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Association Between Various Brain Pathologies and Gait Disturbance

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Abstract

Background—Approximately 30% of older adults have disrupted gait. It is associated with increased risk of cognitive decline, disability, dementia, and death. Additionally, most older adults present with one or more neuropathologies at autopsy. Recently there has been an effort to investigate the association between subclinical neuropathology and gait.

Summary—We reviewed studies that investigated the association between gait and neuropathologies. Although all pathologies reviewed were associated with gait, grey matter atrophy was most consistently linked with poorer gait performance. Studies investigating the association between white matter and gait focused primarily on total white matter. Future research using more parsed regional analysis will provide more insight into this relationship. Evidence from studies investigating neuronal activity and gait suggests that gait disruption is associated with both under- and over-activation. Additional research is needed to delineate these conflicting results. Lastly, early evidence suggests that both amyloid and tau aggregation negatively impact multiple gait parameters, but additional studies are warranted. Overall, there was substantial methodological heterogeneity and a paucity of longitudinal studies.

Key messages—Longitudinal studies mapping changes in different types of neuropathology as they relate to changes in multiple gait parameters are needed to better understand trajectories of pathology and gait.

Keywords

Neuropathology; gait; aging; musculoskeletal and neural physiological phenomena

Introduction

Gait abnormalities affect approximately 30% of older adults [1]. Gait decline is associated with an increased risk of functional and cognitive decline, disability, dementia, and death [2,3]. Gait parameters can be classified into three categories: spatial (e.g., stride length),

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temporal (e.g., support time), and spatio-temporal (e.g., cadence). Intraindividual variation in gait parameters (e.g., stance time variability) has also been shown to be a strong predictor of negative clinical outcomes [4,5]. Additionally, tests such as the timed up-and-go (TUG) can be used to evaluate gait and mobility [6].

Gait is a complex task involving the coordination of both the central nervous system (CNS) and musculoskeletal system [7]. It also requires coordination across regions of the brain [7]. Sensorimotor regions are of course required to initiate, sustain, and coordinate mobility. Recent research has shown that regions involved in higher level cognitive functioning and memory, including the prefrontal cortex, hippocampus, and cerebellar regions, are also required to coordinate mobility. However, the exact extent of the role of brain regions in gait is not yet well defined.

Neurodegenerative disorders (e.g., Parkinson's disease (PD), Huntington's disease (HD), etc.) often present with gait dysfunction, suggesting a connection between the CNS and gait. A recent review hypothesized that, among older adults, CNS dysfunction is the leading cause of mobility impairment (defined as restriction in moving through one's environment, including gait dysfunction) [8]. Neuropathologies are associated with multiple neurodegenerative diseases in the aging brain. For example, amyloid beta (Aβ) plaques and neurofibrillary tangles are the hallmarks of Alzheimer's disease (AD) [9–12]. However, the accumulation of neuropathology is common even among older adults without a clinical diagnosis of a neurodegenerative disease. Indeed, approximately 35% of cognitively normal (CN) adults between ages 70 and 79 and 57% of CN adults between ages 80 and 89 have substantial cerebral Aβ deposition [13]. The toxic and atrophic effects of these pathologies may result in impaired ability of the brain to coordinate gait.

Although multiple studies have examined the association between brain pathology and gait dysfunction in neurodegenerative diseases, fewer studies have investigated the associations between subclinical neuropathology and gait [7]. As an initial step, we evaluated the literature examining neuropathology and gait among non-demented, aging individuals, and highlighted areas for future research. Specifically, we investigated white matter (WM) and grey matter (GM) atrophy; neuronal activity as measured by cerebral glucose metabolism; and Aβ and tau. The majority of studies investigating the association between subclinical neuropathology and gait have focused on cerebrovascular pathology (e.g., white matter hyperintensities (WMHs)). The association between greater cerebrovascular pathology and poorer gait performance has been reviewed in-depth by others [14,15]. Because less is known about the effect of other types of neuropathologies and gait, we focused on summarizing the evidence of non-cerebrovascular pathology and gait in the present review. We aimed to determine whether patterns emerged wherein certain types of gait parameters (e.g., spatial vs. temporal vs. spatio-temporal) were differentially associated with certain types of neuropathologies.

Methods

To identify studies we utilized the Mayo Clinic Library, and searched the following databases: PubMed, MEDLINE, and Cochrane Libraries from January 21 to April 1, 2016.

We searched for studies that examined neuropathology and gait in adult humans using multiple search terms, including “neuropathology,” “volumetric decline,” “brain atrophy,” “brain volume,” “cortical thinning,” “cortical thickness,” “white matter volume,” “gray matter volume,” “hippocampus volume,” “hippocampus atrophy,” “FDG PET,” “cerebral glucose uptake,” “amyloid,” “amyloid beta,” “PiB-PET,” “tau,” “gait,” and “mobility.” We used filters to restrict studies to research conducted in humans and excluding PD patients and falls as an outcome. Searches from PubMed returned 2,016 titles, MEDLINE returned 974, and Cochrane returned 13.

Titles were screened for keywords. Abstracts were screened if titles were insufficient. We excluded studies from review if they were conducted in samples of patients with significant medical conditions (e.g., Down’s syndrome, HD, PD, Creutzfeldt-Jakob), investigated cerebrovascular pathologies, or did not meet our other criteria (i.e., not conducted in humans, only examined falls as an outcome). We included studies for review if they measured both gait and neuropathology either via imaging methods, on autopsy, or in cerebrospinal fluid (CSF) in middle to older aged adults. Additional studies were identified from the reference sections of selected papers.

We included 31 studies, 23 of which measured brain volume or tissue integrity and gait, three that assessed glucose uptake, four that measured Aβ, and one that assessed tau. These studies are summarized in Table 1–Table 4. Although the methods of these studies were too heterogeneous to complete a meta-analysis, we did summarize the findings by regions of interest (ROI) (Table 5 and Table 6). All studies reviewed met quality guidelines set forth by the National Institutes of Health [16].

White matter (WM)

Studies that have investigated the association between WM atrophy and gait have focused mostly on total WM, as measured by structural magnetic resonance imaging (MRI). One cross-sectional study found, among 112 non-demented community-dwelling adults aged 70 years and older, that greater bilateral total WM was associated with faster gait speed (Table 1). However, this association was not significant after excluding participants with mild cognitive impairment (MCI) [17]. Longitudinally, one study among 225 community-dwelling older adults (mean age=71) without severe gait impediments or contraindication to MRI reported that change in total WM atrophy was associated with declining gait speed, step length, and cadence over an average of 30 months [18].

Using diffusion tensor imaging (DTI) techniques, researchers have investigated the association between WM integrity and gait. A study among high-functioning older adults (mean age=83) found that global greater mean diffusivity (MD), was associated with greater step length variability [19]. Additionally, in 173 community-dwelling older adults (mean age=73), lower fractional anisotropy (FA), indicating less white matter microstructural integrity, in the genu, but not the splenium of the corpus callosum, was associated with poorer gait and balance [20]. Importantly, this association was independent of WMH volume. In CN older adults (mean age=71), lower FA in the left anterior thalamic radiation and left corticospinal tract was associated with reduced step width and greater instability

measured during treadmill walking [21]. The corpus callosum is primarily responsible for communication across hemispheres, and the genu primarily connects the left and right prefrontal and anteriorfrontal cortices [22]. Together these findings support the idea that integrity of the frontal areas associated with executive function is important for gait and balance, and that gait and balance involve the coordination of multiple areas across hemispheres.

The association between WM integrity within the context of substantial cerebrovascular burden has also been examined. Among 429 non-demented later middle-aged adults (mean age=65) with cerebral small vessel disease, lower FA and higher MD of the corpus callosum was associated with slower gait speed, reduced stride length and cadence, and increased stride width [23]. In a smaller study of 20 older adults (range=65–84) with significant cerebrovascular pathology, lower FA and higher MD, and axial and radial diffusivity across all WM were associated with freezing of gait [24]. Another study that examined the effect of FA within the context of WMHs found that FA measures throughout WM regions significantly moderated the association between WMH volume and gait speed among 265 community-dwelling older adults (mean age=83) [25]. Specifically, among those with high FA, there was no association between WMH and gait speed. These results suggest that WMHs alone may not be associated with slower gait and are consistent with the hypothesis that the interaction between multiple pathologies is necessary to substantially affect gait performance [26].

In summary, the evidence presented here suggests that WM atrophy is associated with disrupted gait; however, it is not overwhelmingly compelling, particularly compared to the association between other types of pathology and gait (e.g., GM atrophy), as described below. The few studies investigating the association between gait and WM volume have focused on total volume [17,18], This broad type of investigation may be obscuring regional differences. It may be that more parsed analyses investigating individual regions are needed to detect a stronger association between WM and gait.

Ventricles

Ventricular enlargement may be indicative of GM atrophy, declines in CSF reabsorption, and/or total generalized brain atrophy. Among 20 community-dwelling MCI patients (mean age=76), greater left ventricular volume of both the main bodies and temporal horn, was associated with slower gait speed [27] (Table 1). Further, bilateral larger temporal horns were associated with greater stride-to-stride variability among 115 community-dwelling older adults (mean age=70 years) [28]. Similarly, among 321 CN and MCI subjects, slower gait speed was associated with severe ventricular enlargement (i.e., ventricular grade>5) [29]. Ventricular enlargement is a non-specific measure of cerebral damage, which could explain why the association with gait impairment was only observed with severe ventricular enlargement.

Grey matter (GM)

GM volume decreases with age and this decrease is further exacerbated in aging related diseases such as type II diabetes and AD [30–32]. The associations between spatial, temporal, and spatiotemporal gait parameters and reduced cortical thickness have been widespread across cortical regions. Six studies reported that lower total GM volume was associated with poorer performance on multiple gait measures [17,19,33–36] (Table 1). Seven studies showed that smaller GM volume in frontal regions was associated with poorer gait [33,34,37–41]. Five studies showed a relationship between lower GM volume in the parietal lobe and poorer performance on gait parameters [33,37–40]. Four studies found that lower GM volume in temporal lobe regions [37,38,42,43], cerebellum [37,40,43,44] and basal ganglia, insula, and limbic systems [33,37,38,40] was associated with disrupted gait. Three studies found that smaller GM volume in motor areas [33,38,39] and the hippocampus were also associated with poorer gait performance [17,18,45].

Across all ROIs reviewed, the association between GM volume in frontal regions and gait was the most commonly reported. This finding supports the hypothesis that gait involves regions important for higher level cognitive functioning. Indeed, decline in prefrontal ROIs is associated with executive dysfunction [46]. The strong relationship reported between the parietal lobe and gait is also not surprising because parietal regions are central to sensory integration, visuospatial function, and managing the relationship between one’s self and surroundings [39,40,47]. Findings that the caudate nucleus is associated with gait are supported from research in PD and HD, which are both characterized by disrupted gait and marked caudate nucleus atrophy [48,49]. The association between widespread GM atrophy and gait supports the theory that the coordination and interaction of multiple brain regions is necessary for proper gait performance.

The association between GM volume within the context of cerebrovascular pathology has also been examined. De Laat and colleagues studied the association between cortical thickness and gait within the context of small vessel disease [33]. Among 415 community-dwelling adults (age range 50 to 85 years) with cerebral small vessel disease, disrupted gait (i.e., slower gait speed, shorter stride length, lower cadence, wider stride width) was associated with lower GM volume across the cortex, including frontal, orbitofrontal, ventrolateral prefrontal, inferior parietal, visual, primary motor and premotor, temporal and left fusiform gyri, visual areas, insula, and cingulate ROIs. Similarly, Smith and colleagues (2015) [34] found that smaller total GM volume, in the context of cerebral small vessel disease, was associated with slower TUG. These findings suggest that even in the context of small vessel disease, widespread GM atrophy in areas associated with cognition and visuospatial processing is associated with disrupted gait.

Additionally, the relationship between GM volume and gait has been explored specifically in MCI. In a smaller study (N=20) of MCI patients, thinner motor cortex measures were associated with slower gait speed in both single and dual task walking, and greater stride time variability during single task walking [50]. Another study examined the association between both GM and WM volumes and mobility in 170 older adults diagnosed as CN, amnestic (a) MCI, or nonamnestic (na) MCI [35]. Participants completed both the real

(r)TUG and imagined (i) TUG. Smaller total GM volume was associated with slower rTUG, and smaller total and left PFC volume was associated with slower iTUG. The strongest association between brain volume and TUG performance was seen among the naMCI group. This may suggest that the pathological changes occurring in naMCI affects motor imagery, and this is independent of the kinesthetic completion of motor tasks (e.g., rTUG).

GM volume has also been associated with more severe measures of motor dysfunction (bradykinesia and gait disturbance), which is prevalent even among older adults without neurological conditions [42,51,52]. Among 307 community-dwelling older adults (mean age=83) without PD, smaller GM sensorimotor cortical and posterior parietal lobe volumes were associated with bradykinesia and gait disturbance. Smaller GM medial temporal lobe volume was associated only with gait disturbance and smaller GM volume in the cerebellum and dorsolateral prefrontal cortex was associated only with bradykinesia [43].

Together, the above studies suggest that there is a strong association between GM atrophy and gait. However, there is a paucity of longitudinal evidence, so it is difficult to determine trajectories of atrophy and gait. Indeed, only one study [18] examined the association between GM and gait over time. Future studies are also needed to systematically examine specific ROIs and consistently measure multiple gait parameters to elucidate whether GM atrophy in certain ROIs is more or less associated with different gait parameters.

Neuronal activity

Glucose uptake is a measure of neuronal activity, and has been shown to decrease in normal aging, with further decline in dementia [53–55]. Greater glucose uptake is indicative of neuronal activation or up-regulation, whereas reduced glucose uptake is indicative of deactivation or down-regulation. Based on findings from functional magnetic resonance imaging (fMRI) studies, Jahn and colleagues [56,57] proposed a supraspinal locomotor network that includes the frontal cortex, basal ganglia, brain stem tegmentum, and cerebellum. This network, which is activated during locomotion across species and can be interrupted by lesions, provides insight into the locomotive process. Their locomotor network hypothesis is supported by findings from a study that examined glucose uptake measured by with Fludeoxyglucose (^{18}F) (FDG)-PET during locomotion in 16 adults aged 51 to 73 [58] (Table 2). The greatest uptake was in the bilateral central region, particularly focused in the mesial part of the primary cortex, the primary somatosensory cortex, lingual gyrus, fusiform gyrus, and parahippocampal gyrus during walking. Additionally, the authors observed greater uptake in the occipital lobe and precuneus. The first group of brain areas is associated with visually guided navigation, while the latter areas are associated with visual-motor coordination.

A study that measured glucose uptake in 24 community-dwelling women aged 75 to 82 similarly found greater glucose uptake in the occipital lobe, as well as the sensorimotor area and cerebellum during treadmill walking [59]. Their results showed reduced uptake in the orbitofrontal and superior frontal gyrus, dorsolateral prefrontal cortex (dLPFC), supplementary motor area, middle and superior temporal gyrus, posterior cingulate cortex, pons, and hippocampus. Another study separated participants into low step variability (LSV)

and high step variability (HSV) groups, because, as aforementioned, greater step variability is associated with increased risk of negative clinical outcomes [4,5]. The LSV group showed greater sensorimotor activation than the HSV group. Additionally, the HSV group had relative deactivation of the supplementary motor area, dLPFC, and hippocampus during treadmill walking. The authors hypothesized that deactivation, as assessed by lower glucose uptake, of the supplementary motor area and dLPFC in the HSV group indicate that these participants found it more difficult to adapt to the novel walking environment (i.e., the treadmill). While the observed greater activation of the hippocampus is in line with earlier findings [60], indicating that hippocampal metabolism and atrophy are associated with greater step length variability. In contrast, lower glucose uptake in the prefrontal, posterior cingulate, and parietal cortices was associated with slower maximum walking speed and lower cadence at maximum walking speed among 182 community-dwelling women aged 55 to 89 years [61]. This finding indicates that lower neural activation, as opposed to increased neural activation, is associated with poorer gait.

Associations between gait and cerebral glucose uptake are diffuse across brain regions, including frontal, temporal, parietal, and occipital lobes, and the cerebellum and limbic areas. This is consistent with the hypothesis put forth by Jahn et al. [56,57], indicating that locomotion requires coordination of multiple brain regions, including those involved in higher level cognition. It is unclear, however, whether higher glucose uptake (which suggests up-regulation and recruitment of brain regions) is needed to execute gait, or lower glucose uptake (which suggests cerebral dysfunction) is associated with gait. For example, the study from Shimada et al. found HSV participants had lower glucose uptake in sensorimotor areas, but higher glucose uptake in the hippocampus [59]. It may be that different brain regions respond contrarily to the demands of gait functioning, and therefore have varying glucose uptake patterns. Longitudinal studies will be critical for understanding these associations to determine whether decreased and/or increased glucose uptake, perhaps dependent on the ROI, predicts gait decline.

Amyloid Beta (Aβ)

Over 30% of adults over the age of 70 have substantial cerebral Aβ deposition [13]. However, few studies have investigated the association between Aβ and gait. Two autopsy studies reported that greater AD pathology (neuritic plaques, diffuse plaques, and neurofibrillary tangles) deposition in the midfrontal, superior temporal, inferior parietal, entorhinal cortices, and hippocampus was associated with reduced gait speed prior to death and declining gait speed up to 6 years prior to death [62,63] (Table 3). A study in 128 non-demented older adults (aged 70 years or older) found that greater Aβ deposition in the putamen, caudate, precuneus, and occipital, temporal, and parietal lobes was associated with slower gait speed [64]. The association was strongest for Aβ deposition in the posterior putamen. Given its proximity to the motor corticostriatal circuits, this finding suggests that Aβ deposition contributes to gait dysfunction.

Expanding on this study, we investigated the association between C^{11} Pittsburgh Compound B (PiB) [65] PET standardized uptake volume ration (SUVR) and gait parameters in cognitively normal adults aged 50 to 69 [66]. Greater PiB-PET SUVR across ROIs

(prefrontal, orbitofrontal, temporal, parietal, anterior and posterior cingulate, and motor) was associated with slower gait speed, lower cadence, longer double support time, and greater stance time variability, independent of neurodegeneration, as measured by FDG PET and MRI, in AD-signature regions. In sex-stratified analyses, these associations were only significant among women. In conclusion, despite the relatively few studies that have investigated the association between Aβ and gait, it appears that greater Aβ burden is associated with disrupted gait. Longitudinal studies are needed to determine the trajectories between amyloidosis and gait.

Tau

Aggregates of tau protein are part of the pathological process of a number of diseases, including AD and frontotemporal dementia. The majority of research examining the association between gait and tau has been conducted in AD and normal pressure hydrocephalus (NPH) patients [67–69]. However, one study among 86 participants without PD (or AD or NPH), reported that the number of neurofibrillary tangles in the substantia nigra was significantly associated with declining gait in annual exams prior to death [70]. This evidence suggests that gait and mobility are impacted by tau aggregation both in diagnosed and prodromal disease. With the new availability of tau-PET ligands, imaging will provide information on whether regional deposition of cerebral tau affects gait in vivo, which cannot currently be ascertained by measuring tau in the CSF.

Summary of the reported brain regions associated with gait

Pathologies in three regions were most often found to be associated with disrupted gait: the frontal regions were associated with gait in 12 studies, and the limbic system and parietal regions, were each associated with gait in 11 studies (Tables 5 and 6). Although there was not strong evidence for the association between the motor cortices and gait, the motor cortex and somatosensory motor cortex are located in the frontal and parietal lobes, respectively, and are a juncture of the inputs from multiple converging cortical and subcortical regions, such as the frontal lobe and thalamus. Further, the motor areas provide input to the descending corticospinal tract [50,71]. The observed association of the limbic system with gait further suggests that cognition, especially memory, is important for gait. Indeed, past studies have suggested that gait requires memory, particularly in novel situations [35,45,59,60]. Thus, other regions associated with gait and cognitive functioning (e.g., frontal and parietal regions) may impact gait partially through cognitive dysfunction. For additional information, the association between cognition and gait has been reviewed elsewhere [72].

Gaps in the literature and future directions

Future studies should consider potential sex differences in the association between neuropathologies and gait. Past studies have shown that this relationship can differ between men and women [66]. This is unsurprising given the increased recognition of sex differences in aging [73,74], gait changes [73,75–78], and brain and neuropathological development [50,79–85]. An empirical understanding of sexual dimorphism across pathologies is

important. Reasonably, these differences in pathology would translate to differing patterns of gait dysfunction. Thus, future research should attempt to delineate how different pathologies affect different gait parameters by sex. This may translate into sex-specific clinical guidelines for gait impairment associated with brain pathology. Moreover, most studies in this review investigated the association between a particular pathology and gait speed. However, it is important to examine other gait parameters to determine whether they are differentially affected by specific pathologies, show different trajectories of decline, or have sex-specific differences.

Perhaps the most glaring gap in the literature is the lack of longitudinal studies. Of the research we reviewed, only two studies [18,63] had a longitudinal design. Longitudinal studies are needed to determine how gait trajectories are affected by changes in neuropathology over time. Quantifying trajectories of pathology, based on both type and location, with gait decline will allow for a more precise approach to utilizing gait as a measure in-clinic and for therapeutic and intervention trials.

Conclusion

The goal of this review was to summarize research examining the associations between neuropathologies and gait. We found that all pathologies reviewed (i.e., WM, GM, and HVa decline, ventricular enlargement, and amyloid and tau aggregation) were associated with poorer gait performance. The strongest associations were between GM and gait. Regardless, this review further suggests a link between neurodegenerative biomarkers and gait performance.

This review has limitations that should be considered. First, relatively little research has been conducted investigating the association between protein aggregation (i.e., Aβ and tau) and gait, in part because PET ligands have only recently been developed, so it is difficult to draw robust conclusions. However, past reviews have not included these studies, and we hope more research will be conducted investigating the association between protein aggregation and gait. Additionally, we were unable to conduct a meta-analysis due to the heterogeneity of the methods for measuring both neuropathology and gait. For example, some studies used voxel count methods to determine volume while others used ROI methods. These methods produce comparable, but heterogeneous results, [86] and more research is needed to make direct comparisons between these methods [87].Without a meta-analysis, it is difficult to come to quantitative conclusions about findings in the literature, including determining whether gait parameters were differentially associated with different neuropathologies. Still, we hope this review sheds light on the emerging field of research investigating the link between neuropathologies and gait.

Multiple studies have been published since Rosso and colleagues put out the call to better understand the connection between the CNS and gait [7]. However, more research is needed to develop a deeper understanding of the link between neurological mechanisms and different facets of gait and mobility [88]. An empirical quantification of the association between neuropathology and gait parameters will contribute to the increased use of gait measures in the clinic and for clinical trials. Gait has been identified as a potentially useful

clinical tool [89]. This is largely because it is easy to measure and it is associated with several poor clinical outcomes. Understanding and interpreting specific declines in gait parameters throughout the aging process, beginning as early as middle age, could be important to prevent future poor clinical outcomes [8].

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Table 1

Brain volume – white matter (WM), grey matter (GM), hippocampal volume (HVa), ventricular enlargement, and DTI

Study	Sample	Mean age	% Male	Methods	Gait parameters	Results
Ezzati et al 2015 [17]	N=112 (N=20 with MCI) non-demented, community-dwelling adults	79	40	Cross-sectional; 3.0T MRI-measured total WM volume, ventricular volume, and HVa	Gait speed	In unadjusted models, greater WM volume and HVa was associated with faster gait speed; right HVa, in particular the presubiculum, was associated with gait speed. These results were no longer significant when excluding MCI participants
Callisaya et al 2013 [18]	N=225 community-dwelling adults	71	56	Longitudinal; 1.5T MRI-measured changes in brain volume; mean duration between baseline and follow-up=30.6 months	Gait speed, cadence, step length, step width	Change in total WM atrophy associated with declining gait speed, step length, and cadence; hippocampal atrophy associated with declining gait speed and step length
Rosso et al 2014 [19]	N=265 community-dwelling adults	83	43	Cross-sectional; 3T MRI-measured WM integrity	STV	Greater mean diffusivity and FA associated with greater STV, but the association between FA and STV was not significant in fully-adjusted models. Lower total GM and WM volume were associated with greater STV.
Bhadelia et al 2009 [20]	N=173 community-dwelling older adults	73	25	Cross-sectional; 1.5T MRI-measured WM integrity of the corpus callosum and	Tinetti (gait and balance) scale score	Lower FA of the genu, but not the splenium, of the corpus callosum was associated with poorer gait and balance, independent of WMH volume
Bruijn et al 2014 [21]	N=15 younger and N=25 older community- dwelling CN adults	Younger=22; older=71	55	Cross-sectional; 3T MRI-measured WM integrity	Gait stability	Older adults had lower FA and lower FA in the left anterior thalamic radiation and left corticospinal tract was associated with narrower step width and reduced stability during treadmill walking
de Laat et al 2011 [23]	N=429 non-demented later middle aged adults with cerebral small vessel disease	65	55	Cross-sectional association; 1.5T MRI-measured WM integrity of the corpus callosum	Gait speed, stride length, stride width	Among those with cerebral small vessel disease, poorer integrity of the corpus and gait was associated with reduced gait speed, stride length and cadence, and increased stride width
Iseki et al 2015 [24]	N=20 older subjects with age-related white matter change	Range=65–84	unknown	Cross-sectional; 3T MRI-measured WM integrity and FOG	FOG, gait speed, stride length, double support time	Lower FA in the left superior longitudinal fasciculus near the premotor area and bilaterally in the corpus callosum near the anterior cingulate cortex, greater mean diffusivity in the left posterior limb of the internal capsule and right cingulum, and greater axial and radial diffusivity in the left superior corona radiata were associated with FOG
Rosario et al 2016 [25]	N=265 community-dwelling older adults	83	43	Cross-sectional; 3T WM integrity	Gait speed	FA moderated the association between greater WMH volume and gait speed, wherein among

Study	Sample	Mean age	% Male	Methods	Gait parameters	Results
						those with high FA there was no association between WMH and gait speed
Annweiler et al 2014 [27]	N=20 community-dwelling MCI patients	76	56	Cross-sectional; 1.5T MRI-measured ventricular enlargement	Gait speed	Greater main body and temporal horn left ventricular volume was associated with slower gait speed
Annweiler et al 2013 [28]	N=115 non-demented, community-dwelling adults	70	56	Cross-sectional; 1.5T MRI-measured ventricular enlargement	STV	Participants with the highest stride-to-stride variability had larger temporal horns
Rosano et al 2006 [29]	N=321 non-demented, community dwelling adults; mean age=78	78	41	Cross-sectional; 1.5T MRI-measured ventricular volumes	Gait speed	Slower gait speed was associated with more severe ventricular enlargement (i.e., ventricular grade>5)
de Laat et al 2012 [33]	N=415 community-dwelling adults with SVD	65	54	Cross-sectional; 1.5T MRI-measured GM volume	Gait speed, cadence, stride length, stride width	Slower gait speed associated with smaller total GM volume; shorter stride length associated with smaller GM volume in the frontal cortex, orbitofrontal cortex, ventrolateral PFC, inferior parietal lobe, superior temporal gyrus, visual areas, and anterior and posterior cingulate areas of the limbic system; lower cadence associated with smaller volumes of left cingulate, bilateral visual cortex, left fusiform gyrus, and primary and premotor cortices; stride width associated with smaller bilateral orbitofrontal cortex, ventrolateral PFC, cortical areas adjacent to the posterior insula, inferior temporal gyrus, left fusiform gyrus, and dorsal anterior cingulate gyrus volume
Smith et al 2015 [34]	N=803 non-demented, community-dwelling adults	58	41	Cross-sectional; 1.5 & 3T MRI-measured PFC, basal ganglia, and cerebellar volumes	TUG	Smaller PFC and GM volume associated with slower TUG
Allali et al 2015 [35]	N=170 non-demented (n=80 CN; n=25 aMCI; n=66 naMCI) participants referred to the clinic for memory concerns	70	63	Cross-sectional; 1.5T MRI-measured WM volumes	rTUG, iTUG	Smaller total WM and hippocampal volumes associated with slower rTUG in naMCI; smaller left PFC volume associated with slower iTUG in naMCI; smaller right HVa associated with increased rTUG in CN and naMCI
Callisaya et al 2014 [37]	N=305 community-dwelling adults	71	54	Cross-sectional; 1.5T MRI-measured total WM volume	Gait speed, cadence, stride length	Smaller WM volume associated with slower gait speed, shorter step length, and lower cadence. Smaller GM volume in bilateral frontal, cingulate, insula, temporal, parahippocampal, parietal, occipital, cerebellar, thalamus, caudate nucleus, putamen, and claustrum associated with slower gait speed and shorter stride length.
Dumurgier et al 2012 [38]	N=1623 community dwelling adults	73	39	Cross-sectional; 1.5T MRI-measured cortical thickness	Gait speed	Thinner sensorimotor cortex, frontal, parietal, and temporal lobes, insula, thalamus, basal ganglia, and caudate nucleus were associated

Study	Sample	Mean age	% Male	Methods	Gait parameters	Results
						with slower gait speed. Only the caudate nucleus was associated with gait speed after correction for multiple comparisons and adjusting for correlations between other areas of GM volume.
Rosano et al 2008 [39]	N=220 (11 with dementia) community-dwelling adults	78	37	Cross-sectional; 1.5T MRI-measured cortical thickness	Gait speed, step length, step width, stance time, step time, double support time	Smaller pallidum, inferior parietal lobules, and right dLPFC associated with wider step; smaller right motor cortex, bilateral sensorimotor cortex, right superior and bilateral inferior parietal lobules, and dLPFC associated with shorter stride length and longer double support time; smaller left supplementary motor area associated with shorter step length. The associations between step width and right dLPFC and right pallidum were mediated by DSST score
Rosano et al 2012 [41]	N=214 non-demented, community-dwelling adults	73	38	Cross-sectional association between 1.5T MRI-measured cortical thickness	Gait speed	Smaller prefrontal area was associated with slower gait speed; this association was mediated by DSST score
Rosano et al 2012 [43]	N=307 community-dwelling adults without PD or other neurological disease	83	45	Cross-sectional; 3.0T MRI-measured cortical thickness	Bradykinesia, gait disturbance measured by Unified Parkinson's Disease Rating scale	44% of participants had bradykinesia, gait disturbance, and/or tremor; smaller sensorimotor and posterior parietal areas associated with bradykinesia and gait disturbance; smaller medial temporal lobe associated with gait disturbance; smaller cerebellum and dLPFC associated with bradykinesia
Nadkarni et al 2014 [44]	N=231 non-demented, community-dwelling adults	83	42	Cross-sectional; 3T MRI-measured GM volume	Gait speed	Greater cerebellar GM volume (both left and right separately, and bilaterally) associated with faster gait speed, independent of WMH, atrophy, age and gender; however, this association is mediated by DSST
Beauchet et al 2015 [45]	N=47 CN and N=43 MCI participants	70	51	Cross-sectional; 1.5T MRI-measured HVa	STV	Larger HVa associated with higher STV among CN
Beauchet et al 2014 [47]	N=71 community-dwelling adults	69	40	Cross-sectional; 1.0T MRI-measured parietal lobe thickness	STV	Thinner parietal lobe measures associated with greater STV
Annweiler et al 2013 [50]	N=20 MCI participants	76 (median)	70	Cross-sectional; 3.0T MRI-measured motor cortex volume and	Single and dual-task walking performance	Greater primary motor cortex volume was associated with faster gait speed during both single and dual-task walking, and decreased STV during single task walking

MCI, mild cognitive impairment; aMCI, amnestic MCI; naMCI, non-amnestic MCI; WM, white matter; HVa, hippocampal volume; STV, stride time variability; CN, cognitively normal; GM, grey matter; PFC, prefrontal cortex; dLPFC, dorsolateral PFC; TUG, timed up-and-go; iTUG, imagined TUG; rTUG, real TUG; FA, fractional anisotropy; WMH, white matter hyperintensities; DSST, digit symbol substitution test; AD, Alzheimer's disease; CVD, cerebrovascular disease; DTI, diffusion tensor imaging; FOG, freezing of gait.

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Table 2

Association between glucose uptake and gait

Study	Sample	Mean age	% Male	Methods	Gait parameters	Results
la Fougere et al 2010 [58]	N=16 healthy adults	61	56	Two time points; FDG-PET during locomotion and 14 days later at rest	Treadmill walking for 10 minutes at a constant rate	Walking associated with increase glucose uptake in mesial section of the primary cortex, primary somatosensory cortex, lingual gyrus, fusiform gyrus, parahippocampal gyrus, occipital lobe, precuneus, vermal and paravermal cerebellum, and decreased glucose uptake in inferior parietal lobe, superior parietal gyrus, anterior cingulate
Shimada et al 2013 [59]	N=24 community-dwelling women, divided into LSV and HSV groups	78	0	Two time points; FDG-PET at rest and during locomotion 2 days to 2 weeks apart	Treadmill walking for 25 minutes at a constant rate	Sensorimotor areas, occipital lobe, cerebellum were activated during walking; HSV group had significant deactivations in the frontal lobe and the inferior temporal gyrus compared to LSV, and deactivations of white matter of the middle and superior temporal gyrus, and hippocampus during walking compared to at rest; LSV group had significant activations of the primary sensorimotor area compared to HSV
Sakurai et al 2014 [61]	N=182 community-dwelling women	69	0	Cross-sectional; FDG-PET	Gait speed, cadence, step length at comfortable and	Slower maximum gait speed and lower cadence at maximum gait speed was associated with lower glucose uptake in the PFC, posterior cingulate, and parietal cortices

LSV, low step variability; HSV, high step variability; PFC, prefrontal cortex.

Table 3

Association between Aβ and gait

Study	Sample	Mean age	% Male	Methods	Gait parameters	Results
Buchman et al 2008 [62]	N=165 (59 with clinical AD diagnosis at death) community-dwelling adults	85 at baseline; 88 at death	44	AD pathology (tau & Aβ) at autopsy	Gait speed	AD pathology on autopsy associated with gait prior to death.
Buchman et al 2013 [63]	N=791 community-dwelling adults	82 at baseline; 89 at death	34	AD pathology (tau & Aβ) at autopsy	Gait speed	AD pathology on autopsy was associated with declining gait speed over an average of 6.4 years prior to death
del Campo et al 2015 [64]	N=128 non-demented community-dwelling adults	76	40	Cross-sectional; [^{18}F]Florbetapir PET-measured Aβ	Gait speed	Greater Aβ deposition in the posterior and anterior putamen, caudate, semioval center, precuneus, anterior and posterior cingulate and occipital, temporal, and parietal lobes associated with slower gait speed
Wennberg et al, 2016 [66]	N=611 CN adults	63	51	Cross-sectional; PiB-PET SUVR	Gait speed, cadence, stride length, double support time, stance time variability	Greater PiB-PET SUVR in prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, posterior cingulate/precuneus, and motor ROIs was associated with slower gait speed, lower cadence, longer double support time, and greater stance time variability. Results were independent of AD-associated neurodegeneration. In sex-stratified analyses, results were significant only among women.

AD, Alzheimer's disease; SUVR, standardized uptake value ratio; CN, cognitively normal.

Table 4

Association between tau and gait

Study	Participants	Mean age	% Male	Methods	Gait parameters	Results
Schneider et al 2006 [70]	N=86 Catholic clergy without PD	85 at death	Not specified	Neurofibrillary tangles in the substantia nigra on autopsy and	Performance on the UPDRS prior to death	A greater number of tangles at death was associated with a worse score on the UPDRS, with gait the most strongly affected domain, independent of dementia diagnosis

PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

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Table 5

Regions of interest (ROIs) by neuropathology type associated with gait in reviewed papers

ROI	WM	GM	Neuronal activity	Aβ	Tau	Total
Frontal lobe	xxx	xxxxxxx	xx			12
Parietal lobe		xxxxx	xx	x		8
Temporal lobe	x	xxxx	x	x		7
Cerebellum		xxxx	xx			6
Cingulate		xx	xx	x		5
Motor cortex	xx	xxx				5
Somatosensory cortex		xxx	xx			5
Hippocampus		xxx	x			4
Occipital lobe		x	xx	x		4
Caudate		x		x		2
Corpus callosum	xxx					3
Insula		xxx				3
Putamen		xx		x		3
Fusiform gyrus		x	x			2
Parahippocampal gyrus		x	x			2
Precuneus			x	x		2
Thalamus	x	x				2
Cingulum	x					1
Corona radiata	x					1
Lingual gyrus			x			1
Pallidum		x				1
Substantia nigra					x	1
Total by pathology type	17	41	18	7	2	

WM, white matter; GM, grey matter, Aβ, amyloid beta protein

It should be noted that Buchman and colleagues (2008; 2013) [66, 67] investigated the association between AD pathology (neuritic plaques, diffuse plaques, and neurofibrillary tangles) averaged across midfrontal, superiortemporal, inferior parietal, entorhinal, and hippocampal ROIs and gait, so it was not possible to differentiate by ROI or pathology type in these instances.

Table 6

Collapsed regions of interest (ROIs) by neuropathology type associated with gait in reviewed papers

ROI	WM	GM	Neuronal activity	Aβ	Total
Frontal lobe	xxx	xxxxxxx	xx		12
Limbic system	xxx	xxxx	xxx	x	11
Parietal lobe		xxxxxxxx	xx	x	11
Motor areas	xxx	xxxxx	xx		10
Temporal lobe	x	xxxx	x	x	7
Cerebellum		xxxx	xx		6
Basal ganglia		xxx		xx	5
Occipital lobe		x	xx	x	4
Insula		xxx			3
Total by pathology type	10	39	14	6	

WM, white matter; GM, grey matter, Aβ, amyloid beta protein

It should be noted that Buchman and colleagues (2008; 2013) [66, 67] investigated the association between AD pathology (neuritic plaques, diffuse plaques, and neurofibrillary tangles) averaged across midfrontal, superiortemporal, inferior parietal, entorhinal, and hippocampal ROIs and gait, so it was not possible to differentiate by ROI or pathology type in these instances.