Low-dimensional dynamics of brain-muscle networks during gait

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Abstract

The neural control of walking requires the interaction between multiple sensory and motor systems. We assess brain-muscle networks during overground gait to assess the dynamic interactions between neural systems involved in gait control. Mobile electroencephalography (EEG) and electromyography (EMG) was recorded from 24 healthy young adults, 24 healthy older adults, and 21 individuals with Parkinson's Disease during overground walking. We estimated dynamic functional connectivity between bilateral sensorimotor cortices and eight leg muscles within a gait cycle. Using multivariate analysis, we extracted brain-muscle networks and investigated the inter-subject variability in the network activation patterns. We identified three orthogonal brain-muscle networks within a gait cycle: 1) a bilateral network that is left-right symmetric and mostly active during the double support phase, 2) a left-lateralised network that is activated during the left swing phase, 3) a right-lateralised network active during the right swing phase. These networks span a low-dimensional subspace in which neuromuscular gait dynamics unfold: the trajectories reveal that the networks are simultaneously co-expressed during the double support phase but with different networks dominating the initial and terminal double support phase. Assessing the inter-subject variability in trajectories, we found an age-related contraction of the trajectories corresponding to a general reduction in neuromuscular connectivity at older age and a selective enhancement of the bilateral network in participants with impaired tactile sensitivity of the foot. The three brain-muscle networks provide a parsimonious description of neuromuscular connectivity during overground walking. The inter-subject variability in low-dimensional trajectories is associated with age and somatosensory function. The selective increase of the bilateral network may reflect a compensation strategy to maintain mediolateral gait stability in response to impaired somatosensory information from the feet.

Keywords: mobile brain-body imaging, dynamic functional connectivity, network physiology, gait, aging.

1. Introduction

Human gait requires the activation and coordination of numerous muscles, adjusted on the fly to accommodate changing environmental and task demands. This rests upon the integration of sensory information, and the corresponding adaption of spinal and supraspinal motor commands (Grillner, 2011). Spinal interneuron networks generate the basic locomotor pattern, which is modified by incoming peripheral afferent signals and descending supraspinal signals (Takakusaki, 2013). Sensory afferent information contributes to corrective reflexes following sudden perturbations and may be used to adapt and update gait patterns (Nielsen, 2003). In humans in particular, the cortex is not only involved in complex walking tasks such as precision stepping or obstacle avoidance but also in undemanding stereotyped locomotion. While the anatomy and physiology of the human sensorimotor system are well known, the functional organisation of the neural control of human gait remains incompletely understood.

Recent advances in mobile brain-body imaging (MOBI) now allow assessment of cortical processes during gait, in addition to muscle activity and 3D kinematics (Gennaro and de Bruin, 2018; Gramann et al., 2011). Using high-density electroencephalography (EEG), several studies have shown intra-stride modulations of oscillatory activity in the sensorimotor cortex, in particular in the beta band (Bruijn et al., 2015; Gwin et al., 2011; Kaneko et al., 2021; Pizzamiglio et al., 2017; Scanlon et al., 2022; Seeber et al., 2015; Wagner et al., 2016; Wagner et al., 2012; Wagner et al., 2014). Beta-band activity is a well-documented feature of the motor system during voluntary movement (van Wijk et al., 2012), and is likely involved in maintaining a particular sensorimotor state (Baker, 2007; Engel and Fries, 2010; Tan et al., 2016). During walking, beta oscillations have been found to be a sensitive marker for motor system engagement, with decreases in beta power (event-related desynchronisation, ERD) just before and during the double support phase of the gait cycle and increases in beta power during single-support and swing phases (Seeber et al., 2015; Wagner et al., 2012).

Research on corticomuscular connectivity has shown that cortical beta activity is transmitted to spinal motoneurons during walking (Artoni et al., 2017; Gennaro and de Bruin, 2020; Petersen et al., 2012), particularly during the double support phase of the gait cycle (Roeder

et al., 2018; Zandvoort et al., 2021). This cortical input to spinal motor neurons appears to be reduced in the elderly and may be linked to changes in the temporal coordination of gait (Roeder et al., 2020). Zandvoort and colleagues (2021, 2022) found that cortical beta-band activity was linked with specific patterns of distributed muscle activity (i.e. muscle synergies), which are involved in controlling shear forces to decelerate and accelerate the body (Dominici et al., 2011). Indeed, it is thought that these cortical beta oscillations may be linked to postural stability during locomotion (Bruijn et al., 2015). For instance, mechanical perturbations to standing balance increased connectivity between the supplementary motor area and other central motor areas, while visual perturbations decreased connectivity between parietal and occipital regions (Lau et al., 2014; Peterson and Ferris, 2019). These findings suggest that synchronized oscillatory activity has a functional role in how the central nervous system (CNS) coordinates behaviours such as gait (Boonstra, 2013; Engel et al., 2001; Farmer, 1998), and may be particularly involved in the coordinating muscle activities for balance control.

A key challenge remains the high dimensionality of functional connectivity data. While several studies have revealed interactions between specific muscles or areas of the CNS (Baker, 2007; Schnitzler and Gross, 2005; van Wijk et al., 2012), the global organisation of the sensorimotor system remains elusive. Complex network analysis offers the opportunity to investigate the large-scale organisation of distributed networks (Bullmore and Sporns, 2009) and the role of neural synchronisation in motor coordination (Brovelli et al., 2004). For example, network analysis has been used to map and analyse functional muscle networks during postural tasks, showing functional connectivity between different muscle groups at multiple frequency bands (Boonstra et al., 2015; Kerkman et al., 2020; Kerkman et al., 2018) and between groups of spinal motor neurons (Hug et al., 2022). While complex network analysis allows mapping of interactions in large-scale systems, the dimensionality of these networks remains a challenge when comparing their topologies between experimental conditions or patient groups (Rubinov and Sporns, 2010; Zalesky et al., 2010). Moreover, functional networks are not static but reorganize and adapt to a task at different time scales (Bressler and Menon, 2010; Hutchison et al., 2013; Vidaurre et al., 2018). However, the dynamics in these large-scale networks generally unfold on a low-dimensional manifold or

subspace (Breakspear, 2017; Cunningham and Yu, 2014; Mehrkanoon et al., 2014; Shine et al., 2019b), making them tractable for statistical comparisons.

Here we assess brain-muscle networks to investigate the distributed neural circuitry supporting locomotor behaviour. We estimate dynamic functional connectivity between bilateral sensorimotor cortices and eight leg muscles during overground walking in healthy young, older and people with Parkinson's Disease (PD). Using orthogonal non-negative matrix factorisation and graph theoretical analyses we assess the dynamics of the brain-muscle network across the gait cycle within a low-dimensional subspace. The topology and time-frequency profiles of brain-muscle networks offer a unique window into the dynamics of the neural circuitry driving the musculoskeletal system during walking and may provide novel insights into the neural mechanisms of gait control in humans.

2. Materials and Methods

Three groups participated in this study with 69 participants in total: 1) 24 healthy young adults (12 females, mean (SD) age 25.9 (3.2) years), 2) 24 healthy older adults (12 females, mean (SD) age 65.1 (7.8) years), 3) 21 individuals with PD (8 females, mean (SD) age 67.4 (7.3) years). All experimental protocols were approved by the Human Research Ethics Committee of Queensland University of Technology (#1300000579) in accordance with the Declaration of Helsinki, and all participants gave written informed consent prior to participation. These data were previously reported in Roeder et al. (2020).

2.1 Experimental protocol

Participants performed overground walking for 12-14 minutes. Participants walked barefoot at their preferred speed (3.3 – 4.8 km h^{-1}) with natural arm swing. Participants walked back and forth along a straight path (~14 m) on a firm surface in the gait laboratory and turned at each end of the room. The turning sections, including acceleration at the beginning of the straight-line path and deceleration at the end (~2.4 m), were excluded from further analyses and only straight-line walking (8.9 m) was used for analysis.

Healthy older people and people with PD also completed a peripheral sensation test on a different day. We assessed tactile sensitivity at different sites of their feet (lateral malleolus,

plantar surfaces of the great toe, midfoot/arch and heel) using Semmes-Weinstein pressure aesthesiometer with nylon monofilaments (Lord et al., 2003). People with PD were also assessed for disease severity using the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Hoehn & Yahr scoring (Goetz et al., 2008; Hoehn and Yahr, 1967). People with PD presented in their optimally medicated state for all experiments.

2.2 Data acquisition

EEG, EMG and kinematic events (heel strike and toe off) were recorded while participants performed overground walking. Bipolar surface EMG was recorded from the left and right tibialis anterior (TA), soleus (SOL), medial and lateral gastrocnemii (GM, GL) muscles. Simultaneously, EEG signals were recorded using water-based AgCl electrodes placed at 10 cortical sites according to the international 10-20 standard (P3, P4, C3, Cz, C4, F7, F3, Fz, F4, F8). Footswitches were attached onto the participants' sole at the heel and the big toe of both feet. All signals (EEG, EMG and footswitches) were recorded synchronously with a wireless 32-channel amplifier system (TMSi Mobita, The Netherlands) and sampled at 2 kHz. The recording system and wireless transmitter were placed in a belt bag and tied around the participants' waist.

2.3 Data analysis

EEG, EMG and footswitch data were pre-processed as reported in (Roeder et al., 2020). In short, electrophysiological data were normalized to unit variance and segments with excessive noise (large-amplitude movement artefacts, EMG activity) were removed. EEG signals were band-pass filtered (2nd order Butterworth, 0.5-70 Hz) and re-referenced to a common average reference (EEGLAB version 13.6.5, Delorme and Makeig, 2004). Independent components containing eye blink, muscle, or movement artefacts were removed from the data. Finally, we calculated bipolar EEG montages to assess cortical activity from bilateral sensorimotor cortices: C3-F3 for the left sensorimotor cortex, and C4-F4 for the right sensorimotor cortex (Long et al., 2015).

EMG data were high-pass filtered (4th order Butterworth, 20 Hz cut-off) and full-wave rectified using the Hilbert transform (Boonstra and Breakspear, 2012). For coherence

analysis EMG signals were also demodulated to avoid spurious coherence estimates resulting from periodic changes in EMG amplitude (Boonstra et al., 2009).

2.3.1 Time-frequency analysis

We used time-frequency analysis to assess changes in spectral measures within the gait cycle (Boonstra, 2019). EEG and EMG signals were segmented into 220 segments of 600 ms length (-300 to +300 ms with respect to heel strike). Heel strike served as reference point (t = 0) in the gait cycle to which all segments were aligned. Event-related coherence spectra were estimated across the 220 segments using Short-time Fourier transform (a 375-ms Hanning window with increments of 25 ms) by squaring the absolute value of coherency. We computed coherence pairwise between all possible channel combinations (EMG-EMG or intermuscular coherence; EEG-EMG or corticomuscular coherence; EEG-EEG or corticocortical coherence). To minimize the effect of volume conduction, we used imaginary coherence to estimate corticocortical connectivity between bilateral sensorimotor cortices (Nolte et al., 2004). With a total of 10 channels (8 EMG and 2 bipolar EEG), we hence assessed dynamic functional connectivity between 45 channel pairs. Event-related coherence spectra were computed for each participant during overground walking.

2.3.2 Network analysis

We used orthogonal non-negative matrix factorisation (NNMF) (Ding et al., 2006) to decompose coherence spectra across all channel combinations, time points of the gait cycle and participants into gait-cycle dependent activation patterns and their corresponding weights (i.e. coupling strength). These weights define the undirected weighted network for each frequency layer that is fixed across participants. In contrast, the activation patterns of these networks across the gait cycle vary between participants. We used an open-source MATLAB toolbox for computing the orthogonal NNMF (Li and Ngom, 2013), which is similar to non-negative sparse PCA (Li and Ngom, 2013; Zass and Shashua, 2006).

Weights were thresholded and binarized to obtain minimally connected networks for visualisation purposes, as described in Kerkman et al. (2018); we used the Matlab Brain Connectivity Toolbox for the thresholding calculations (Rubinov and Sporns, 2010). This

yields a single, unique value, which corresponds to the percolation threshold, and yields sparse networks in which each node is connected to at least one other node by an edge at one of the layers of the multilayer network. That is, in this study connectivity at each frequency band (alpha, low beta, high beta, gamma) represents a layer of the multilayer network. To describe the multilayer networks further, we calculated multilayer strength centrality (De Domenico et al., 2013) using the R package MuxViz (v3.1, De Domenico, 2022; De Domenico et al., 2015). For this purpose, we treated the layers of each network as non-interconnected (i.e., a network has multiple layers, which encode a specific relationship between nodes, and nodes preserve their identity across layers but they are not connected across layers) and we used non-thresholded weights. Multilayer strength centrality is the sum of weights of edges connected to a node added up across all layers (De Domenico, 2022). Multilayer strength centrality helps to identify the importance of specific nodes (i.e., muscles and cortical regions in this study) within a network: higher weights at a specific node indicate stronger connectivity to other sites/regions (and hence, stronger interactions). By looking at the distribution of strength centrality across the nodes (i.e., muscles and cortical regions) it is possible to identify which nodes are 'key players' in a network and which ones only contribute weak links.

To further investigate the dynamics of brain-muscle connectivity and its temporal evolution throughout the gait cycle, we assessed the state space trajectories in the low-dimensional subspace (Shine et al., 2019a). This was possible because the networks we extracted via NNMF were orthogonal. To visualise these results, we projected the mean state space trajectory for each group (young, old, PD) onto a 3D plot.

2.3.3 Statistical analysis

To statistically compare the activation patterns of these networks across groups, we extracted the network activation amplitude by averaging the activation pattern across all time points of the gait cycle for each participant and network separately. These activation amplitude values were compared across groups (young, old, PD) using three separate one-way ANOVAs (one for each network). We controlled the false discovery rate by using the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) using an opensource Matlab script (Groppe, 2015).

To investigate the inter-subject variability in the network activations in the 3D subspace, we performed principal component analysis (PCA; Boonstra et al., 2007; McIntosh and Lobaugh, 2004; Mehrkanoon et al., 2016). The 3D trajectory of each participant was reshaped into a vector and PCA was performed across all participants (n=66), which decomposed this data into principal components (PCs) and the eigenvector coefficients that capture the contribution of each participant. We then compared the eigenvector coefficients of PC1 and PC2 between groups using a one-way ANOVA and explored the association with participant characteristics (age, sex, weight) and clinical scores ($TouchSensitivity_{total}$, $UPDRS_{motor}$, Hoehn&Yahr) using correlation analysis. We controlled the false discovery rate for these $2 \times 6 = 12$ correlations using the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995).

The significance level (alpha) was set at 0.05 for all statistical analyses. We used student t-tests as post-hoc analysis when the group effect was significant.

3. Results

Due to excessive EEG artefacts across all channels and conditions (large-amplitude movement artefacts (>300µV) occurring with regular rhythmicity in each gait cycle throughout the entire record) we excluded two healthy young participants and one participant with PD. Hence, analyses were based on n = 22 for the younger group, n = 24 for the older group, and n = 20 for PD group. Clinical measures such as MDS-UPDRS, Hoehn & Yahr scores and touch sensitivity scores were only available for the PD and old groups.

3.1 Time-frequency coherence

Time-frequency coherence between muscles and cortical regions revealed a distinct functional organisation of intermuscular coherence (IMC) and corticomuscular coherence (CMC, Figure 1; Figure S1 to S3 Supplementary Material). Greatest IMC was observed amongst muscles of the same leg (e.g., TA, SOL, GM, GL of the left leg), and particularly amongst triceps surae muscles. IMC was modulated with the gait cycle, with peak values at

frequencies <20 Hz during the double support phase. IMC was much lower between muscles of different legs. Overall, CMC was lower than IMC and mainly restricted to the double support phases of the gait cycle. Cortico-cortical coherence (CCC) was elevated throughout the gait cycle and showed minor increases during the double support phase. These time-frequency profiles were similar for all groups across all channel combinations (see Supplementary Material), with coherence slightly reduced in older people and people with PD.

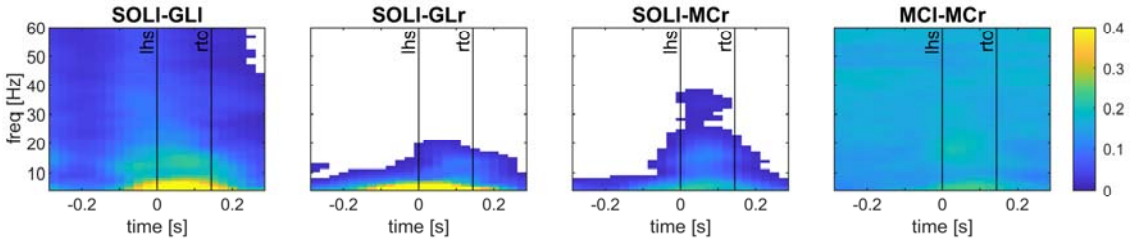

Figure 1. Time-frequency coherence between EMG and EEG channels during overground walking in healthy young people. Coherence is shown between left Soleus muscle (SOLl), left and right lateral gastrocnemii (GLl, GLr), left and right motor cortices (MCl, MCr). Coherence values are thresholded: average coherence values below the 95% CI are set to zero (white). The x-axis shows the time in seconds relative to heel strike (t=0) of the left foot and the y-axis the frequencies in Hz. Black vertical lines indicate the footswitch events. lhs, left heel strike; rto, right toe-off.

3.2 Brain-muscle networks

To extract the low-dimensional subspace in which the brain-muscle networks unfold, we decomposed time-frequency coherence in canonical frequency bands using orthogonal NNMF. Three orthogonal components (networks) were extracted that explained most of the variance (72.7%). We used the scree plot criterion to determine this meaningful number of dimensions in our latent dimension-reduction analyses (Figure S4 Supplementary Material). Each component consists of the weights of a multilayer network and the temporal activation within the gait cycle for both gait events (left and right heel strike) and for each participant (Figure 2).

The first network (Figure 2A) shows strong connectivity between lower leg muscles within and across legs particularly at alpha frequencies, i.e., symmetric activation in the left and

right leg. Temporal activation profiles reveal peak magnitude at middle of the double support phase, which is symmetrical with respect to left and right heel strike. This network is only weakly activated during the swing phase. Visual inspection of the activation plots suggests higher activation in the older and PD groups, however this effect is not statistically significant ($F_{2, 65} = 1.23$, $p_{adj} = 0.30$).

The second network (Figure 2B) also shows coherence across all frequency bands with strongest connectivity at alpha and low beta frequencies. Edge weights are highest between muscles of the left leg, and temporal activation peaks at left toe-off, remains elevated during the swing phase of the left leg, and then peaks again at the left heel strike. Activation amplitude is lowest in the PD group compared to the young and old groups, but the group effect is not significant ($F_{2, 65} = 2.81$, $p_{adj} = 0.10$).

The third component (Figure 2C) is right lateralised with peak weights at alpha and low beta frequencies. The temporal activation and network weights are a mirror image of network 2: the strongest edges are between muscles of the right leg and the network is activated from right toe-off to right heel strike, i.e., during the right leg swing phase. A one-way ANOVA revealed a significant group effect ($F_{2, 65} = 6.88$, $p_{adj} = 0.006$). Using post-hoc tests, we found that the young group had a significantly higher activation amplitude than the older group ($t(44) = 2.78$, $p_{adj} = 0.012$) and PD group ($t(40) = 3.43$, $p_{adj} = 0.004$), but no difference between the older and PD groups ($t(42) = 0.56$, $p_{adj} = 0.58$).

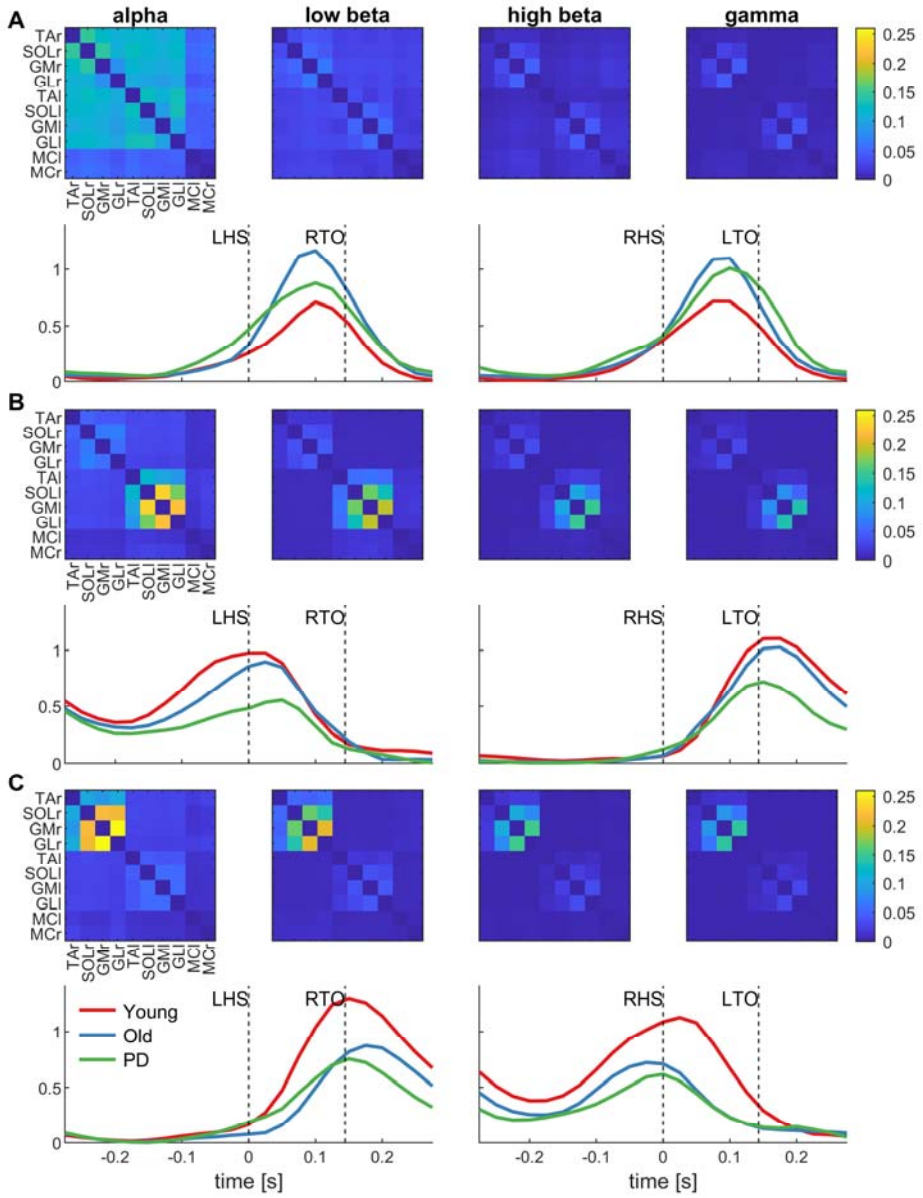

Figure 2. Network weights and activations obtained using orthogonal non-negative matrix factorisation of inter-/corticomuscular coherence. Coherence spectra of all EEG and EMG channel combinations, participants, conditions (left, right) and time points of the gait cycle are decomposed into three components (networks). Each network (A, B, C) is characterised by the weights (adjacency matrices) and activations time course throughout the gait cycle. The adjacency matrices show the average weights across participants for each frequency band separately (alpha, low beta, high beta, gamma). These weights give the edges between the 10 nodes of each network. The temporal activation patterns of each component are disaggregated by group (young, old, PD). LHS, left heel strike; LTO, left toe-off; MCl/MCr, motor cortex left/right; GMl/GMr, gastrocnemius medialis left/right; GLl/GLr, gastrocnemius lateralis left/right; RHS, right heel strike; RTO, right toe-off; SOLl/SOLr, soleus left/right; TAl/TAr, tibialis anterior left/right.

3.3 Network topologies

To visualise the topologies of the three networks that we extracted, we thresholded the weights to obtain minimally-connected binary networks that include the different frequency bands as layers (multilayer networks, see methods, Figure 3). The threshold was 0.145 for network 1, 0.278 for network 2, and 0.30 for network 3. Figure 3 shows how the thresholded, binarized networks are spatially distributed across the body (plotted separately per network and layer). Multilayer network analysis (De Domenico, 2022) was used to describe the identified networks further; for these analyses we used the non-thresholded weights. Specifically, we calculated the multilayer strength centrality for each network (bar graphs in Figure 3). The distribution of strength centrality shows that network 1 has a bilateral distribution with high weights across all muscles of both legs, which indicates that all muscles have similarly strong connectivity and are therefore equally important in the network. Network 2 shows peak weights at the triceps surae muscles of the left leg suggesting that these muscles have the strongest links within this network. Similarly, network 3 shows peak weights at the triceps surae muscles of the right leg.

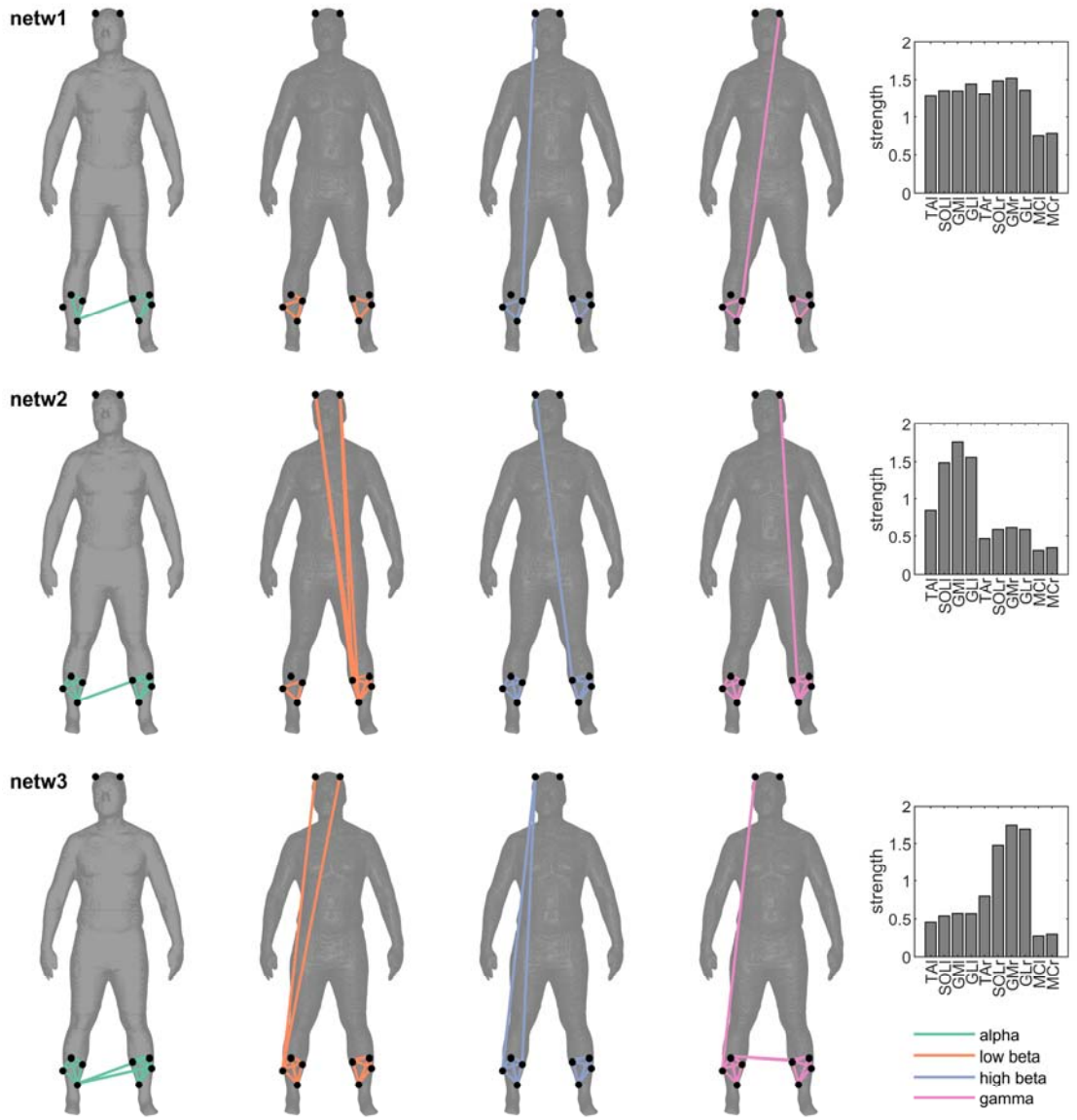

Figure 3. Topologies of binarized multilayer networks and multilayer strength centralities. Topologies displayed over human body shape show minimally connected networks (thresholded and binarized edge weights) per network (network 1, 2, 3) and layer (alpha, low beta, high beta); the threshold was 0.145 for network 1, 0.278 for network 2, and 0.30 for network 3. Connections at alpha (green), low beta (orange), high beta (blue) and gamma (pink) frequencies are shown; each frequency band represents a layer in multilayer networks. The right-hand side panels show multilayer strength centrality for each network using non-thresholded weights. Each bar graph shows the strength metric for each node (i.e., muscles, cortical sites) of each multilayer network. The higher the strength of a node, the stronger the connectivity is with other nodes of the multilayer network. MCl/MCr, motor cortex left/right; GMl/GMr, gastrocnemius medialis left/right; GLl/GLr, gastrocnemius lateralis left/right; SOLl/SOLr, soleus left/right; TAl/TAr, tibialis anterior left/right.

3.4 Low-dimensional subspace of network activations

The orthogonal nature of NNMF decomposition allows us to project the high-dimensional dynamic connectivity data onto the low-dimensional subspace spanned by the three networks. This reveals how the complex brain-muscle network follows a closed trajectory with the gait cycle that captures a continuous transition in relative dominance of each of these network modes (Figure 4A). That is, there is no serial activation of these networks, but rather they are co-expressed, although each stage of the gait is associated with relative dominance of each of the networks.

The temporal order of activation of the three networks (i.e., network 1 during the middle of the double support phase, network 2 at LHS and network 3 at RTO; see Figure 2) results in a rotation through in the three-dimensional subspace. The trajectories do not pass through the origin (0,0,0) as networks 2 and 3 remain activated during the left and right swing phase, respectively. The 2D projections show that while the younger group has a relatively stronger activation of the lateralized networks 2 and 3, the older and PD groups show relatively stronger activation of the symmetric network 1. The root mean square differences (RMSD) between the group-average trajectories show that phases of the gait cycle during which trajectories differ most (Figure 4B). We used permutation testing to statistical test for group differences in the trajectories: individual participants were randomly swapped between the groups and the overall RMSD in the empirical trajectories were compared against these resampled null distributions. This shows that the trajectory of the young group differed from the old group (RMSD = 0.19, $p = 0.046$) and the PD group (RMSD = 0.24, $p = 0.017$), while there was no significant difference between trajectories of old and PD groups (RMSD = 0.12, $p = 0.24$).

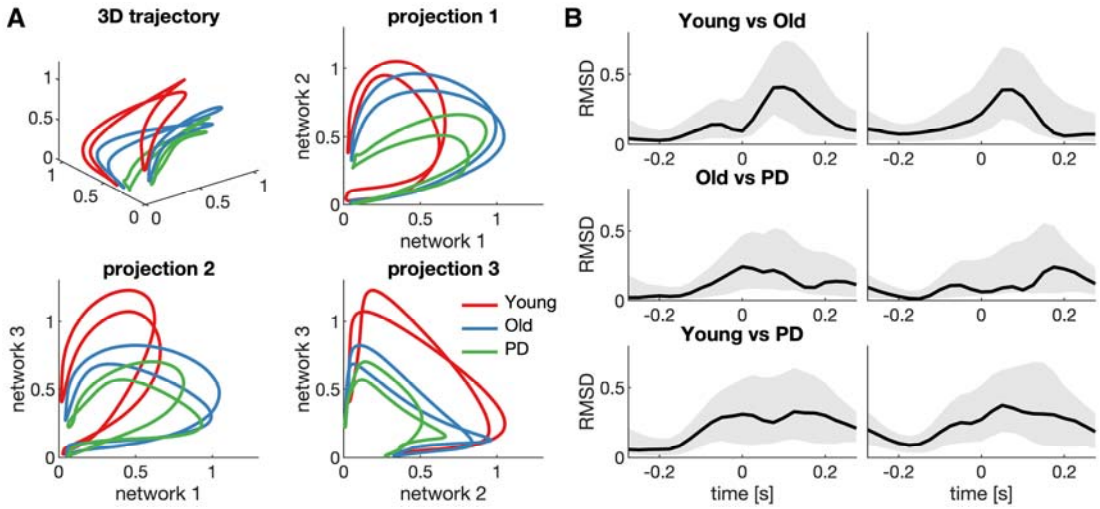

Figure 4. State-space embedding of the trajectories of the temporal activations of the three extracted networks. A) Different lines depict the group-average trajectories (Young, Old, PD). In addition to the trajectories in the 3D subspace, the projections on each of the three axis is shown. **B)** The root-mean-square deviation (RMSD) of the group-average trajectories of young vs old, old vs PD, and young vs PD. Grey patches show the 95% confidence interval estimated based on 1000 bootstrapped samples.

3.5 Inter-subject variability in network activations

We then performed principal component analysis (PCA) to further assess the inter-subject variability in the network activations in the 3D subspace (Boonstra et al., 2007; McIntosh and Lobaugh, 2004; Mehrkanoon et al., 2016). PC1 explained 41% of the inter-subject variability in the 3D trajectories and reflected the average pattern of the 3D trajectories: bilateral network 1 peaked in the middle of the double support phase, left-lateralized network 2 peaked at left heel strike and toe off, and right-lateralized network 3 peaked at right heel strike and toe off (Figure 5, top row). The eigenvector coefficients showed a significant group effect ($F_{2,63}$ = 4.27, p = 0.017). Post-hoc test showed that the younger group had higher eigenvector coefficients than the PD group (t(40) = 2.89, p_{adj} = 0.019), but no difference between the younger and older groups (t(44) = 1.33, p_{adj} = 0.19) or between the older and PD groups (t(42) = 1.86, p_{adj} = 0.10). As this PC reveals large excursions in all three dimensions, the group effect captures a general reduction of network activation, that is, a shrinking of the 3D trajectories. PC2 explained 24% of the inter-subject variability and revealed a selective activation of the bilateral network 1 (Figure 5, bottom row). Although the eigenvectors coefficients were higher in the old and PD groups, the group effect was not statistically significant ($F_{2,63}$ = 2.18, p = 0.12).

Finally, we explored the association between the eigenvector coefficients and several participant characteristics (age, sex, weight) and clinical scores ($TouchSensitivity_{total}$, $UPDRS_{motor}$, Hoehn&Yahr). When controlling the false discovery rate, we found a significant correlation between PC1 and age ($r = 0.33$, $p_{adj} = 0.042$, $n = 66$) and between PC2 and $Touch_{total}$ ($r = -0.41$, $p_{adj} = 0.042$, $n = 43$; see Supplementary Material S5 and ST1). The correlation effect between PC1 and age is negative showing that PC1 decreases with older age. The correlation between PC2 and touch sensitivity is also negative indicating that in older people with and without PD (touch sensitivity data only available in old and PD groups) PC2 is reduced as touch sensitivity deteriorates.

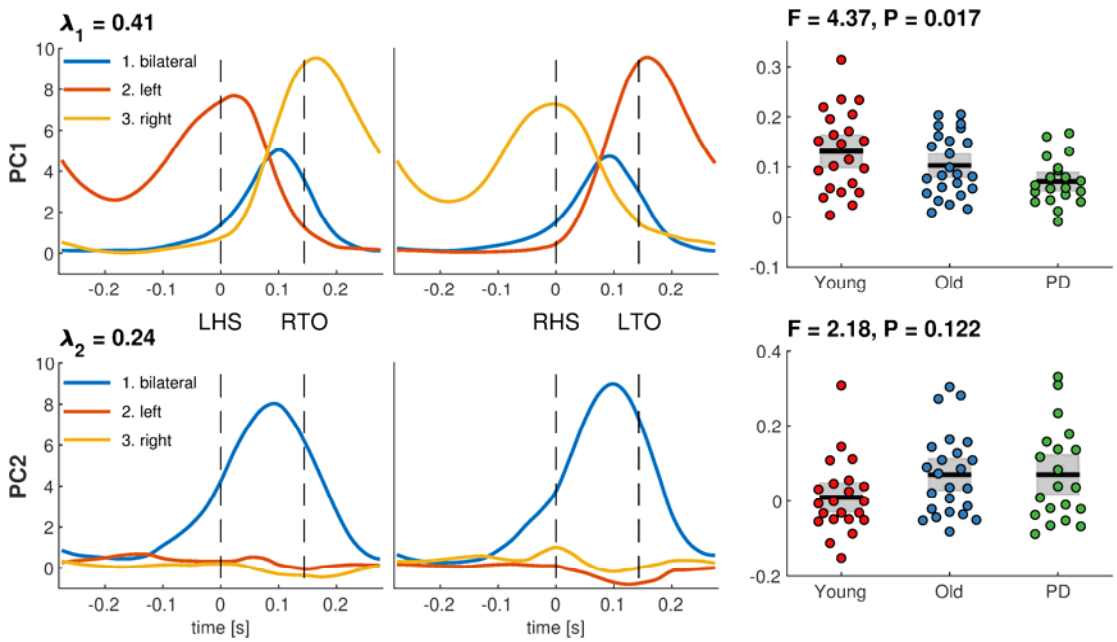

Figure 5. Principal component analysis and group effects of network activations. Network activations time course throughout the gait cycle per PC (left column), and eigenvector coefficients per PC per group (right column). Coloured dots show individual data of each participant, black horizontal lines show the group mean, grey boxes show the SEM. PC, principal component; λ, explained variance; LHS, left heel strike; RTO, right toe-off; RHS, right heel strike; LTO, left toe-off.

4. Discussion

We used a network approach to study distributed neuromuscular activity contributing to human locomotor behaviour. We estimated dynamic functional connectivity between

cortical sensorimotor regions and lower leg muscles during overground walking in healthy young, older and people with PD. Using orthogonal NNMF, we identified three distinct brain-muscle networks: 1) a bilateral network that is left-right symmetric and mostly active during the middle of the double support phase, 2) a left-lateralised network that is activated during the left swing phase and peaks at the left heel strike and toe-off, 3) a right-lateralised network that mirrors the left-lateralised network. The three networks span a low-dimensional subspace in which neuromuscular gait dynamics unfold. These trajectories reveal that these networks are simultaneously co-expressed during the double support phase but with different networks dominating the initial and terminal double support phase. Assessing the inter-subject variability in trajectories, we found an age-related contraction of the trajectories corresponding to a general reduction in neuromuscular connectivity at older age and a selective increase in activation of the bilateral network in participants with impaired tactile sensitivity of the foot sole.

The current findings provide a parsimonious description of neuromuscular connectivity during gait in three spatiotemporal patterns. These three patterns have similar spectral profiles – with strongest coherence in the alpha and lower beta band – and are all primarily recruited during the double support phase. However, these modes have distinct network topologies and temporal profiles that are aligned to specific behavioural events. These findings demonstrate that neuromuscular connectivity followed a low-dimensional manifold (that is, most variance was explained by few components; Figure S4). By assessing dynamic brain-muscle networks, we show that neuromuscular connectivity is not shaped by a simple cortical drive to the muscle but reveals distinct network motifs that likely reflect different neural circuits. These circuits – rather than alternating – perform a low-dimensional rotation in neural space, in which the connectivity is cycling through all phases continuously during the gait cycle, similar to the ensemble dynamics observed in spinal motor networks (Lindén et al., 2022). This low-dimensional rotation may reflect a spiral attractor of the spinal interneuron network, in which changes in the processing of afferent or efferent activity may shape the underlying manifold and therefore change the attractor (Bruno et al., 2017; Khona and Fiete, 2022).

Previous research has shown increased beta activity during the double-support phase in cortical activity (Bruijn et al., 2015; Gwin et al., 2011; Seeber et al., 2015; Wagner et al., 2012) and corticomuscular coherence (Roeder et al., 2018; Zandvoort et al., 2021, 2022), suggesting a corticospinal drive to the muscles (Artoni et al., 2017; Jensen et al., 2019). Here we show the modular organization of common spinal input to different lower leg muscles, which compliments previous notions of modular control of gait (Dominici et al., 2011; Ivanenko et al., 2007; Kiehn, 2016). In particular, muscle synergy analysis has revealed two lateralized muscle synergies that are involved in the touch-down and lift-off of the left and right legs, which show coherent activity with the motor cortices (Zandvoort et al., 2021, 2022) and emerge around the onset of independent walking in children (Dominici et al., 2011). The two lateralized brain-muscle networks identified in the current study were also precisely timed to the critical events of the gait cycle – lift-off and heel strike – and remained activated while the foot was in the air. It appears therefore likely that these networks are involved in stabilising the ankle joint rather than in generating forward propulsion, in line with the suggested role of beta activity maintaining sensorimotor states (Engel et al., 2001).

The PCA of the network activations showed that PC1 captures a general decline (contraction/shrinking) in activation of all three networks between groups (Young > Old > PD) and is negatively correlated with age. That is, PC1 is reduced in older people with and without PD. Overall, this reflects a general reduction in neuromuscular connectivity with older age.

This finding agrees with previous studies showing decreased corticomuscular and intramuscular coherence during walking in older people (Dos Santos et al., 2020; Gennaro and de Bruin, 2020; Roeder et al., 2020; Spedden et al., 2019) or in people with PD (Yokoyama et al., 2020), which may be indicative of sensory processing in older people (Sato and Choi, 2021). Older people exhibit reduced reactive locomotor adjustments to perturbations (Bruijn et al., 2012; Vervoort et al., 2019) and particularly temporal aspects of gait control are affected by age, e.g., double support time (Vervoort et al., 2020). Such reactive gait adaptations are mainly driven by proprioceptive and visual feedback, which is processed by spinal circuits (Sato and Choi, 2021), and involved in modifying reactive changes in muscle activity (Choi et al., 2016). Importantly, spinal reflex pathways appear to be affected by age, such as reduced amplitude of the H-reflex (Chalmers and Knutzen, 2000)

and reduced modulation of the H-reflex (Lavender et al., 2020) during walking. Together this suggests that the general reduction in neuromuscular connectivity may reflect reduced input from spinal circuits into lower leg muscles that are involved in temporal gait control.

In addition to the general reduction in neuromuscular connectivity, PC2 revealed a selective modulation of the bilateral network 1, which was enhanced in the older and PD groups. We found a significant negative correlation between the weights of PC2 and touch sensitivity scores. That is, PC2 is higher in older and PD people, and within this group of older people the component is reduced as touch sensitivity deteriorates. This indicates that older people with and without PD use more of the bilateral network to control their gait rather than the left and right lateralised networks. This strategy may reflect a preference for a more stable, symmetric gait pattern in older people, particularly when touch sensitivity is impaired. Kinematic studies found older people show a reduced medio-lateral shift of the centre of mass (COM) – a strategy which is more robust towards perturbations and prioritizes maintaining mediolateral balance – compared to young adults who shift their body centre away from the fast foot during split-belt treadmill walking leading to an asymmetric balance control that may be metabolically more efficient (Afschrift et al., 2019; Fettrow et al., 2021). Indeed, older people who are destabilised through visual perturbations increase step width to gain stability (De Sanctis et al., 2022). The selective activation of the bilateral network in older participants may be linked to a reduction in muscle spindle afferent information relevant for the control of medio-lateral gait stability (Arvin et al., 2018) or a decrease in sensitivity of cutaneous mechanoreceptors of the feet (Perry, 2006; Peters et al., 2016; Verschueren et al., 2002). Receptors in the skin around the ankle and foot sole may provide information about ankle rotation (Kennedy and Inglis, 2002; Trulsson, 2001) and influence foot trajectory variability during walking (Yamashita et al., 2021). Decreased sensory information from skin receptors and muscle spindles in older people likely affects foot placement and stepping strategy, and thereby affects mediolateral balance control. Hence, the observed increase of the bilateral network 1 may therefore reflect a compensation strategy to maintain mediolateral gait stability in response to impaired sensory processing at the feet.

As the primary aim of our study was descriptive, the explanatory or causal interpretations of the possible neuronal origins of these three spatiotemporal patterns should be made with

caution. Recording 3D kinematics would allow assessment of the link between neural activity and locomotor behaviour more directly, for example by manipulating mediolateral stability through experimental perturbations (De Sanctis et al., 2022; Fettrow et al., 2021). In addition, the limited number of EEG channels available did not allow us to perform a source reconstruction of the signals, which would have provided a clearer neurophysiological understanding of the current results and delineate the cortical regions involved in the neural control of gait. While we estimated imaginary coherence between sensors over bilateral sensorimotor cortex (Ewald et al., 2012), functional connectivity in channel space should be interpreted cautiously as the channel locations cannot be seen as an approximation of a source's anatomical location and spurious connectivity can occur between sensors (Van de Steen et al., 2019). Finally, EMGs were only recorded from lower leg muscles, and hence our conclusions are restricted to the control of the ankle joint. Future studies should record a higher number of EMG channels from leg, hip and arm muscles, as this will provide a more complete picture of brain-muscle network modular gait control. For example, directed connectivity analyses have revealed that upper limb muscles drive and shape lower limb muscle activity during gait via subcortical and cortical pathways (Weersink et al., 2021).

5. Conclusion

Despite the numerous muscle groups and their sensory afferents involved, human gait is a relatively smooth and cyclic rhythm, which adjusts to small fluctuations in execution and the environment from cycle to cycle. Here we show that neuromuscular connectivity during the gait cycle is performing a low-dimensional 'rotation' within a high dimensional phase scape spanned by the large number of degrees of freedom of the locomotor system. The low-dimensional subspace in which the rotational dynamics unfolds is spanned by three brain-muscle networks, the symmetric bilateral network and the left- and right-lateralized networks. The variability in low-dimensional trajectory between participants is associated with age and tactile sensitivity of the foot. Future studies should demonstrate whether these differences reflect altered processing of afferent or spinal input with age or a strategy for compensating for the age-related decrease in postural stability.

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Conceptualization: LR, TWB, MB, GK. Data curation: LR. Formal analysis: LR, TWB. Investigation/Data collection: LR. Methodology: LR, TWB, MB, GK. Project administration: LR. Resources: GK. Software: TWB, LR. Supervision: TWB, GK. Visualization: TWB, LR. Roles/Writing - original draft: LR. Writing - review & editing: LR, TWB, MB, GK.

Additional information

The authors declare no competing interests.