006$; $d = 0.57$) and alpha/low beta ERD around toe-off ($p = 0.003$; $d = 0.68$) were reduced compared to healthy controls. When PD patients walked with enhanced arm swing, this naturally reduced high beta/low gamma ERS in the swing phase was found to be increased ($p = 0.004$; $d = 0.52$), together with an increase in alpha/low beta ERD during toe-off ($p = 0.018$; $d =$

Table 2
Spatiotemporal gait characteristics in the four experimental conditions.

	HC norm (N = 35)	HC no swing (N = 30)	PD norm (N = 27)	PD swing (N = 19)
Walking speed out (m/s)	1.31 ± 0.27[a]	1.32 ± 0.24[a]	1.18 ± 0.33[d]	1.28 ± 0.29
Walking speed back (m/s)	1.33 ± 0.22[a]	1.33 ± 0.19[a]	1.09 ± 0.24[d]	1.25 ± 0.28
Step length out (m)	0.71 ± 0.09[b]	0.73 ± 0.08[a]	0.65 ± 0.17[d]	0.70 ± 0.14
Step length back (m)	0.74 ± 0.09[bd]	0.72 ± 0.09[a]	0.63 ± 0.15[d]	0.69 ± 0.12
Swing Symmetry	1.05 ± 0.06	1.11 ± 0.36	1.06 ± 0.07	1.09 ± 0.08
STCV (%)	4.12 ± 2.78[ac]	4.09 ± 3.05[b]	7.32 ± 8.18	6.48 ± 4.08

Walking speed and step length (based on accelerometers and video recordings) are depicted as median ± interquartile range and swing symmetry and stride time coefficient of variation (STCV) are expressed as mean ± standard deviation. Abbreviations: [a] difference with PD norm $p < 0.05$; [b] difference with PD norm $p < 0.001$; [c] difference with PD swing $p < 0.05$; d difference with PD swing $p < 0.001$; [d] difference with HC no arm swing $p < 0.05$; HC norm = healthy controls walking normally, HC no swing = healthy controls walking without arm swing, PD norm = Parkinson patients walking normally, PD swing = Parkinson patients walking with enhanced arm swing, out = outward trajectory, back = backward trajectory.

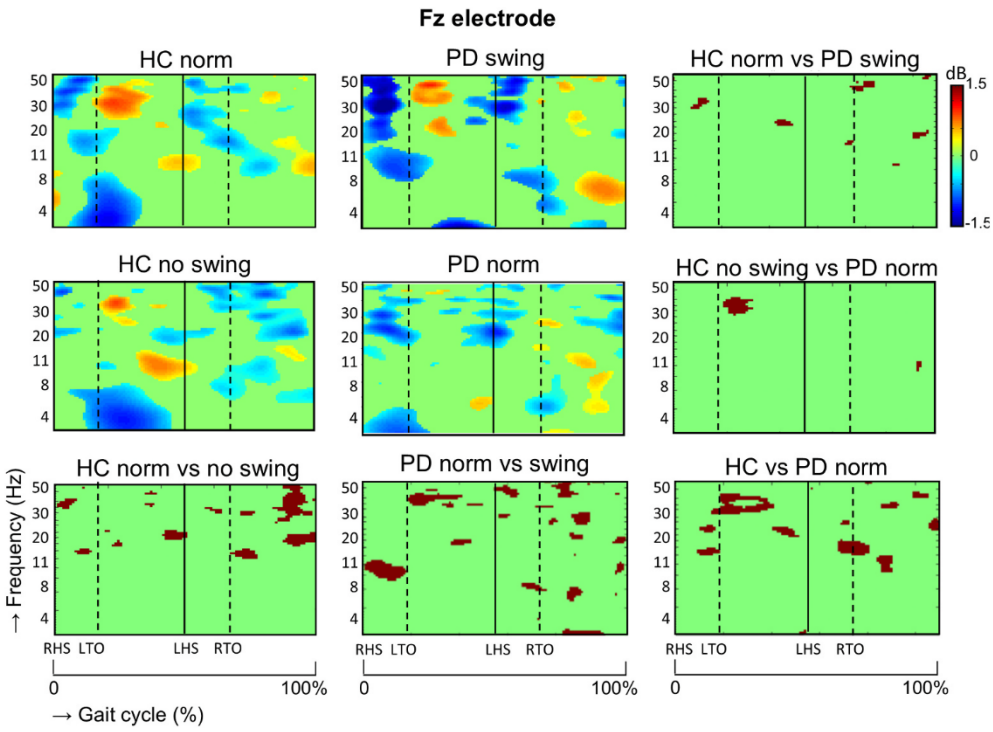

Fig. 1. Group averaged gait related ERSP plots of the mediofrontal Fz electrode. Gait cycle related significant event related desynchronization (blue) and event related synchronization (red) from the Fz electrode located over the mediofrontal cortex. Significant differences ($p < 0.05$) between the groups are shown in the third row and column. Non-significant changes ($p > 0.05$) are set to 0 dB (green).
Abbreviations: HC norm = healthy participants walking normally, HC no swing = healthy participants walking without arm swing, PD norm = Parkinson patients walking normally, PD swing = Parkinson patients walking with enhanced arm swing, dB = decibel; RHS = right heel strike; LHS = left heel strike; RTO = right toe-off; LTO = left toe-off. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

0.48). This resulted in a restored ERD-ERS pattern that was virtually normalized to that of healthy controls. Vice versa, when healthy controls walked without arm swing, their alternating ERD-ERS pattern also became less demarcated and more comparable to PD patients walking normally, although ERS during the left swing phase was relatively preserved. Compared to normal walking, walking without arm swing resulted in a reduced high beta/low gamma ERS in the right swing phase that even transitioned to ERD ($p = 0.002$; $d = 0.49$). Additionally, alpha/low beta ERD around toe-off ($p = 0.029$; $d = 0.32$) was also reduced.

As the Fz electrode was the primary scope of the present study, we refrained from extensive ERSP analysis of other electrodes. The spatial distribution of high beta/low gamma alterations in distinct intervals of the gait cycle are provided in the ERSP scalp maps (Fig. 2). Reduced within-step ERD-ERS alternation in PD patients compared to healthy controls and normalization when walking with enhanced arm swing are present over the whole sensorimotor cortex, but are especially present over the frontal areas (Fz, F3, F4).

4. Discussion

In the present study, we used ambulatory EEG and accelerometer recordings to explore the effect of enhanced arm swing on putative SMA activity and gait characteristics in PD patients. Walking with enhanced arm swing appeared to normalize the reduced within-step pattern of ERD-ERS alternation at the mediofrontal Fz electrode in PD patients,

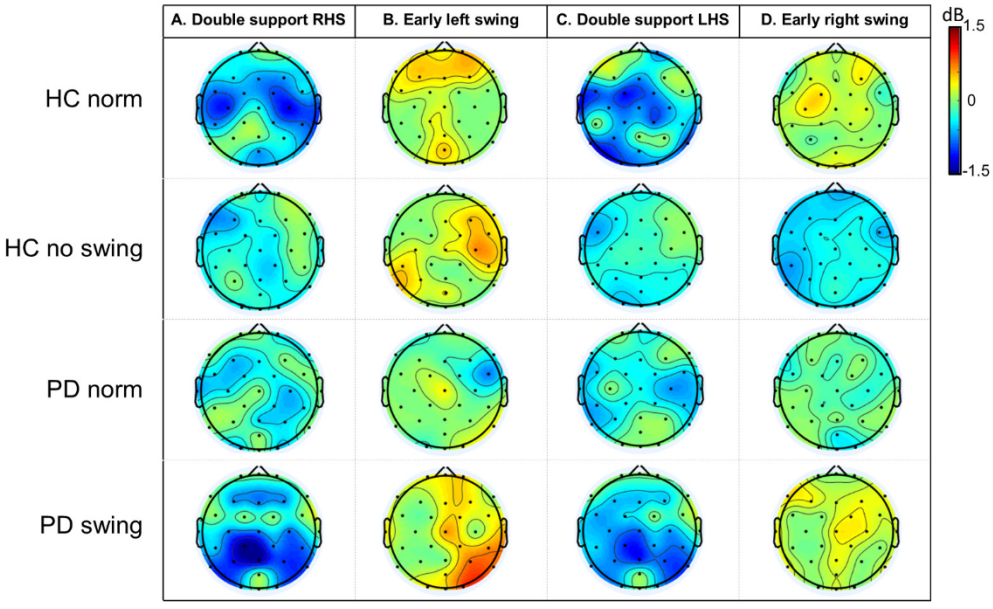

Fig. 2. Event related spectral perturbation scalp distribution maps (20–50 Hz). Group averaged topographic distribution over 32 channels depicting significant event related desynchronization (blue) and event related synchronization (red) during 5% time intervals of the gait cycle for high beta/low gamma (20–50 Hz) frequencies. Non-significant changes ($p > 0.05$) are set to 0 dB (green).
Abbreviations: HC norm = healthy participants walking normally, HC no swing = healthy participants walking without arm swing, PD norm = Parkinson patients walking normally, PD swing = Parkinson patients walking with enhanced arm swing, RHS = right heel strike; LHS = left heel strike; dB = decibel. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

accompanied by increased step length and walking speed. These findings support the concept that disturbed gait in PD patients is associated with impaired mediofrontal activity, assumed to reflect impaired SMA function, which may functionally normalize by enhancing arm swing, thereby improving gait.

The SMA is important for multi-limb coordination during walking with anti-phase arm swing, due to its strong and widespread connections with motor fields of the contralateral cortex. This is reflected in power modulations over sensorimotor areas, including the putative SMA [12,13], with particularly within step ERD-ERS alternation during normal gait [1,8,16,22–24]. Arm swing-associated activity at specifically the mediofrontal Fz electrode during gait, which we demonstrated in our previous healthy subject study by comparing gait with and without arm swing [1], was confirmed in the present healthy participants: walking without arm swing resulted in diminished ERD-ERS alternation. This changed ERD-ERS pattern in healthy subjects mimicked the pattern of less demarcated ERD-ERS alternation over the mediofrontal cortex of PD baseline gait, accompanied by reduced or absent arm swing. In both groups, reduced power modulations were accompanied by shorter steps, while only in PD patients this resulted in reduced walking speed. This points at a consistent association between well-demarcated ERD-ERS alternations over the mediofrontal cortex, arm swing and efficient gait, which can be attentively modulated in both healthy participants (by reduced arm swing) and PD patients (by enhanced arm swing). This association is further underscored by the beneficial effect of enhanced arm swing, not only during steady-state walking in PD, but also during the pre-movement stage of cued gait initiation, which we have recently demonstrated [8]. Beta power variability in PD motor circuitry has been described to be negatively correlated to symptom severity [25], implying that normalized power modulations may reduce symptom severity and improve Parkinsonian gait. The present study supports this model: attentively enhanced arm swing in PD gait resulted in gait improvement, based on normalized within step ERD-ERS alternation over the mediofrontal cortex.

Since especially SMA activity has previously been associated with disturbed gait in PD [4,5], we consider the SMA to be major contributor to the observed effects at the mediofrontal Fz electrode. Moreover, combined EEG-fMRI measurements have indeed demonstrated a significant correlation between Fz and SMA activity [26]. It should further be recognized that the SMA is an important cortical node in basal ganglia-thalamus-cortical loops implicated in motor control [27–29]. This implies that an affected striatum due to dopaminergic denervation, as seen in PD, leads to functional impairment of the SMA [30], while SMA activity has been found to be functionally improved by dopaminergic medication and deep brain stimulation [31,32]. Disturbed gait in PD, including reduced arm swing, is associated with functional changes beyond the SMA and basal ganglia, comprising an extended network of subcortical and cortical nodes [33]. In this respect, the arm-swing-associated effects that we recorded over the putative SMA may thus well reflect an index of functional change in such distributed circuitry. The embedding of the SMA in cortical and subcortical circuitries that are involved in both motor and cognitive control, further supports our inference that attentively enhanced arm swing may serve as an SMA-mediated driving force to overcome impaired gait control in PD patients.

Interestingly, verbal instructions to increase step length may also improve Parkinsonian gait [10,11]. This begs the question whether either verbal instruction, arm swing movement, or a combination of the two is responsible for the facilitating effect found in this study. Both strategies employ instructional sets and attention focused on specific elements of 'normal' walking that may bypass basal ganglia circuitry and activate (pre)frontal brain areas to prepare the motor cortex for locomotion [34]. Regarding basic motor control, neural linkage at spinal and brain level leading to gait-related coupling of upper and lower limb muscles has been described [35–37]. In this respect, we recently demonstrated that upper limb muscles drive and shape lower limb muscle activity during healthy gait, while the effect in opposite direction is less [37]. This directional effect is consistent with the idea that the instruction 'enhanced arm swing' is a stronger cue than e.g. the instruction 'make large steps'. Theoretically, the cue 'enhanced arm swing' fuels the mediofrontal cortex along pathways additional to those involved in generating lower limb movements and therefore additionally boosts lower limb activity compared to other verbal instructions. This effect needs further evaluation in daily life. Using Nordic walking sticks, which also has a positive effect on PD gait, provides continuous somatosensory feedback to maintain enhanced arm swing, demonstrating how current findings can be implemented in daily life [38]. Future studies should explore additional strategies that may provide more continuous cueing to enhance arm swing outside an experimental setting.

Regarding cortical activity at Fz, one needs to keep in mind that the recorded activity may result from a mixture of underlying sources. One might question whether the observed arm-swing related effects at the Fz electrode are not simply a consequence of volume conduction from the motor area of the arms (i.e. C3 and C4). However, as the scalp maps demonstrated that these effects in PD walking with enhanced arm swing are not observed in the FC1 and FC2 electrode, which lie between Fz-C3 and Fz-C4, we regard it unlikely that the observed midline effects are the result of volume conduction. Nonetheless, the observed effects cannot be unequivocally assigned to a distinct single brain region such as the SMA. Future studies with more EEG channels, enabling higher spatial resolution, are necessary to further identify contributions of the SMA, pre-SMA and/or cingulate motor cortex to the observed effects.

5. Conclusion

Ambulatory EEG and accelerometer recordings during overground walking demonstrated that baseline PD gait, characterized by reduced arm swing, exhibited reduced within-step 20–50 Hz ERD-ERS alternation over the mediofrontal cortex accompanied by reduced step length and walking speed compared to healthy participants. When these patients walked with enhanced arm swing, this ERD-ERS pattern became similar to that of healthy participants while step length and walking speed normalized. This provided neural support for arm swing as a driving force in gait control, which is mediated by the mediofrontal cortex (including the SMA). Enhancing arm swing in PD patients could therefore serve as an effective rehabilitation concept for improving Parkinsonian gait.

Authors' roles

Experiments were performed in the University Medical Center Groningen. Conception and design: J.B.W., T.v.L., B.M.J. and N.M.M. Data acquisition: J.B.W. Analysis and interpretation: J.B.W., B.M.J. and N.M.M. First draft of the manuscript: J.B.W. Revising manuscript: B.M.J., N.M.M. and T.v.L. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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B.M.J. None.

Declaration of competing interest

The authors have no conflict of interest to report.

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