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Brain imaging of locomotion in neurological conditions

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Summary

Impaired locomotion is a frequent and major source of disability in patients with neurological conditions. Different neuroimaging methods have been used to understand the brain substrates of locomotion in various neurological diseases (mainly in Parkinson's disease) during actual walking, and while resting (using mental imagery of gait, or brain-behavior correlation analyses). These studies, using structural (i.e., MRI) or functional (i.e., functional MRI or functional near infra-red spectroscopy) brain imaging, electrophysiology (i.e., EEG), non-invasive brain stimulation (i.e., transcranial magnetic stimulation, or transcranial direct current stimulation) or molecular imaging methods (i.e., PET, or SPECT) reveal extended brain networks involving both grey and white matters in key cortical (i.e., prefrontal cortex) and subcortical (basal ganglia and cerebellum) regions associated with locomotion. However, the specific roles of the various pathophysiological mechanisms encountered in each neurological condition on the phenotype of gait disorders still remains unclear. After reviewing the results of individual brain imaging techniques across the common neurological conditions, such as Parkinson's disease, dementia, stroke, or multiple sclerosis, we will discuss how the development of new imaging techniques and computational analyses that integrate multivariate correlations in "large enough datasets" might help to understand how individual pathophysiological mechanisms express clinically as an abnormal gait. Finally, we will explore how these new analytic methods could drive our rehabilitative strategies.

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Keywords

Gait disorders; Neuroimaging; Neurological conditions; Methods; Review; Dementia; Parkinson's disease; Stroke; Multiple Sclerosis

Introduction

Locomotion is often affected in neurological conditions. Gait disorders are found in 60% of patients hospitalized in neurological units [196]. Parkinson's disease (PD), stroke, multiple sclerosis (MS) and dementia are the leading causes of gait disorders in neurological settings. In PD, the presence of freezing of gait (FOG) — likely the most debilitating gait symptom— is reported in 38.2% in the “on medication” state, and is associated with poor quality of life [157]. After a stroke, 32–47% of stroke patients are not able to walk unsupervised [116,158]; age, severity of the paresis, size of brain lesions and presence of hemianopia are the major factors associated with gait disorders within 30 days post-stroke [35]. In MS, the leading cause of non-traumatic disability in young adults, mobility impairment affects 80% of the patients [149], even in the earliest stages of the disease [195]. Gait impairment in neurological conditions increased with advanced age, especially in older adults with non-Alzheimer's dementia [196]: gait disorders have been reported in 93% of patients with PD with dementia, 79% with vascular dementia, 75% with dementia with Lewy bodies and 25% with Alzheimer's disease (AD) [6].

Gait disorders are clinically divided in neurological or non-neurological causes, such as arthritis, or cardiovascular conditions. Among the neurological gait abnormalities, different patterns of gait disorders, such as parkinsonian gait, frontal gait or spastic gait, have been identified [227]. Identifying neurological from non-neurological clinical gait abnormalities is clinically important, because only neurological gait abnormalities have been associated with poor clinical outcomes, such as falls [225] or dementia [227]. Gait has been recently used to define a new pre-dementia syndrome, called the Motoric Cognitive Risk (MCR) syndrome [228]. The MCR syndrome is defined by the presence of slow gait and cognitive complaint; this syndrome represents an early risk factor for developing dementia [226].

The brain correlates of gait have been extensively studied in aging [70] and in individuals with specific neurological diseases [17,47,125] during the last few years using various techniques, such as electroencephalography, magnetic resonance imaging (MRI), nuclear medicine, non-invasive brain stimulation (i.e., transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS)) or functional near infrared spectroscopy (fNIRS). These various techniques give us access to the brain structures and the functional substrates involved in gait control during real walking or during mental imagery of gait. Each neuroimaging technique presents its own advantages and limitations and will be reviewed in detail in this article by including the different common neurological diseases. This review will be articulated around three aspects of the relationship between brain changes and gait disorders in neurological conditions: correlation between brain abnormalities evidenced by the different techniques and clinical measures of gait; online

measurements performed with some of these techniques (i.e. fNIRS and EEG) during actual gait; impact on gait modification following stimulation of cortical regions using TMS/tDCS.

We will then discuss the development of future methodological approaches aimed to better understand the pathophysiological mechanisms affecting gait control in neurological diseases. This article is not a systematic review of the literature, but a targeted review that aims to describe the brain-related gait changes in adults with common neurological conditions.

Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) is a non-invasive neuroimaging technique that has been used to identify the structural and functional brain substrates and pathologies associated with human locomotion in a number of neurological conditions — including PD, stroke, Alzheimer's disease and related dementias (ADRD), and MS (see Table 1). Standard three-dimensional structural images have been used to link locomotion in neurological conditions to brain volume or atrophy in a particular brain region, or a set of regions. The integrity of a particular white matter tract, or a set of white matter tracts, have also been linked to locomotion in neurological conditions using diffusion-weighted imaging (DWI). In addition, fluid attenuated inversion recovery (FLAIR) and susceptibility-weighted imaging (SWI) have been used to link small vessel disease pathologies, including lacunes, white matter hyperintensities (WMH), and microbleeds, to loco-motion in neurological conditions. Finally, functional MRI (fMRI) has been used to linked functional activation of a brain region, or a set of brain regions, during imagined (or motor imagery of) locomotion, as well as to functional connectivity during rest (resting-state fMRI).

Parkinson's disease

A large number of MRI studies of locomotion have been completed in PD (see Table 1A). These studies typically contrast the structural and functional brain substrates and pathologies in (a) PD with FOG (PD-FOG+) to PD without FOG (PD-FOG-), or (b) PD with postural instability and gait difficulty (PD-PIGD) to PD with tremor dominant phenotypes (PD-TD). PD-FOG+ relative to PD-FOG- has been associated with more gray matter atrophy [162,172,211], less white matter integrity [25,162,224,234,246], more white matter hyperintensities, altered functional connectivity [46,48,51,111,183,239,248] and altered functional activation patterns during imagined locomotion [160]—in a number of different brain regions, tracts, and functional networks: more specifically, cerebellar, parietal, precuneus, cingulate, and prefrontal cortex regions, white matter tracts that connect these regions (e.g. superior and inferior longitudinal fasciculus, corpus callosum, pedunclopontine nucleus and corticospinal tract) and functional networks that include many of these regions (e.g., fronto-parietal and default mode networks). PD-PIGD relative to PD-TD is also associated with more gray matter atrophy [171], white matter integrity [232] and altered functional connectivity [118,230,236], yet in a more restricted set of brain regions and tracts, including the amygdala, globus pallidus, corpus callosum, superior longitudinal fasciculus, and functional connectivity between the substantia nigra and putamen, and the caudate and putamen.

Stroke

MRI studies of locomotion that have been completed post-stroke are summarized in Table 1B. These studies have linked gait and other motor outcomes post-stroke to white matter integrity [2,44,78,79,81,159,243], small vessel disease pathologies [24,33,115] and functional connectivity [27]. White matter integrity of the corpus callosum and the pedunclopontine nucleus have been linked to gait speed and the ability to walk following a stroke, respectively [44,243]. Increased white matter hyperintensity burden in older adults with three or more subcortical strokes have been shown to increase the risk for multiple falls [24], and subcortical infarcts and microbleeds strengthens the negative association between white matter lesions and gait following a stroke [33]. Finally, a resting-state fMRI study suggests that interhemispheric functional connectivity, particularly between the left and right central sulcus, is associated with the extent of corticospinal damage, which in turn is associated with walking ability [27].

Alzheimer's disease and related dementias

A more limited number of MRI studies of locomotion have been completed in ADRD (see Table 1C). One study found that gait dysfunction in a sample of older adults with probable AD, possible AD, and AD with cerebrovascular disease, was associated with gray matter atrophy in a number of different brain regions—including the motor cortex, middle cingulate, insula, and the caudate [152]. Another study found that gait impairment in AD was associated with high small vessel disease burden [233]. Finally, a third study found that subcortical white matter hyperintensity burden in frontal and basal ganglia regions was associated with gait speed and stride length in both mild AD and control participants, although the relationship with gait speed was stronger in control participants [146]. Note also that the Motoric Cognitive Risk (MCR) syndrome—a pre-dementia syndrome characterized by slow gait and cognitive complaint [229]—have been linked to gray matter atrophy in supplementary motor, pre-motor, insular and prefrontal cortex regions [10,14], lacunar infarcts in the frontal lobe [235], but not to white matter hyperintensities [134].

Multiple sclerosis

A substantial number of MRI studies of locomotion have been performed in MS (see Table 1D). These studies examined the relationship between neuroimaging measures and locomotion in a) relapsing-remitting MS (RRMS), b) primary progressive MS (PPMS), or c) MS in general. In RRMS, gray matter volume of putamen, caudate, globus pallidus, and nucleus accumbens has been linked to the 25-foot timed walking (25FTW) test [154], while cerebellar volume has been associated with the 25FTW test in PPMS [34]. In MS in general, the 25FTW test and a 6-minute walking test have been linked to gray matter volume of the pallidum and caudate [142], and pallidum volume has been shown to increase following a running intervention [49]. White matter integrity in the corticospinal tract has been linked to quantitative gait parameters in RRMS [54] and the 25FTW test in MS in general [100], while white matter integrity of the cerebellar peduncle has been linked to gait speed in PPMS. Decreased functional connectivity in RRMS relative to controls has also been observed in a number of resting-state functional networks, including sensorimotor, visual, cerebellar, basal ganglia, and executive control networks. Finally, increased functional

connectivity in motor and somatosensory cortices has been observed following physical exercise interventions in MS in general [174,209].

Molecular imaging methods

Molecular imaging methods include positron emission tomography (PET) and single photon emission computed tomography (SPECT), which can image the brain during actual and during mental imagery of gait. Some studies have also correlated PET or SPECT imaging results with gait performance. These imaging techniques use radiolabeled ligands that interact in vivo with biological process (i.e., neurotransmitter receptors for the DAT-Scan, amyloid deposition for the Pittsburgh compound B–PiB-PET); measure brain metabolism (i.e., fludeoxyglucose-FDG PET), or the cerebral blood flow (i.e.; SPECT). The molecular imaging studies including patients with neurological conditions have mainly focused on patients with parkinsonism [5,16,18–20,97], or dementia [39].

In PD, the extent of dopaminergic [20,97] and cholinergic [16,18,19] denervation has been largely studied. Dopamine transporter (DAT)-PET has been studied in PD patients: striatal DAT-uptake in de novo PD patients predicted the development of FOG [97]. Interestingly, DAT activity was not associated with gait performance in non-PD population [5] or falls in PD [18]. Cholinergic denervation is a major contributor to poor gait in PD: cholinergic denervation has been associated with falls [18] and slow gait [16]. FOG phenomenon—defined by brief, episodic absence or marked reduction of forward progression of the feet despite intention to walk [150] – frequently observed in PD has been associated with reduced fronto-parietal activation and increased parietal activation while actual walking [205]. Hypoperfusion of bilateral frontal areas has been reported in PD patients with FOG in comparison to those without FOG [76,130], explaining also why FOG patients are presenting poorer executive function performance than non-FOG patients [168,193,206,210].

In the field of dementia, the development of radioligands targeting the pathological process of dementia, such as amyloid- or tau-PET, has greatly improved the in-vivo understanding of the pathophysiological cascade leading to dementia. Amyloid deposition measured by the [18F]florbetapir PET in specific brain regions involving the putamen, the precuneus, the anterior cingulate and the occipital cortex has been associated with gait speed in a cohort of older adults with and without cognitive impairment [39]. An increased β -amyloid deposition measured by the PiB-PET in PD has been associated with an increased severity of postural instability and gait difficulty features [145] that is a phenotype known to be a risk factor for developing PD dementia [166].

Functional near-infrared spectroscopy

Functional near-infrared spectroscopy (fNIRS) is a portable non-invasive optical imaging method. Similar to functional MRI that measures the blood oxygenation level-dependent (BOLD) signal of neural activity [151] – an estimation of variation of deoxy-hemoglobin concentrations – fNIRS uses the light-tissue interaction (within the near-infrared spectrum) to measure the changes in cortical oxygenation [83,197]. The main advantage of fNIRS

technique for studying gait control relies on its portable nature to allow a measurement of brain activity during real walking; however, its low spatial resolution (only few centimeters under the skull) represents its main limitation [15]. Several fNIRS studies measuring brain activity while walking have been conducted in aging, showing an increased oxygenation levels in the prefrontal, premotor and supplementary motor area while walking (for a review, see [70]). A systematic review of fNIRS studies focusing on patients with gait disorders has been also recently performed [59]. In neurological conditions, the majority of fNIRS studies while walking have included patients with PD [120–122,148,215] and stroke [4,67,137–140], while few studies involved MS patients [31,69], or patients with early dementia [43]. Although these studies included a limited number of patients with neurological diseases, they demonstrated the feasibility of using fNIRS while walking in neurological conditions. Furthermore, these studies found that prefrontal cortex activations play a key role during walking across this spectrum of various neurological conditions.

Electroencephalography

Electroencephalography (EEG) is another non-invasive brain imaging modality with fNIRS that allows studying cortical activation with a high degree of precision in time (1 ms). One of the strength of EEG is the possibility to assess brain functioning during online walking and to correlate brain functioning with gait measures. Indeed, PET scan or SPECT metabolic changes occur during several minutes following the injection according to the marker used. However, until recently, several concerns limited the use of EEG during real locomotion. First, spatial resolution is low compared to PET, SPECT or MRI. Source localization using scalp electrodes can be used to improve this spatial resolution at a cortical level. The main limit is that signal recorded by scalp electrodes is mostly the consequences of post-synaptic potentials of cortical neurons. Hence, intracerebral recordings of local field potentials (LFPs) with deep brain stimulation electrodes can be used to explore profound source [104,213]. Second, artifacts caused by movement and muscle activity can contaminate EEG activity. Of course, adequate filtering and selection of the epochs not contaminated by obvious artifacts must be performed first. Despite that, two studies [28,99] investigated movement related artifacts in the EEG and found contamination of the EEG data at frequencies from 1 to 150 Hz. As frequencies of EEG investigated during walking include theta (4–7 Hz), alpha (8–12 Hz), beta 1 (13–20 Hz) beta 2 (20–30 Hz) and gamma band (> 30 Hz), these artifacts are taken into account in the analysis of cortical activity during walking and should be removed before considering changes in a power frequency band. The current method to remove these artifacts used Independent Component Analysis (ICA) to separate sources of artifacts from cortical signal [62]. Then, two methods are used, either event related potentials (ERPs) if the EEG signal changes are time-locked to an event; or time frequency analysis to study induced changes in EEG activity in different frequency bands. More recently, some groups used brain connectivity methods to study the links between different cortical areas [64,182] or between cortex and basal ganglia structures [213]. The nonlinear behavior of EEG signals has also been developed using entropy as an index of signal complexity or irregularity [65,201]. The most frequent pattern during normal gait is a modification of alpha- and beta-band power with decrease in beta band power starting during gait initiation over sensorimotor cortex [218]. Changes in alpha and beta

power also occur at different phases of gait cycles [61]. The changes of spectral power in the different cortical areas are associated with the level of motor task demands [153].

Electroencephalography in neurological diseases

Recent studies correlated brain changes with gait measures, for example during a FOG in PD (see Table 2a). Some authors also directly assessed online brain functioning while walking in neurological patients; most of these EEG studies in neurological diseases have been conducted in PD patients (Table 2b). They emphasized the role of abnormal alpha and beta oscillations during locomotion and their impact in FOG occurrence. These results are summarized in Table 2b. There are few studies investigating EEG in post-stroke patients, most of them aiming to evaluate EEG-based brain-computer interfaces (BCIs) in rehabilitation, for example detection of movement intention or stopping [131,179]. Other studies aimed to determine the best algorithms to detect FOG for example are excluded from this review.

Transcranial magnetic stimulation and transcranial direct current stimulation

Transcranial Magnetic Stimulation involves the delivery of brief magnetic pulses through the skull that can depolarize the underlying neuronal circuits and trigger physiological effects. The main limit of TMS is due to the strength and shape of the induced magnetic field, which mainly depends on the stimulation coil. Focal ones induce accurate but superficial effects and cannot be used to stimulate deep regions (as for example, lower limb motor area in the interhemispheric sulcus). Other coils allow reaching deeper regions but are less focal and induce (sometimes unwanted) effects in widespread territories. Right now, single- and paired-pulses TMS remain an invaluable tool to explore the changes in primary motor cortex excitability that can occur in neurological diseases. It has been extensively used to better understand the pathophysiology of brain networks including lower limb M1 area in gait disorders. TMS may also induce lasting effects on neurons excitability when the stimulus is delivered by trains and can be used to modulate brain activity in disturbed neural circuits most likely via LTP- and LTD-like mechanisms [250]. The net effect of rTMS on brain neurons depends on several parameters such as stimulus intensity, frequency, pattern or train duration. Repetitive TMS may also be influenced by factors that may alter or enhance induction of brain plasticity. For instance, the level of brain excitability [187] or the practice of physical activity before the train [132] are able to change the net effect of rTMS. Another way to induce long lasting changes in cortical networks is to deliver an electrical current through the scalp (tDCS) that shifts the resting membrane potential toward depolarization or hyperpolarization depending on the current flow regarding axonal orientation. Although the mechanism of action of rTMS and tDCS are very different, these two non-invasive brain stimulation (NIBS) techniques share the capacity to decrease or increase brain excitability depending on the paradigm used with effects lasting beyond the duration of the stimulus. In addition to the clinical usefulness to counterbalance the deficits of excitability occurring in neurological disease, the disruptive effect of NIBS on brain circuits is also helpful to understand the role of various cerebral regions in gait and balance processing.

In this chapter, we will firstly focus on TMS studies that aimed at correlating brain excitability changes with clinical aspects of gait alteration. Then, we will consider some of

the NIBS studies that allowed assessing the role of cerebral regions in gait control in patients with PD.

Brain excitability changes in neurological diseases with gait disorders

Most TMS studies of neurological diseases have been conducted in PD. In PD patients, only slight changes in lower limb cortical excitability have been shown [222]. An increase in MEP amplitude and reduction in motor threshold was reported in the quadriceps muscle [217], but not in the Tibialis anterior muscle, where only a decrease of intra-cortical facilitation was shown [222]. After stroke, the loss of neurons associated with maladaptive cortical reorganization may lead to functional impairments of gait. As in the upper limbs, TMS studies have revealed a striking unbalance between the affected and the non-affected hemispheres controlling the lower limbs, with a reduction of excitability on the paretic side and an increase on the non-paretic side [155,156,241]. Corticomotor impairment was shown to be more severe in plantarflexor than in dorsiflexor muscles in stroke patients with poor walking recovery [156]. The presence of motor responses in the Tibialis anterior in the post-acute phase of stroke was a good indicator of lower limb motor recovery [163] and the asymmetry between the paretic and non-paretic sides (calculated from MEP motor thresholds or MEP amplitude) directly relates to walking recovery in chronic stroke patients [155,156]. In multiple sclerosis, only one study showed that cortical excitability of the Tibialis anterior was more enhanced than in healthy subjects after a fatiguing exercise [214].

Non-invasive brain stimulation-induced changes in cerebral networks and gait performance in clinical diseases

After first reports showing that rTMS over the vertex could have positive effects on walking performance in PD [126], numerous studies have tried to improve the beneficial influence of rTMS by targeting different cortical areas and looking for the best stimulation paradigms. Although some authors did not find any improvement of gait after rTMS, some studies suggest that high frequency stimulation of the upper limb motor area [106], the lower limb motor area [30,105,129,244] or both of them [93] have positive influence on gait in PD. Similarly, anodal tDCS of M1 area exerts a beneficial effect on gait with a decrease in walking speed [12,245] and a reduction of FOG episodes [36,223]. However, two studies reported no significant effect of tDCS alone over M1, but the same stimulation became effective to improve gait and decrease FOG episodes when coupled with pre-frontal tDCS [96] or motor training [89]. This latter region seems to play an important role in the neural gait network and related motor symptoms in PD, although the results of NIBS on walking performance are controversial with some studies showing gait amelioration after tDCS over the dorsolateral prefrontal cortex [103,127] whereas others did not [200]. One study also reported an improvement of the TUG test after rTMS of the dorsolateral prefrontal cortex [105] and another showed that gait variability and FOG occurrence were decreased after high frequency rTMS over the medial prefrontal cortex [37]. In contrast, neither cerebellum [80], nor premotor cortex stimulation [207] have a positive influence on FOG in PD. Contrasting results have been obtained for the supplementary motor area: whereas a benefit of rTMS for anticipatory postural adjustments duration [77] and FOG [98] were shown; one study did not report significant effects compared with sham stimulation [105]. And tDCS over SMA is not efficient to improve gait initiation [117]. Taken together, these studies

confirm the usefulness of non-invasive brain stimulation methods to better understand gait disturbances in PD and suggest a dysfunction of several regions involved in gait control, mainly the prefrontal cortex, SMA, M1 and the cerebellum. In stroke patients, the deficits observed in locomotion are directly the consequence of brain lesions. Right now, NIBS methods have been used to induce plasticity in M1 and improve lower limb motor function but their effectiveness remain difficult to assess (for a review, see [50]).

Advanced methods and perspectives

Differentiating neurological from non-neurological clinical gait abnormalities is nowadays critical in clinics for early onset detection of developing neurodegenerative and mental disorders. Kinetic and kinematic characteristics might be similar between the two disorders, and they are unfit to fully reveal the neural correlates underlying walking deficits further misidentifying the two disorders. A clear distinction of the two entails, therefore, the observation of brain alterations that might be predominant in neurological conditions, and the definition of robust measures of these abnormal neural activity patterns for risk assessment and intervention procedures [242].

The definition of reliable imaging-based biomarkers for clinical decision and therapeutic interventions necessitate the identification of strong associations between brain and objective behavioral measures. The majority of previous works correlated individual signature of gait abnormalities with localized brain features extracted from single imaging technique. However, numerous brain structures, including basal ganglia, cerebellum, frontal and parietal cortices, jointly subserve to generate walking with multifaceted components. Even a priori focal conditions such as stroke have been reconsidered as a distributed network disease [188] leading to a new definition of diaschisis (i.e., connectional diaschisis) that indicates structural and functional changes between brain areas distant to the lesion [26]. Therefore, future studies should investigate multivariate correlations both in terms of brain parcels, acquisition modalities, and gait quantifications [70].

A possible method to identify multiple underlying associations between two sets of variables is canonical correlation analysis (CCA), which seeks significant correlations between combinations of variables in both sets and both at group- and individual-subject level [66]. This method requires large enough datasets for proper validation, but can then be successful in spotting strong relationship between demographic and psychometric measures and functional connections across brain regions within the default mode network [192]. The demand of “large enough datasets” has led to the emergence of several publicly available initiatives to promote data sharing across groups (see Parkinson’s progression markers initiative, Alzheimer’s Disease Neuroimaging initiative, UK biobank for some examples). However, the usage of these datasets requires transfer-learning techniques to match multi-site data acquired from mismatch subjects and with different imaging parameters [112].

In addition, multivariate brain features could be inferred from combinations of anatomo-functional components. Indeed, despite various neurophysiological origins, neuro-logical gait disorders are associated both with structural origin, such as atrophy and/or damage to the grey or white matters in the locomotion networks and reduced integrity (e.g., reduced

fractional anisotropy and increased mean diffusivity) between these areas, and with flawed functional networks. However, whether structural and functional abnormalities operate synergistically or in opposition is still unknown. Determining this relationship would lead to a more complete characterization of the pathology and its stage, and, thus, to the definition of more robust and reliable biomarkers. Several approaches have been proposed to map functional connectivity from anatomical features extracted directly from white matter streamlines or enforced from graph-theoretical properties [11,38,169,170]. Brain-graphs can be constructed associating nodes to anatomically defined parcels or recording sensors and edges to structural or functional connections. Measures of information transfer, efficiency, and structure can be extracted from structural and functional-based graph and associated to clinical symptoms [9]. Brain graph measures, for instance, have revealed a decreased efficiency in cortico-basal ganglia motor circuits significantly correlating with Unified Parkinson's Disease Rating Scale motor scores in PD patients [237]. These results are in line with the pathophysiology (i.e., dopamine depletion of the cortico-basal ganglia) of PD, suggesting that graph-based metrics are suitable biomarkers to track the evolution of the pathology and inform clinical-decision making.

Current approaches applying graph-theoretical analysis extract information from data defined in regular domains such as time or space and do not account for the dynamics of the networks. Moreover, functional connectivity is classically computed by pairwise correlations over the complete resting-state run, disregarding moment-to-moment fluctuations. To overcome these limitations and to allow analyzing spatiotemporal elements, the emerging field of signal processing on graphs has tailored an increasing number of conventional operations to signals expressed at the nodes of the graph [32]. Among others, the main operation deployed to analyze brain activity is the graph Laplacian operator defined from the structural connectome [73]. The eigen decomposition of the Laplacian then defines a spectral graph domain corresponding to the Fourier transform on regular grids [185]. Projections on the eigenvectors of the Laplacian (i.e., Graph Fourier Transform) allows separating low graph frequency components representing signals that are more "aligned" with the structural backbone, and high graph frequency components representing signals that are more "liberal" with respect to brain structure [74]. This separation highlighted that low frequency functional components are associated with greater task switching flexibility [73,133], which is thought to originate in cortico-basal ganglia-thalamo-cortical loops and is often reduced in patients with neurological syndromes [202]. Additionally, Graph Fourier Transform permits generating surrogate graph signals in which the correlation structure of the signals is imposed by the empirical data allowing stronger statistical assessment, a pivotal feature in clinical applications [73,165].

The dynamics underlying brain networks, however, could also be encoded either through direct voxel- or region-wise signal measures (second-order statistics) or by feeding established brain states into temporal models (first-order methods) [88,167]. In primordial strategies, second-order methods, such as pairwise correlation over temporal sliding-windows, were deployed to compute dynamic functional connectivity. Despite the limiting window length trade-off, this basic sliding-window framework allowed demonstrating that abnormal connectivity in neurodegenerative diseases could be better explained by shortening dwell time in sub-networks configurations, rather than stationary connectivity magnitude,

proving the importance of dynamic methods [42,84,94,110]. However, fluctuating brain activity could also be captured with time-resolved analysis where informative timepoints retained by thresholding—either on the original timeseries as in point process analysis [203,204] or on innovation signals [87]—are temporally clustered in spatial co-activation patterns (CAPs) [114]. Spatiotemporal regression of the established repertoire of CAPs allows computing networks-based temporal measures such as occurrence percentage, duration, or state switching frequency, which can be used to related pathological brain dynamics to clinical manifestation. For instance, in a recent study a reduced switching probability among CAPs correlating with motor symptom severity was observed in early stage of PD [249].

Similarly, temporal clustering approaches were applied also to EEG data showing that electrical fluctuations can be discretized in semi-stable potential topographies (a.k.a., microstates), whose temporal properties, identified with analogous temporal measures, change with neurological and psychiatric conditions [92,136]. The EEG microstates demonstrated to be relevant for assessing patient's clinical status and treatment efficacy [199,247]. For instance, Zappasodi and colleagues [247] showed that preserved microstate duration in post-stroke acute phase correlated with a better effective recovery.

Despite the relevance of this extended repertoire of imaging-based biomarkers that exploit network and dynamical organization to better characterize diseases phenotypes and progression, nowadays studies should capitalize on these measures to improve therapeutic strategies. Preliminary applications in this direction utilized fMRI and EEG dynamic brain models to drive neurofeedback showing that network measures-based close-loop instead of single brain region features could target more relevant large-scale interactions leading to potentially more powerful regulation protocols [41,102,190]. Similarly, pretherapeutic grey matter density and network(s) interconnectivity strength could predict clinical effects of stereotactic radio-surgical thalatomy [219–221] and brain stimulation [71], which has been shown to be useful in brain imaging assessment and treatment of gait disturbances. Moreover, these anatomo-functional components and particularly the large-scale impact of regional stimulation detected by dynamical brain networks could optimize the stimulation protocols improving their efficacy and reducing secondary effects [144]. In this framework, the advent of multimodal recordings and stimulation techniques such as TMS-EEG and more recently TMS-fMRI is critical [13,101,186]. Moreover, these applications require the extension of the methods here elucidated and originally designed for analysis of resting-state brain activity to task-based paradigms. Attempts in this direction are, therefore, emerging [21,22,58,164,189] and they would be critical to characterize the neural correlates underlying neurological gait abnormalities.

Conclusion

Complementary neuroimaging techniques have been used in various neurological conditions (mainly in PD) in supine position or during actual walking to study the brain substrates of locomotion. The extent networks involved in the control of locomotion include grey and white matter structures in key regions, such as the prefrontal cortex, the basal ganglia and the cerebellum, explaining the strong relationship between locomotion and cognition

(especially executive functions) that are both controlled by these cortical and subcortical regions. However, the role of individual pathophysiological mechanisms encountered in each neurological condition on the phenotype of gait disorders is still not clear. Advanced neuroimaging methods and computational analyses that integrate multivariate correlations, such as information on brain structures, functions, or acquisition modalities, in “large enough datasets”, might solve that issue of the phenotypical gait signature due to a unique or combined neurological conditions. These multivariate computational methods will not only “decode” the brain substrate of impaired locomotion, but may also drive the rehabilitative strategy, by using a close loop neurofeedback training (see Fig. 1). The success of these future approaches will depend on the collaborative efforts between neurologists and scientists from mathematics, physics and computer science.

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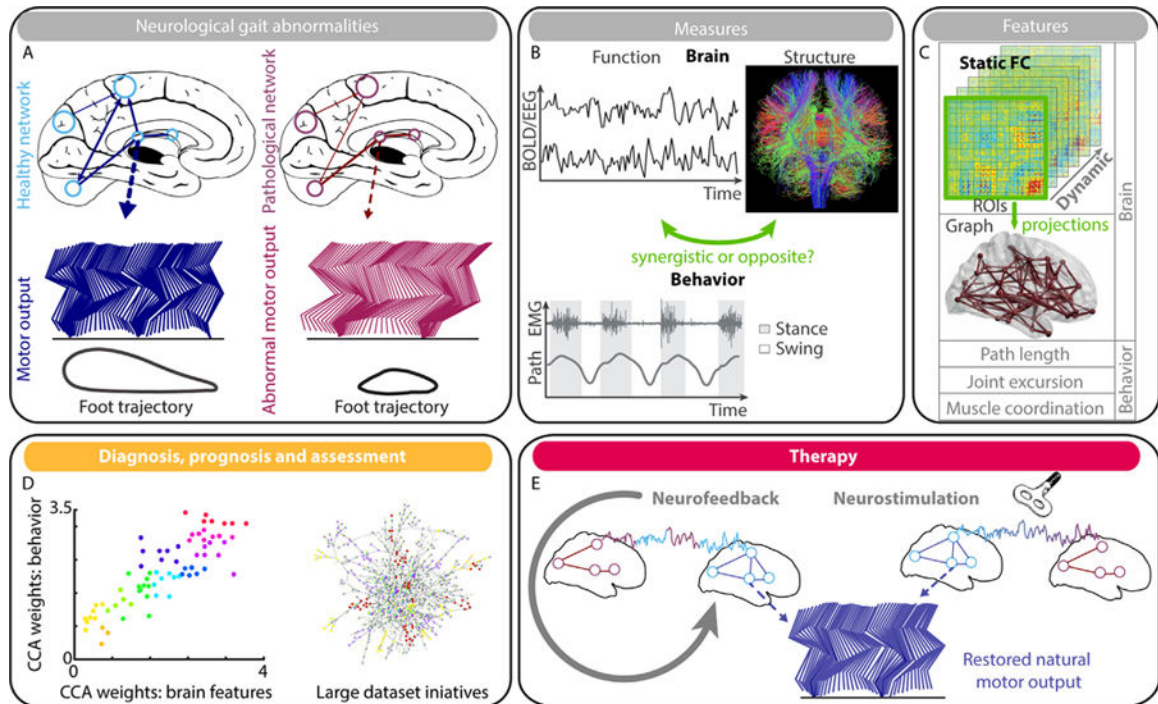


Figure 1.

Schematic representation of the contribution of advanced neuroimaging techniques for “decoding” brain substrates of gait disorders and their treatment. A. Disrupted distributed brain networks reflect on neurological gait abnormalities. B. The neural alterations can be captured through both functional and structural modalities; while gait disorders can be characterized by kinetic and kinematic observations. Yet it remains to be elucidated whether anatomo-functional abnormalities operate synergistically or in opposition in the generation of pathological walking. C. Despite this open question, several features can be extracted from neural observations and exploited as biomarkers. However, because correlation between parcels exhibits meaningful temporal variations, brain networks dynamics has to be kept in consideration. The spatiotemporal elements can be captured by graph signal processing techniques, which require projection of the brain activity over the structural backbone, or via first- and second-order statistics, which encode the dynamics directly from voxel- or region-wise signal measures. D. Because of the multifaceted nature of gait and the underlying numerous brain structures, the identified features should be related through multivariate correlation methods, such as canonical correlation analysis (CCA), for a more complete characterization of the pathology and its stage. However, these multivariate techniques require “large enough datasets” for proper validation. E. Finally, the identified brain features and their dynamics should not only inform rehabilitative-decision processes, but also be deployed to directly drive the therapy. For instance, close-loop neurofeedback training can impose neuroregulation of the networks dynamics instead of single brain region; while neurostimulation parameters can be optimized by considering the impact of regional stimulation over dynamical brain networks. The efficacy of these therapies would still require proper assessment via the identified imaging biomarkers.

Table 1

Magnetic resonance imaging in neurological diseases.

Reference	Design, methods, participants	Key findings
A. Parkinson's disease		
Maidan, 2016 [123]	Cross-sectional, imagery, fMRI, PD vs. controls	Controls, but not PD participants, had increased activation during virtual navigation relative to virtual walking
Maidan, 2017 [124]	RCT, imagery, fMRI, PD. Treadmill training + Virtual imagery (TT+VI) vs. Treadmill training (TT) alone	TT+VI relative to TT had: a) Improved attention and gait speed b) Decreased activation in anterior and inferior frontal gyrus c) Decreased activation in left anterior lobe of cerebellum and mid temporal gyrus
Peterson, 2014 [160]	Cross-sectional, imagery, fMRI, PD-FOG+ vs. PD-FOG-	During imagined gait, PD-FOG+ had less activation in right globus pallidus and cerebellar regions than PD-FOG-
Peterson, 2014 [161]	Cross-sectional, imagery, fMRI, PD vs. controls	During imagery, PD participants had less activation in globus pallidus and more activity in SMA than controls. Activation of SMA, putamen, globus pallidus and brain stem correlated with gait speed in PD, but not in controls
Snijders, 2011 [194]	Cross-sectional, imagery, fMRI, PD-FOG+ vs. PD-FOG-	PD FOG+ participants had increased activation during imagery, and more brain volume atrophy in brainstem than PD-FOG- participants
Li, 2018 [111]	Cross-sectional, resting-state fMRI, PD-FOG+ vs. PD-FOG-	Reduced interhemispheric functional connectivity was observed in the inferior parietal lobule of PD FOG+ participants compared to PD FOG- and healthy controls
Zhou, 2018 [248]	Cross-sectional, resting-state fMRI, PD-FOG+ vs. PD-FOG-	PD FOG+ participants had reduced regional functional connectivity in SMA and left superior PFC relative to PD FOG- and controls
Gilat, 2018 [56]	Cross-sectional, resting-state fMRI, PD-FOG+ vs. PD-FOG-	PD-FOG+ participants had increased functional connectivity between right amygdala and putamen compared to PD-FOG-
Mi, 2017 [135]	Cross-sectional, resting-state fMRI, PD-FOG+ vs. PD-FOG-	PD FOG+ participants had increased spontaneous neural activity in anterior cingulate, intraparietal lobule, and decreased activity in superior frontal gyrus, bilateral cerebellum, and thalamus
Ma, 2017 [118]	Cross-sectional, resting-state fMRI, PD-TD vs. PD-PIGD, controls	PD-PIGD participants had disrupted functional connectivity in cerebellum relative to PD-TD
Shen, 2017 [181]	Cross-sectional, resting-state fMRI, PD vs. controls	Increased functional connectivity between substantia nigra and sensory-motor cortex was observed in PD patients on medication
Gallea, 2017 [55]	Cross-sectional, resting-state fMRI, PD vs. controls, with or without impaired postural control and/or sleep disorder	PD patients with sleep disorders displayed decreased functional connectivity between pedunculopontine nucleus and anterior cingulate
Wang, 2016 [236]	Cross-sectional, resting-state fMRI and DWI, PD-FOG+ vs. PD-FOG-, controls	PD-PIGD participants had reduced functional connectivity between left putamen and substantia nigra and increased connectivity between substantia nigra and occipital lobe
Wang, 2016 [234]	Cross-sectional, resting-state fMRI, PD-TD vs. PD-PIGD, controls	PD FOG+ participants had abnormal functional connectivity in pedunculopontine nucleus and visual temporal areas
Vervoort, 2016 [230]	Cross-sectional, resting-state fMRI, PD-TD vs. PD-PIGD, PD undetermined, controls	PD-PIGD participants had reduced functional connectivity between caudate and putamen compared to PD TD
Lenka, 2016 [109]	Cross-sectional, resting-state fMRI, PD-FOG+ vs. PD-FOG-	PD FOG+ participants had reduced interhemispheric functional connectivity between left parietal opercular cortex and primary somatosensory and auditory regions

Reference	Design, methods, participants	Key findings
Vervoort, 2016 [231]	Cross-sectional, resting-state fMRI, PD-FOG+ vs. PD-FOG-, controls	PD-PIGD participants had reduced functional connectivity between the caudate and superior temporal lobe and increased connectivity between the dorsal putamen and preuncus, which correlated with worse dual-task gait performance
Jiang, 2016 [82]	Cross-sectional, resting-state fMRI, PD-TD vs. PD-PIGD, controls	PD-PIGD participants had reduced synchronicity of activation in frontal, parietal, occipital, temporal, limbic lobes, basal ganglia and thalamus regions
Chen, 2015 [32]	Cross-sectional, resting-state fMRI, PD-TD vs. PD-PIGD, controls	PD-PIGD participants had lower spontaneous neural activity in the putamen and cerebellar posterior frontal gyrus, and parietal gyrus
Camu, 2015 [25]	Cross-sectional, resting-state fMRI and DWI, PD-FOG+ vs. PD-FOG-	PD-FOG+ participants had decreased functional connectivity in primary motor and supplementary motor regions of the sensorimotor network, frontoparietal regions of the default mode network, and occipital cortex regions of the visual network - as well as reduced white matter integrity in the pedunculopontine tracts, corpus callosum, corticospinal tract, cingulum, superior longitudinal fasciculus
Hou, 2015 [72]	Cross-sectional, resting-state fMRI, PD vs. controls	PD-PIGD participants had increased spontaneous neural activity in right postcentral gyrus, and decreased spontaneous neural activity in putamen, pre and supplementary motor area, frontal lobes, temporal lobes, and insula
Fling, 2014[51]	Cross-sectional, resting-state fMRI and DWI, PD vs. controls	PD-FOG+ participants had greater functional connectivity between the supplementary motor and cerebellar regions compared to both PD-FOG- and controls - and was correlated with increased (worse) clinical, self-reported and objective ratings of FOG
Tessitore, 2012 [212]	Cross-sectional, resting-state fMRI, PD-FOG+ vs. PD-FOG-, controls	PD-FOG+ participants had reduced connectivity in middle frontal gyrus, angular gyrus and right occipito-temporal gyrus
Wen, 2018 [239]	Cross-sectional, DWI, PD-TD+ vs. PD-PIGD, controls	White matter integrity in genu of corpus callosum was more strongly associated with motor severity in PD-FOG+ than PD-TD
Hall, 2018 [63]	Cross-sectional, DWI, PD-FOG+ vs. PD-FOG-	PD-FOG+ participants had reduced structural modularity and integration in caudate, thalamus, hippocampus, and superior frontal and parietal cortex regions
Pietracupa, 2018 [162]	Cross-sectional, DWI, PD-FOG+ vs. PD-FOG-	PD-FOG+ participants had reduced cortical thickness in cerebellar, superior frontal, paracentral, posterior cingulate, precuneus, pericalcarine and dorsolateral prefrontal cortex regions — as well as reduced white matter integrity in superior longitudinal fasciculus, uncinate fasciculus, cingulate, and inferior longitudinal fasciculus
Lenfeld, 2016 [108]	Longitudinal DWI, PD-FOG+ vs. PD-FOG-, PD-undetermined	PD-PIGD participants had reduced white matter integrity in the prefrontal cortex, external capsule, the and lateral horn of the anterior ventricle relative to PD-TD – the integrity of these regions was also lower at baseline among those that developed PiGD symptoms during follow-up
Nagae, 2016 [147]	Cross-sectional, DWI, PD-TD vs. PD-PIGD, controls	PD patients had reduced had reduced white matter integrity in the substantia nigra
Youn, 2015 [246]	Cross-sectional, DWI, PD-TD vs. PD-PIGD, controls	PD-FOG+ participants had reduced structural connectivity in regions connected to pedunculopontine regions — including basal ganglia, thalamus and cerebellum
Chan, 2014 [29]	Case-control, DWI, PD vs. PiGD, controls	Structural connectivity in the body of the corpus callosum body differentiated PD-PIGD from PD
Marumoto, 2012 [128]	Cross-sectional, DWI, INPH vs. PD, controls	INPH participants had reduced white matter integrity in anterior thalamic radiation and forceps minor compared to PD participant. The addition of DWI assisted in the differential diagnosis of INPH from PD beyond what could be deduced from ventricular size alone
Kanno, 2011 [85]	Cross-sectional, DWI, INPH vs. AD, PD	Reduced white matter integrity is related to motor and cognitive dysfunction in INPH
Skorpil, 2012 [191]	Cross-sectional, DWI, PD vs. controls	PD participants had reduced white matter integrity in substantia nigra relative to controls

Reference	Design, methods, participants	Key findings
Karagulle Kendi, 2008 [86]	Cross-sectional, DWI, PD vs. controls	PD participant had reduced structural connectivity in the supplementary motor area, pre-supplementary motor area, and cingulum
Surova, 2016 [198]	Cross-sectional, DWI, PD vs. controls	PD participants had white matter integrity changes in the putamen, the thalamus, and the superior longitudinal fasciculus — yet, these changes do not aid in the diagnostic work-up of PD
Vervoort, 2016 [232]	Cross-sectional, DWI, PD-TD vs. PD-PIGD, controls	PD-PIGD participants had reduced white matter integrity in superior longitudinal fasciculus and corpus callosum compared to controls — as well as increased grey matter atrophy in the rostral head of the caudate
Vercruyse, 2015 [224]	Cross-sectional, DWI, PD vs. controls	PD participants had reduced white matter integrity in striato-frontal tracts including putamen, caudate, pallidum, subthalamic nucleus, cerebellar peduncle, subthalamic nucleus and pedunculo-pontine nucleus
Gu, 2014 [60]	Cross-sectional, DWI, PD-PIGD+ vs. PD-PIGD-, controls	PD-PIGD is associated with reduced white matter integrity was greater in superior longitudinal fasciculus relative to PD-PIGD
Lenfeldt, 2013 [107]	Longitudinal, DWI, PD-PIGD, PD-TD	White matter integrity in thalamus was reduced in PD-TD than PD-PIGD
Al-Bachari, 2017 [3]	Cross-Sectional, WMH, PD-TD vs., PD-PIGD, controls	PD-PIGD participant had more white matter lesions than PD-TD participants
Acharya, 2007 [1]	Cross-Sectional, WMH, old-PD young-PD vs. old-controls, young-control	White matter changes was not different between the groups
Sartor, 2017 [176]	Cross-Sectional, WMH, PD	Gait performance was poorer, and reduction in bradykinesia following a single dose of levodopa was reduced, in PD participants with WMH than in those without WMH
Arena, 2016 [8]	Cross-Sectional, WMH, PD with acute L-DOPA challenge	PD participant with greater deep WMH burden was less responsive to levodopa on axial motor symptoms
Herman, 2013 [68]	Cross-Sectional, WMH, PD	The mean WMHs scores and the percent of subjects with lesions in specific brain regions were similar in the two subtypes
Moccia, 2016 [141]	Longitudinal, WMH, PD	Developing PiGD symptoms during follow-up was associated with higher WMH burden
Kim, 2015 [95]	Longitudinal, SVD, IPD vs. VP	Cerebral microbleeds were more common in vascular parkinsonism than in idiopathic PD. In IPD, cerebral microbleeds were also associated with white matter hyperintensities and concurrent lacunar infarctions
Schneider, 2016 [180]	Longitudinal, SVD, PD vs. PiGD	PD-PIGD had less SWI hypointensity in the putamen and globus pallidus PD patients
Rosenberg-Katz, 2016 [171]	Cross-Sectional, brain volume, PD-TD vs. PD-PIGD	PD-PIGD had more atrophy in amygdala and globus pallidus relative to PD-TD. In both PD-PIGD and PD-TD, hippocampal volume was positively associated with dual task gait performance, and putamen volume was negatively associated with FOG score
Rubino, 2014 [172]	Cross-Sectional, brain volume, PD-FOG+ vs. PD-FOG-	PD-FOG+ participants had more gray matter atrophy in left posterior parietal gyrus compared with PD-FOG-
Tessitore, 2012 [211]	Cross-Sectional, brain volume, PD-FOG+ vs. PD-FOG-, controls	PD-FOG+ had less gray matter volume in cuneus, precuneus, lingual gyrus, and posterior cingulate cortex compared to PD-FOG- and controls
B. Stroke		

Carter, 2012 [27] Cross-Sectional, resting-state fMRI, subacute stroke vs. controls
The extent of corticospinal damage was associated with functional connectivity between the left and right central sulcus

Reference	Design, methods, participants	Key findings
Peters, 2018 [159]	Cross-Sectional, DWI, post-stroke	Structural connectivity between primary and supplementary motor regions and the cerebral peduncle, thalamus, and red nucleus in the same hemisphere as stroke lesion was associated with upper and lower extremity motor functions post-stroke
Jang, 2014 [79]	Cross-Sectional, DWI, chronic stroke	White matter integrity was associated with motor functions in chronic stroke
Dubey, 2016 [44]	Cross-Sectional, DWI, chronic stroke, controls	Reduced white matter integrity of corpus callosum was observed in chronic stroke relative to controls and was associated with gait speed
Jang, 2013 [78]	Cross-Sectional, DWI, stroke with complete injury of CST	White matter integrity (fiber volume) in unaffected (but not in affected) hemisphere was positively associated with the ability to walk
Jayaram, 2012 [81]	Cross-Sectional, DWI and TMS, chronic stroke	Greater relative connectivity between motor cortex and lower limbs in affected and unaffected hemisphere was associated with poorer gait speed
Yeo, 2011 [243]	Cross-Sectional, DWI, chronic stroke	White matter integrity in pedunculopontine nucleus was greater in stroke patients with the ability to walk
Ahn, 2006 [2]	Cross-Sectional, DWI, ambulatory chronic stroke	Some stroke patients retained the ability to walk despite complete lateral corticospinal tract injury in the affected hemisphere
Loos, 2017 [115]	Cross-Sectional, SVD, lacunar vs. non-lacunar stroke	Total cerebral small vessel disease burden was associated with gait impairment in non-lacunar (but not lacunar) stroke patients
Callisaya, 2014 [24]	Cross-Sectional, WMH, subcortical infarcts vs. controls	The risk of multiple falls was increased in older adults with three or more subcortical infarcts and highest quartile of white matter hyperintensity volume
Choi, 2012 [33]	Cross-Sectional, WMH and microbleeds, subcortical infarcts vs. microbleeds	Subcortical infarcts and microbleeds amplified the negative association of WML volume with gait. Subcortical infarcts, but not microbleeds amplified the negative association of WML volume with postural stability
C. Alzheimer's disease and related dementias		
Olazaran, 2013 [152]	Cross-Sectional, brain volume, DWI, probable AD vs. possible AD, AD-CVD+	Gait dysfunction was related to brain atrophy in motor cortex, cingulate, insula, caudate (total sample), and cerebellar (total sample and probable AD) regions
Verwer, 2017 [233]	Cross-Sectional, SVD, AD vs. MCI, vascular brain injury	High small vessel disease burden, particularly white matter hyperintensities, co-occurred with impairments in physical performance (gait speed, short physical performance battery)
Nadkarni, 2009 [146]	Cross-Sectional, subcortical hyperintensities, mild AD vs. controls	Subcortical hyperintensity burden — particularly in frontal and basal ganglia — was associated with stride length and velocity in both mild AD and controls
D. Multiple sclerosis		
Shardella, 2015 [177]	Cross-Sectional, DWI, RRMS vs. controls	Gray matter atrophy and white matter integrity in RRMS was associated with upper-limb motion and cognition, but not 25-foot timed walk
Li, 2013 [113]	Cross-Sectional, DWI, RRMS vs. controls	RRMS participants had reduced communicability in frontal and hippocampal/parahippocampal regions. Communicability in superior frontal and superior temporal regions was associated with 25-foot timed walk. Increased communicability was observed in thalamus, putamen, corpus callosum and cingulum
Anderson, 2011 [7]	Cross-Sectional, DWI and gray and white matter, RRMS vs. PPMS, controls	White matter integrity in cerebellar peduncle was reduced in PPMS relative to RRMS and controls. In PPMS white matter integrity in cerebellar peduncle was also associated with upper limb function and gait speed

Reference	Design, methods, participants	Key findings
Kern, 2011 [90]	Longitudinal, DWI, RRMS vs. controls	White matter integrity associated with fine hand motor control but not 25-foot time walk
Freund, 2010 [53]	Longitudinal, DWI, MS vs. controls	White matter integrity of the cortico-spinal tract at baseline was associated with better clinical outcomes
Wetter, 2016 [240]	Cross-Sectional, White matter lesions, MS (RRMS, SPMS and PPMS)	White matter lesion volume explained additional variance in six-minute-walk performance after adjusting for age, white matter volume and gray matter volume
Sanfilippo, 2005 [175]	Cross-Sectional, DWI, MS vs. controls	MS participants had significantly lower gray matter and parenchymal volume, and a trend towards lower white matter volume, relative to controls. Gray matter atrophy was associated with clinical status, lesion load and central brain atrophy. White matter volume was associated with central brain volume
Goncalves, 2018 [57]	Cross-Sectional, corpus callosum index and volume, MS vs. controls	Corpus callosum index was associated with white matter and lesion volume, whole brain volume, some (not all) cognitive measures and functional status, but not with clinical status or 25-foot timed walk
Cocozza, 2017 [34]	Cross-Sectional, brain volume, PPMS vs. controls	MS participants had reduced cerebellar volume relative to control. Cerebellar lobules VI, Crus I and VIIa was associated with cognitive measures. Anterior cerebellum and Lobule I-IV atrophy was associated with the 25-foot timed walk
Dupuy, 2016 [45]	Longitudinal, brain volume, RRMS with dimethyl fumarate therapy	RRMS patients on dimethyl fumarate therapy had a reduced rate of whole brain and putamen atrophy
Khalid, 2017 [91]	Longitudinal, brain volume, RRMS and PPMS with natalizumab therapy	Natalizumab therapy was not associated with any changes in annual gray matter volume, parenchymal volume, lesion load, clinical status or 25-foot time walk
Motl, 2016 [143]	Cross-Sectional, brain volume, MS vs. controls	MS participants had reduced subcortical gray matter lesion load and slower 25-foot timed walk. 25-foot timed walk was associated with subcortical gray matter in both MS and controls. Thalamic volume partially accounted for the difference in 25-foot timed walk between MS and controls
Ruggieri, 2015 [173]	Cross-Sectional, brain volume, PPMS vs. controls	PPMS was associated with reduced brain, gray and white matter volume relative to controls. Thalamic atrophy was associated with cortical lesions, particularly in frontal lobes
Onu, 2015 [154]	Cross-Sectional, brain volume, RRMS vs. controls	RRMS participants had reduced gray matter volume, particularly in thalamic, putamen, caudate, globus pallidus and nucleus accumbens - and volume in these regions (as well as sensory motor and primary motor regions) was associated with 25-foot timed walk
Feys, 2017 [142]	Cross-Sectional, brain volume, MS	The 6-minute walk and 25-foot timed walk is associated with gray matter volume of the pallidum and caudate in MS
Maghzi, 2014 [119]	Longitudinal, brain and lesion volume, MS	Baseline volume of the whole, the gray matter and normal appearing white matter was associated with changes in a functional and the 25-foot timed walk in MS
Wen, 2015 [238]	Cross-section, gray matter volume, MS vs. controls	Age-adjusted differences between MS and control participants were observed in cortical gray matter, normal appearing white matter — and was associated with cognitive measures, but not clinical status or 25-foot timed walk
Tovar-Moll, 2015 [216]	Cross-Sectional, DWI, MS (both RRMS & PPMS)	White matter integrity in corticospinal tract was associated with disability status and 25-foot timed walking speed — but correlation with 25-foot timed walking speed disappeared when correcting for lesion volume
Tavazzi, 2018 [209]	RCT, fMRI, MS, neurorehabilitation	Increased functional connectivity in precentral and postcentral gyrus, more restricted functional activation, improved gait and improved balance was observed following 4 weeks of neurorehabilitation
Sandhoff, 2018 [174]	RCT(secondary analysis), resting-state fMRI, MS	Increased functional connectivity in thalamus, superior frontal gyrus and medial frontal gyrus and improved processing speed was observed following 12-week treadmill walking intervention

Reference	Design, methods, participants	Key findings
Sbardella, 2015 [178]	Cross-Sectional, resting-state fMRI and DWI, RRMS vs. controls	Decreased functional connectivity in a number of resting-state functional networks (sensorimotor, visual, cerebellar, basal ganglia, and executive control) was observed in RRMS relative to controls. In RRMS white matter integrity of the corpus callosum was also associated with functional connectivity in cerebellar and auditory networks
Klineova, 2016 [100]	Cross-Sectional, DWI, MS with gait impairment	White matter integrity in corticospinal tracts and overall gray and white matter volume was associated with 25-foot timed walk
Fritz, 2017 [54]	Cross-Sectional, DWI, RRMS	White matter integrity in corticospinal tract was associated with quantitative gait measures in RRMS
Hubbard, 2016 [75]	Cross-Sectional, DWI, MS	Some (median diffusivity, radial diffusivity, axial diffusivity), but not all (fractional anisotropy) measure of structural connectivity was associated with quantitative gait measures
Deppe, 2016 [40]	Cross-Sectional, DWI, RRMS vs. controls	RRMS participants in general had reduced white matter integrity and white matter volume relative to controls. Early and mild RRMS had reduced white matter integrity, but not white matter volume relative to controls
Feys, 2017 [49]	RCT, DWI and gray and white matter, MS, ('start-to-run') running program vs. wait list	Pallidum volume increased following start-to-run program

fMRI: functional magnetic resonance imaging; PD: Parkinson's disease; RCT: randomized controlled trial; PD-FOG+: PD with freezing of gait; PD-FOG-: PD without freezing of gait; PD-PGID: PD with postural instability and gait difficulty; PD-TD: PD with tremor dominant phenotype; DWI: diffusion-weighted imaging; CST: corticospinal tract; INPH: idiopathic normal pressure hydrocephalus; TMS: transcranial magnetic stimulation; AD: Alzheimer's disease; MCI: mild cognitive impairment; WMH: white matter hyperintensities; SVD: small vessel disease; CVD: cardiovascular disease; MS: multiple sclerosis; RRMS: relapsing-remitting MS; PPMS: primary progressive MS; SPMS: secondary progressive MS.

Electroencephalography in Neurological Diseases—Studies evaluating the association between brain changes and gait measures.

Table 2a

Reference	Objective	Methods (task/recordings/signal analysis)	Principal results
Thevathasan, 2012 [213]	Nature of oscillations in the PPN in 7 PD freezers	Gait LFPs of the PPN Time frequency analysis Connectivity (scalp electrodes)	Peaks of alpha power during gait correlated with gait speed FOG associated with attenuation of alpha activity Alpha oscillations in a network involving the caudal subregion of the PPN and the cerebral cortex
Fraix, 2013 [52]	Dynamic changes in PPN area in 7 PD freezers	Step in place/sitting and standing Off and On dopa LFPs Time frequency analysis Connectivity (scalp electrodes)	ON levodopa increases in alpha power during step in place and decrease in beta and gamma bands. Increased coherence with scalp electrodes.
Shine, 2014 [182]	Brain dynamic changes during turning in 24 PD freezers	Turning Scalp EEG Time-Frequency analysis Connectivity	Increase in theta band power within the central and frontal areas during FOG Increased theta frequency coupling between the central and frontal leads
Handojoseno, 2015 [64]	Brain dynamic changes during turning in 4 PD freezers	Turning Scalp EEG Time-Frequency analysis Brain effective connectivity	Increase power in beta2 band over posterior areas during actual FOG Increased connectivity towards the visual area
Handojoseno, 2015 [65]	Brain dynamic changes in 16 PD freezers	Timed up and go Scalp EEG Time frequency analysis Connectivity	Posterior alpha power decreases during transition to FOG compared to normal walking decrease of entropy in most frequency bands and electrodes during FOG Connectivity: increase of beta synchronization
Syrkin-Nikolau, 2017[201]	STN dynamic changes during gait and turning in 14 PD freezers	Stepping in Place, forward walking, Turning and Barrier Course STN LFP Time-Frequency analysis Entropy	The FOG STN demonstrated a greater decrease of beta power during stepping and gait than the Non-FOG STN During actual FOG, increased alpha entropy is observed

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Table 2b

Reference	Objective	Methods (task/recordings/signal analysis)	Principal results
Lau, 2015 [104]	Nature of oscillations in the PPN and STN (14 patients)	Gait LFPs of PPN and STN Time frequency analysis	The majority of PPN neurons are modulated during gait, contrary to STN neurons
Shoushatarian, 2011 [184]	Cortical changes during gait initiation in 20 patients PD (with and without gait initiation difficulties) and controls (young and old)	Gait initiation Scalp EEG ERP	Differences in MRCP peak amplitude only between young and PD patients (mixing with gait initiation difficulties or not) at Cz
Tard, 2016 [208]	Interference of cognitive function and motor preparation in 15 FOG and 15 non FOG PD patients	Gait initiation Scalp EEG ERP Time frequency analysis	Abnormal increased beta oscillation during motor preparation in FOG group No differences in P3 in the 2 groups
Butler, 2017 [23]	Interference of cognitive function and motor preparation in 10 FOG and 10 non FOG PD patients	Gait initiation Scalp EEG ERP	Motor preparation potential is larger in freezers during gait initiation No differences in P3b in the 2 groups

PPN: pedunculopontine nucleus; PD: Parkinson’s disease; LFP: local field potential; FOG: freezing of gait; STN: subthalamic nucleus; MRCP: movement related cortical potentials; ERP: event-related potential.