Neural correlates of gait disorders in neurological conditions

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" Neural correlates of gait disorders in neurological conditions "

Thesis submitted to the Medical School of
the University of Geneva

for the degree of Privat-Docent
by

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Geneva

2016

Acknowledgments

This work would have been impossible without the intense support of my family (the oldest and of course the youngest – special thanks to Salomé) and my scientific mentors from Geneva, Paris, New York and Montreal. Frédéric Assal, François Herrmann, Patrice Lalive, Bruno Dubois, Richard Lévy, Joe Verghese, and Olivier Beauchet have largely contributed (pseudo-R^2 = 90%) to my motivation and my curiosity to this research topic that perfectly combines the translational approach between clinical and research activities. A growing part of this pseudo-R^2 comes now from my younger collaborators and students that gave me a new view on this topic.

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Abstract

Among the oldest old, around 20 % still walk normally, suggesting that gait disorders are not an unavoidable consequence of aging. Intense researches involving clinicians and neuroscientists are focusing on the neural mechanisms of gait control, in order to understand the pathophysiology of gait disorders affecting neurological conditions. This thesis aims to present an overview of the behavioral and the neuroimaging studies that investigate the "neural correlates of gait disorders in neurological conditions". The combined approach of behavioral measures (i.e. dual-tasking) with various neuroimaging techniques, such as functional MRI or metabolic studies, suggests a major role of the prefrontal cortex in gait control, with the involvement of an extended cerebral network involving the basal ganglia, the hippocampus and the parietal cortex. These new findings offer new perspectives in term of pharmacological and non-pharmacological treatments of gait disorders in neurological conditions, such as Parkinson's disease or Alzheimer's disease.

Chapter 1. Introduction

1.1 Gait disorders in neurological conditions

Gait disorders become very common in community-dwelling adults with aging (1): the prevalence of gait disorders increases from 15 % at the age of 60 years to more than 80 % after 85 years (2). However, gait disorders are not an unavoidable consequence of aging, because among the oldest old individuals, around 20 % walk normally (3). This epidemiology suggests that an underlying medical condition constitutes the cause of gait disorders. Hence, as for young adults, clinicians should investigate the cause of gait disorders in older adults, even for the most elderly.

Gait disorders are clinically divided in neurological or non-neurological causes, such as arthritis, cardiovascular conditions or foot deformities (4). Non-neurological causes of gait disorders and the extrinsic influences on gait, such as impaired vision, will be not the focus of this work. Among the neurological gait abnormalities (5), we identified different patterns of gait disorders. In Table 1, different types of neurological gait disorders are presented along with their clinical characteristics and illustrated by some examples of neurological conditions.

Table 1. Pattern of neurological gait disorders (personal contribution)

Type	Characteristics	Neurological conditions
Unsteady	Marked sway, loss of balance or falls while the individual is walking in straight line, placing one foot directly in front of the other.	Multiple sclerosis (early stage)
Ataxic	Wide-based gait with other cerebellar features, such as intention tremor or incoordination.	Wernicke encephalopathy Chronic alcohol consumption Cerebellar stroke Multiple system atrophy Spinocerebellar ataxia
Frontal	Short steps, wide-based, magnetic, very slow, symmetric.	Normal pressure hydrocephalus Vascular dementia Progressive supranuclear palsy Alzheimer's disease (later stages)
Parkinsonian	Short and shuffling steps, flexed posture, "en bloc" turns, absence of arm swinging.	Parkinson's disease Dementia with Lewy bodies Chronic neuroleptic consumption
Neuropathic	Uni or bilateral foot drops and other neuropathic signs, such as sensory loss or absence of deep-tendon reflexes.	Diabetes with neuropathy Toxic neuropathy (e.g. chimiotherapy) Guillain-Barré syndrome Chronic polyradiculonevritis
Hemiparetic	Asymetrical circumduction of the hip in addition to other focal signs of stroke (e.g. aphasia).	Frontal or subcortical strokes
Spastic	Bilateral legs circumduction, legs crossing (when severe).	Multiple sclerosis (later stages) Anterior spinal cord conditions (e.g.tumor, compression)

Identifying the type of neurological gait abnormalities is not only useful to improve diagnostic accuracy, but also for the prediction of future neurological conditions, such as dementia: the presence of neurological gait abnormalities, especially the presence of unsteady, frontal and hemiparetic gaits can predict the development of non-Alzheimer dementia in non-demented older adults (5). The identification of neurological gait abnormalities, especially unsteady and neuropathic gaits, has also been associated with future adverse medical events, such as falls (6), in non-demented older adults. Even for similar gait patterns, such as frontal and parkinsonian gait, the determination of specific gait types may improve the

identification of vascular risk factor assessment as parkinsonian gait, but not frontal gait, has been strongly associated with vascular risk factors (7).

Although the clinical assessment of gait is a core feature of neurological examinations, it is not enough to identify the underlying neurological conditions or medical adverse events, such as falls. We recently showed that combining a quantitative assessment of gait, such as measuring gait speed, to the clinical gait assessment improves the identification of future fallers (8).

Experts and national organizations recommend the quantification of gait for the identification of clinical adverse events (9-12). Gait speed is a strong predictor of disability, cognitive decline or mortality (5, 6, 13, 14). The huge development of user-friendly portable tools, such as instrumented walkway or footswitches with accelerometers, to measure gait offers new perspectives to clinicians. The availability of such devices now allows clinicians an easy access to quantitative gait parameters that are more sophisticated than gait speed alone, such as the measure of gait variability. For instance, gait variability, specifically stride time variability that reflects the regularity of gait, has been associated with the cortical control of gait (15). Stride time variability (expressed in percentage) calculated by the following formula:

(SD of stride time/mean value of stride time) x 100

has been extensively studied in neurological conditions, such as Parkinson's disease (16-19), multiple sclerosis (20-22) and dementia (23-26). This parameter that has been linked to a specific subtype of executive functions (27) represents an interesting biomarker of disease progression (25), treatment response (28-31), or diagnosis of neurological disease (24, 26, 32, 33). High stride time variability that reflects disturbed gait regularity has been suggested as an appropriate biomarker for identifying subtypes and stage of dementia (34). Vascular and/or neurodegenerative mechanisms that interfere with the various brain regions involved in the control of gait would have a direct impact on gait variability. Different models (3, 35, 36), as presented in Figure 1, has been tried to synthesize the complexity of the various brain regions and their related networks involved in the control of gait.

As suggested by the identification of different clinical patterns of gait disorders and their link with dementia and/or vascular risk factors, individual quantitative gait parameters have been related with specific cognitive functions (37). For instance, based on a factor analysis approach, three factors – pace, rhythm and variability – have been identified from the original gait variables, such as gait speed, stride length or stride time variability, measured in healthy older adults without dementia. These individual factors have been linked with specific cognitive domains (i.e. executive function or memory): pace factor with decline in global cognitive functions and executive functions and the rhythm factor with decline in episodic memory. In term of dementia prediction, both rhythm and variability factors predict future risk of dementia (37). Alternative factor analyses based on studies focusing on discrete aspects of gait suggest five main factors: pace (step velocity, step length, step time variability, swing time variability, and stance time variability); rhythm (step time, swing time, and stance time); asymmetry (step time asymmetry, swing time asymmetry, and stance asymmetry); variability (velocity variability, step length variability, and step width variability); and postural control (step width and step length asymmetry). Some of these factors are associated with cognitive functions and behavior (i.e. executive functions with postural control; balance self-efficacy with pace and asymmetry) (38). This factor analysis has been associated with functional deficits encountered in rare neurological conditions, such as mitochondrial disease (39). Interestingly, in Parkinson's disease, these factors have been able to identify disease progression or response to levodopa therapy (40). In addition to these two approach relying on factor analysis, a third one suggests the inclusion of two additional domain: the tandem factor that reflects errors during tandem gait and the turning domain that includes the characteristics of turning (i.e. number of turning step and turning time) (41). These both domains have been related to falls (42, 43). Using a similar approach that consists of using the link between individual gait parameters and cognitive domains, we focused on a newly developed predementia syndrome called the Motoric Cognitive Risk (MCR) syndrome (44). This syndrome associates the presence of a cognitive complaint to a slow gait speed in older adults without dementia. The worldwide prevalence of this syndrome has been evaluated at 9.7 % among 26'802 individuals without dementia older than 60 years (45). The MCR syndrome predicts the future

development of dementia and presents the main advantage of relying on criteria independent on time or cost-consuming factors, such as expansive neuroimaging methods or comprehensive neuropsychological assessments (44-46). We identified five individual subtypes of MCR, based on different gait parameters: gait speed, stride length, swing time, stride length variability and swing time variability. We showed that each individual MCR subtype was associated with specific cognitive domains, decline in individual cognitive domains and with various risk factors (47).

Studying the clinical pattern of gait disorders and/or quantifying gait parameters improve the diagnosis, the follow-up and the treatment of neurological conditions. In neurodegenerative conditions, such as dementia, clinical gait abnormalities (5) as well as quantitative gait parameters (37) contribute to better identify Alzheimer's disease from non-Alzheimer's dementia. In terms of follow-up or disease progression, using the example of multiple sclerosis – the most prevalent non-traumatic disabling condition in young adults - the measurment of gait parameters predicts the long-term disability (48, 49). The use of quantitative gait parameters also contributes to measure the treatment response in neurological conditions, and improve the understanding of the physiological mechanisms of the pharmacological drugs and the rehabilitative strategies (28-31, 50-52).

1.2 Classification and clinical approach of neurological gait disorders

Besides the clinical classification of neurological gait disorders presented in Table 1, many other classifications coexist based on a hierarchical, etiological or anatomical approach (3, 53). The hierarchical approach divides the nervous system into 3 levels (36):

Table 2. Hierarchical approach (personal contribution)

Levels	Anatomy	Examples
Lower	Muscles; Motor and sensitive peripheral nerves (including vestibular and ophthalmic nerves)	Motor or sensitive neuropathy;
Middle	Corticospinal or lemniscal pathways; Cerebellum.	Tabes dorsalis; Spinal cord compression; Wernicke encephalopathy;
Higher	Basal Ganglia; Cortex	Parkinson's disease; Vascular dementia

The etiological classification relies on the underlying pathology, such as vascular or neurodegenerative conditions, and the anatomical classification focuses on the localization of the lesions (i.e. frontal lobe, cerebellum, peripheral nerves). Every classification has its own limitations, and none of them is broadly accepted in clinical or in research settings (35). As the gait assessment is a core feature of the neurological examination, the clinicians need a structured approach to identify the neurological conditions behind the gait disorders. Here, an integrative hierarchical approach is suggested to better improve the diagnosis of gait disorders:

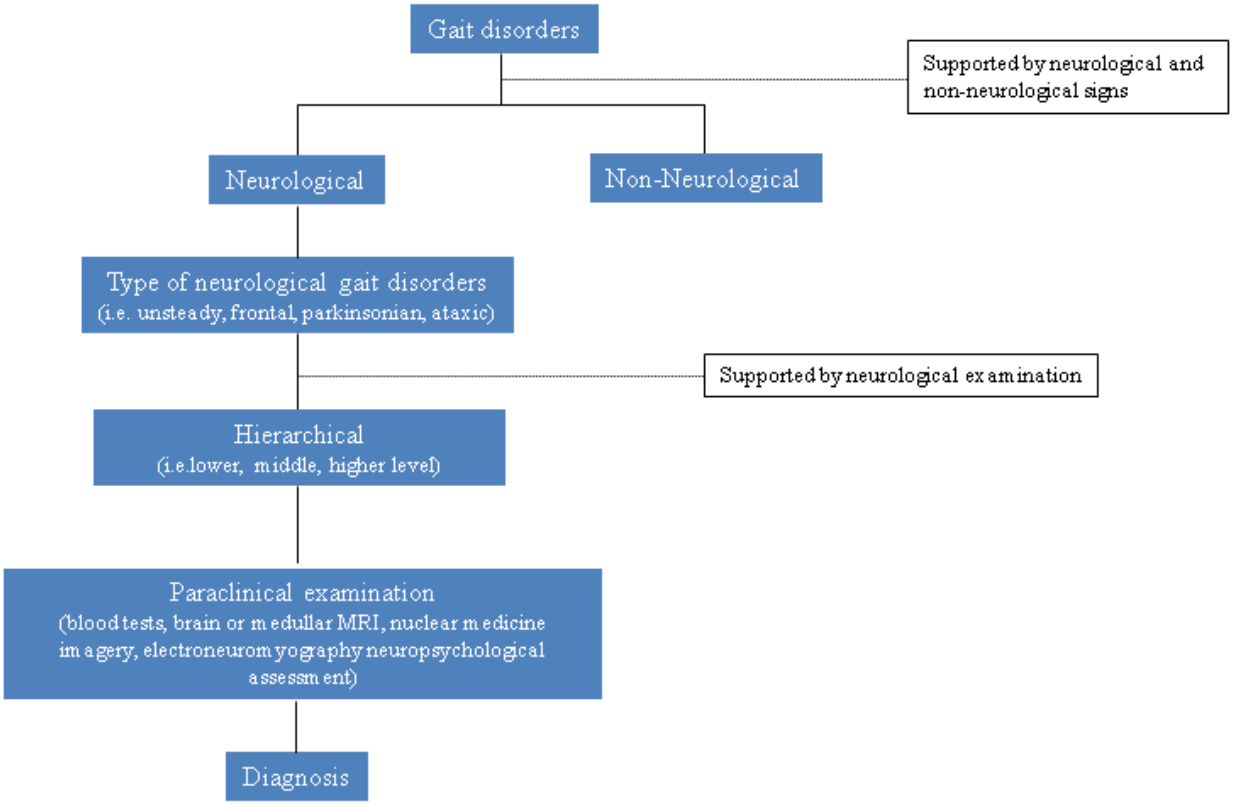

Figure 1. Clinical approach of gait disorders (personal contribution)

The different classifications and the suggested clinical approach of gait disorders (Figure 1) highlight the complexity of the diagnosis of gait disorders from a neurological origin. Furthermore, as suggested in Figure 1, the clinical approach of gait disorders relies on the medical interview; the general and neurological examinations; and the paraclinical examinations. The integration of this multimodal approach contributes to the diagnosis of the underlying neurological condition that often combines different etiologies in older adults (54). This integrative approach of the diagnosis of gait disorders highlights the interaction of gait control with various individual subsystems, such as cognitive functions.

1.3 Interaction between gait and cognition

Although early research suggested the involvement of higher levels of gait control (55, 56), gait has been traditionally considered as an automatic function independent from cognition, relying on spinal networks

called “central pattern generators” (57). However, with new advances of functional neuroimagery techniques, as well as the easy access to user-friendly and low expensive gait analysis systems, intense clinical and engineering collaborative researches have recently demonstrated the cerebral (cortical and subcortical regions) correlates of gait control and its relationship with cognitive functions (3, 58).

Initially based on clinical observations linking gait disorders to cognitive disturbances, adapted cognitive paradigms, such as the study of gait during dual tasking, have been developed to better understand the close interaction between gait and cognition (59-61). The dual task paradigm relies on the realization of a simultaneous interfering task (i.e. motor or cognitive) during gait. An intact ability to appropriately allocate attention to both tasks (gait and the interfering task) is required to correctly perform this paradigm. Thus, the study of the gait (i.e quantitative gait parameters) and the interfering task performances allow easy access to the interaction between gait and cognition (59, 60). It has been demonstrated that healthy older adults present a decreased gait speed during dual tasking in comparison to young adults, suggesting an increased age-related attentional demand to walking (62). Similarly in older adults with cognitive dysfunction, especially with disturbed frontal lobe functions, the use of dual tasking showed decreased gait performances in comparison to healthy older adults (18, 23, 60, 63-65). Interestingly, such an approach revealed an unknown symptomatic walking deficit in neurodegenerative conditions that were traditionally known to affect cognitive and behavioral functions, as demonstrated in the behavioral variant of the frontotemporal dementia (23). The use of dual tasking also revealed infraclinical gait disorders in patients with neurological conditions that don’t show any gait disturbances when walking is assessed without any interference (66, 67). This dual-task interference has been related not only with dementia or specific cognitive deficits, but also with falls, disability or accelerated disease progression (21, 68-73).

Another aspect of this interaction between gait and cognition revealed by the dual task paradigm concerns task prioritization. The competition between gait and the interfering task is not always prioritized the same way in healthy adults and in patients with neurological conditions (74). Healthy adults safely prioritize the

gait stability instead of the interfering task performances (75). This "unconscious" behavior adopted by healthy adults, defined as the posture-first strategy, prevents the occurrence of falls while walking. Inversely, patients with Parkinson's disease adopt a posture-second strategy in which they prioritize the interfering cognitive tasks with the consequence of an unsafe gait leading to falls (76). This posture-second strategy frequently adopted by patients with neurological conditions may be part the reason why patients with very mild gait disorders, such as patients with early Alzheimer's disease, present an abnormal increased rate of falls in comparison to healthy older adults. This "bad judgment" of the posture-second strategy may be explained by cognitive deficits, especially disturbed executive functions (77). However, this model of the posture second strategy used by patients with Parkinson's disease has been reconsidered in patients with intact cognition (77).

Besides the use of dual task paradigms, epidemiological studies conducted in aging have contributed to a better understanding of this complex relationship between gait and cognition. Gait abnormalities in healthy older adults have been related cross-sectionally with cognitive performances (26, 27, 37, 58, 60, 68) and behavioral disturbances, such as fear of falling (78-80). Furthermore, it has been shown that quantitative (37) or clinical gait abnormalities (5) precede the onset of mild cognitive impairment (24, 25, 58) and dementia (23, 25, 58, 59, 81, 82). Finally, this interaction between gait and cognition has been largely studied by the use of cerebral imaging as presented in the following chapters.

1.4 Cerebral correlates of gait control

The neural correlates of gait control have been extensively studied during the last few years using different neuroimaging techniques, such as electroencephalography, magnetic resonance imaging (MRI), nuclear imaging or functional near infrared spectroscopy (fNIRS) (83-86). These various techniques give us access to the brain structure and functional substrates involved in gait control. Each neuroimaging technique presents its own advantages and limitations that we will review in detail here, in addition to the cerebral regions involved in the control of gait. We will then focus on four articles (Chapter 3), their detailed methodological approaches and their associated results.

1.4.1 Morphological study

The recent advance of neuroimaging allows a quantification of white matter (WM) and grey matter (GM) volumes. Cross-sectional and longitudinal studies have correlated gait performances with WM or GM volumes (87-89). WM volumes reduction and abnormalities have been associated with poor gait (90, 91). Age-related white matter abnormalities that reflect lesions in the WM due to aging (92, 93) have been associated with poor gait performances that are similar to gait disturbances found in Parkinson's disease. One of the major differences is that older adults with WM disease walk with increased stride width (94). Small well-defined subcortical infarcts, called lacunes, and diffuse areas of white matter disease, called leukoaraiosis contribute to the cerebral microangiopathy. Several studies showing this association between poor gait and age-related white matter abnormalities used different mobility outcomes, such as quantitative gait parameters or different mobility scales (89, 95, 96). These converging results suggest that these WM abnormalities disrupt the fronto-subcortical networks linking the dorsolateral prefrontal, orbitofrontal, anterior cingulate, motor and supplementary areas with the basal ganglia. These neuronal networks are also involved with executive function, this explains the co-occurrence of gait disorders and cognitive deficits in older adults (97).

An extended pattern of GM volume reduction has been associated with poor gait control (29, 98-101). Besides the important role of the frontal cortex, hippocampus and parietal regions have been also associated with gait control (29, 98, 102-104). The role of the hippocampus is also key in topographical orientation and spatial navigation (9, 105-110), both functions that contribute to gait efficiency. Regarding the parietal cortex, it regulates the body coordination in relation to the environment (111), this represents a cognitive function essential to body movement. This complex relationship between volume reduction involving different brain regions and gait control highlights that the control of gait relies on different cognitive and motor domains.

1.4.2 Functional study

a. Functional magnetic resonance imaging (fMRI)

The success of functional MRI – a non-invasive technique detecting the blood oxygen level-dependent (BOLD) changes that follow a change in brain activation (112) - offers the opportunity to study the neural substrate of locomotion. The main limitation of this neuroimaging technique needs that the subject remains immobile in a supine position during the scanning protocol, this prevents the study of actual gait. Mental imagery of locomotion protocols have been developed to study the cerebral regions activated by gait tasks – reflecting the brain areas activated by the actual execution of gait (113). These mental imagery protocols include comparison of brain activation between gait and standing position (114-116); between older and younger adults (28, 117); or between healthy controls and pathological populations (118-120). An extended network involving the prefrontal cortex, the hippocampus and subcortical regions, such as the cerebellum and the pedunculopontine nucleus, showed increased activation during gait tasks. An emerging approach studying the spontaneous BOLD fluctuation during rest, called resting-state fMRI, examines the brain regions functionally connected independently to any activation tasks (121). Individual cortical networks in relationship to specific cognitive functions or neurological conditions, such as Alzheimer's disease or Parkinson's disease, have been identified (122-125). This approach has been also used to identify the functional networks associated with gait in non-demented older adults: sensorimotor, visual, vestibular and fronto-parietal areas have been associated with gait speed (126). The identification of disrupted resting-state networks involving the executive and the visual areas have been associated with the development of freezing of gait in patients with Parkinson's disease (101).

b. Functional near-infrared spectroscopy (fNIRS)

Functional near-infrared spectroscopy (fNIRS), a non-invasive neuroimaging techniques, measures the cortical blood oxygen changes using the interaction between the light (within the near infrared spectrum) and the brain tissue. This method, less sensitive to motion artifacts, offers the possibility to study the brain oxygenation, reflecting the brain metabolism, during the online locomotion, but with a limited coverage of the scalp (85). Most studies assessing mobility focused on the prefrontal cortex (127-131). Increased brain oxygenation in the prefrontal cortex has been shown during gait in healthy younger (131, 132) and older (129, 130, 133) adults and in stroke patients (134). Furthermore, whilst performing challenging cognitive tasks while walking (i.e. dual-task), healthy younger and also older adults required more brain oxygenation than during usual walking (129, 130, 135). This greater prefrontal activation during dual-tasking has been related to the maintenance of the cognitive performance, but not to the gait velocity (130) that is consistent with the model of neural compensation (136). A similar involvement of the prefrontal cortex has been also demonstrated in patients with Parkinson's disease during freezing episodes (137).

1.4.3 Metabolic study

The use of radioactive tracers, such as fludeoxyglucose-18 - a glucose analog crossing the blood-brain barrier – reflects the cerebral metabolism during the minutes following its injection that allows an access to the brain regions activated during this time. In addition to correlation studies, this neuroimaging method gives the opportunity of an "online" measure of the brain activity during the motor task (i.e. gait). Studies correlating the resting-state glucose metabolism with gait performances showed the involvement of prefrontal, posterior cingulate and parietal cortices in gait control (138). The same neuroimaging method was used to understand the neural pattern of neurodegenerative conditions affecting gait, such as the pure akinesia with gait freezing that shows similar pathophysiological mechanisms as the progressive supranuclear palsy (139).

The "online" measurement of brain activity during gait using glucose metabolism showed that healthy older adults activates in addition to the sensorimotor area, the prefrontal cortex as well as the hippocampus

(140). A similar approach has been used to study the neural substrates of gait disturbances in parkinsonian syndrome, such as Parkinson's disease or progressive supranuclear palsy (141, 142). In patients with progressive supranuclear palsy, a decreased activation during locomotion was observed in the prefrontal cortex, the subthalamic nucleus and the pedonculopontine nucleus, whereas an increased activation was reported in the primary motor cortex, suggesting a compensatory mechanism (142). Similarly, by comparing patients with Parkinson's disease with and without freezing of gait, patients with freezing episodes presented an impaired metabolic activity during gait in the prefrontal cortex, but an increased activation in the parietal pole that was interpreted as a need for external cues (141).

Another advantage of metabolic imaging concerns the access of ligands that label specific neurotransmitter pathways, such as the cholinergic or the dopaminergic systems by using positron emission tomography (PET) or single photo emission computerized tomography (SPECT). The cholinergic denervation plays a key role in the decreased gait speed observed in patients with Parkinson's disease (143), even early in the course of the disease (144), and contributes to the pathophysiology of freezing of gait in patients with Parkinson's disease (145). If previous studies (146, 147) suggest a correlation between ligands labeling the dopaminergic system and gait in patients with Parkinson's disease, we explored the association between quantitative gait parameters and DAT-Scan binding in patients with parkinsonian syndrome in a specific study (148).

1.4.4 Electrophysiological study

Despite the limitation of artifact movements, the feasibility of recording electroencephalographic signals during walking under certain definite circumstances has been demonstrated by different research groups (149-152). The high temporal resolution of EEG and the entire brain coverage represent the main advantage of this technique to measure the cortical activity during locomotion. The study of power spectral changes during gait cycle demonstrated the role of the anterior cingulate, the sensorimotor and the posterior parietal cortices (152). High-density EEG has been also used to study the connectivity during locomotion and showed reduced functional connectivity during walking in the sensorimotor cortex in

comparison to standing (153). The use of event-related potential (ERP) during walking while performing a cognitive task revealed differences in amplitude, latency and topography of the ERP associated with inhibitory controls between walking and sitting (149). Although the use of EEG for measuring the neural substrate of gait is increasing, recent findings suggest that more sophisticated methods for identifying and removing EEG artifact are still needed (154).

Chapter 2. Behavioral Studies

2.1 Frontotemporal dementia: Pathology of gait?

This paper has been published in Movement Disorders 2010;25(6):731-737 by Gilles Allali, Bruno Dubois, Frédéric Assal, Elise Lallart, Leonardo C. de Souza, Maxime Bertoux, Cédric Annweiler, François R. Herrmann, Richard Lévy, and Olivier Beauchet.

The behavioral variant of the frontotemporal degeneration (bvFTD) associates classically a behavioral presentation with impaired executive function. The presence of gait disorders is not included in the diagnosis criteria of this neurodegenerative dementia (155). Following the strong relationship between executive function and gait control in older adults, we hypothesized in this study that patients with bvFTD will present more disturbed quantitative gait parameters in comparison to healthy older adults, but also to patients with another neurodegenerative dementia, such as Alzheimer's disease, that classically shows a less impaired executive functioning than bvFTD. Using a footswitch system for quantifying gait parameters, this study showed that patients with bvFTD presented more gait instability than healthy older adults, but also than patients with Alzheimer's disease. These findings suggest that the diagnosis of bvFTD should be considered in demented older adults with gait instability.

Movement Disorders
Vol. 25, No. 6, 2010, pp. 731–737

Frontotemporal Dementia: Pathology of Gait?

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Abstract: The main diagnostic criteria of the behavioural variant of frontotemporal degeneration (bvFTD) include neurobehavioral and dysexecutive syndromes, but not specific gait characteristics although strong relationship between gait and prefrontal functions are increasingly recognized. Accordingly, we tested the hypothesis that patients with bvFTD would have more gait changes than older healthy controls and demented patients with Alzheimer's disease (AD). Sixty subjects were included in the study: 19 with bvFTD, 19 with AD and 22 healthy controls. Mean values and coefficients of variation (CV) of stride time while just walking (i.e., single tasking) and while walking with backward counting (i.e., dual tasking) were measured using the SMTEC®-footswitch system. Stride time, mean value, and CV were significantly increased in both patient groups compared with healthy controls during single task or walking alone ($P < 0.001$) and during dual tasking ($P < 0.001$). After adjusting for age, Mini-mental examination, psychoactive drugs, gender, and history of previous fall, only the patients with bvFTD group was associated with an increase of CV of stride time during single walking ($P < 0.001$) and dual tasking ($P < 0.001$). These data suggest that gait instability during single and dual tasking could represent a supportive argument for bvFTD. In clinical practice, such a diagnosis should be at least considered in any demented patient with gait instability. © 2010 Movement Disorder Society

Key words: frontotemporal dementia; gait disorders; Alzheimer's disease; executive function; motor control

INTRODUCTION

Gait was considered as an automated motor activity independent of cognition, but recent studies underscored that gait and higher-level cognitive function seem to be closely related in healthy older adults and demented subjects.[1–4] Gait changes are frequently observed in the latter[2] and predict further development of dementia in nondemented subjects, either of any type[3] or specifically of non-Alzheimer's disease type.[4]

Dual-task paradigms, measuring the ability to accurately allocate attention between two tasks performed simultaneously (two cognitive tasks or gait and cognitive one) are increasingly recognized as a marker of executive dysfunction.[1,5] Stride time variability was significantly associated with executive function in nondemented older adults.[6] Patients with Alzheimer's disease (AD) or mixed dementia presenting with impaired executive functions exhibited an increase in stride-to-stride variability during single and dual tasking.[7,8] From a methodological perspective, we also showed in a group of demented patients with executive dysfunctions that the best dual-task parameter was the coefficient of variation (CV) of stride time.[5] Previous data

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Potential conflict of interest: None reported.

Received 24 July 2009; Revised 20 October 2009; Accepted 5 November 2009

Published online 19 February 2010 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22927

strongly suggest that altered executive functions play a crucial role in gait disorders and specifically in dual-task related gait changes. We thus decided to shift the focus of interest from AD, where the dysexecutive syndrome is associated with other cognitive dysfunctions that may also contribute to gait changes, to patients presenting with long-lasting isolated prefrontal syndrome such as patients with a behavioral variant of frontotemporal degeneration (bvFTD).

Patients with bvFTD, a subgroup of frontotemporal lobar degeneration, present a neurobehavioural syndrome usually associated with a dysexecutive syndrome. Clinical diagnosis criteria for bvFTD include an insidious onset, a gradual progression, early decline in social interpersonal conduct, early impairments in regulation of personal conduct, an emotional blunting and loss of insight.[9] Apart from primitive reflexes that are minor criteria, other motor impairments, and particularly gait disorders, are not required for establishing the diagnosis, despite that it seems to exist some overlap between bvFTD and other pathologies involving motor system (such as amyotrophic lateral sclerosis). In a comparative study, a subgroup of patients in an early stage of bvFTD showed more involuntary trunk movements than AD.[10] Although substantial data suggest that executive functions are involved in gait control in older adults, there is no data regarding gait analysis in bvFTD or comparing gait parameters of bvFTD and AD.

The goal of this study was to compare gait variability between bvFTD, AD, and healthy controls and to describe the specificity of gait disorders in bvFTD using normal gait and gait during dual-tasking. On the basis of the strong relationship between executive functions and gait variability, we hypothesized that bvFTD patients could have higher gait variability than patients with AD and healthy controls.

METHODS

Subjects

The subjects' population involved 19 bvFTD, 19 AD, and 22 controls. They were evaluated at Pitié-Salpêtrière Hospital in Paris and at Angers University Hospital (France). They underwent a full neurological examination, a clinical interview including the use of psychoactive drugs (benzodiazepines, antidepressants and neuroleptics) and the number of drugs taken per day, behavioral evaluations, neuropsychological testing, brain MRI or CT-Scan imagery and 99mTc-ECD brain SPECT perfusion (for bvFTD and patients with AD).

The diagnosis of bvFTD was based on the revised Lund and Manchester criteria.[9,11] Additional criteria for the diagnosis were a hypoperfusion strictly restricted to the frontal lobes on the SPECT and absence of significant limb apraxia, visuospatial deficit or cued recall impairment (after successful encoding) in episodic memory tasks in the neuropsychological evaluation. Patients with both bvFTD and motor neuron disease or with familial history of both pathologies were also excluded to avoid a motor deficit that would potentially interfere with gait. AD subjects met NINCDS-ADRDA criteria for probable Alzheimer's disease.[12] Control subjects had no neurological complaints, normal neurological and neuropsychological examinations. In all groups, exclusion criteria included extrapyramidal rigidity of the upper limbs with a score above 2, based on item 22 of the UPDRS-motor score; acute medical illness in the past months; neurological and psychiatric diseases except dementia; severe orthopaedic or rheumatologic condition affecting normal walking, as well as use of walking aids. All subjects gave informed consent according to the ethical standards set forth in the declaration of Helsinki (1983). For severely demented individuals who could not give informed consent, consent was provided by the closest family member or caregiver. The local ethics committee approved the project.

Neuropsychological Evaluation

The patients were evaluated with a standardized neuropsychological battery including the Mini Mental State Examination of Folstein (MMSE),[13] the MATTIS Dementia Rating Scale,[14] the Frontal Assessment Battery (FAB),[15] and the Free and Cued Recall Test.[16]

Gait Recordings

Gait analysis included the following tasks that were randomized to minimize practice effect: walking only; backward counting down by one from 50 to 1 while walking, and backward counting while sitting. Before testing, a trained evaluator gave standardized verbal instructions on the test procedure along with a visual demonstration of the walking test. For dual-tasking, the subjects were asked to walk and to count backwards at the best of their capacity. To get the participants used to gait testing, they undertook one walking trial. The figures enumerated while walking were the only one taken into account. The cognitive performance was counted as the sum of correct answers. The time needed to achieve the 10 meters walking distance and the number of enumerated figures during this time were recorded using SMTEC® system (SMTEC®, Sport & Medical Technologies SA, Nyon Switzerland), which

TABLE 1. *Clinical characteristics of the control group, the Alzheimer's disease group (AD) and the behavioral variant of frontotemporal degeneration group (bvFTD)*

	Control (n = 22)	AD (n = 19)	bvFTD (n = 19)	*P*-value
Clinical measures				
Sex (female), n (%)	14.0 (63.6)	13.0 (68.4)	9.0 (47.4)	0.454
Age (mean ± SD)*	71.0 ± 0.5	79.3 ± 8.4	66.8 ± 9.7	<0.001
Age at onset (mean ± SD)*		76.3 ± 8.9	62.1 ± 9.6	<0.001
Level of education (>16 years), n (%)*	3.0 (13.6)	1.0 (5.3)	11.0 (57.9)	0.001
Number of comorbidities ≥ 3, n (%)	8.0 (36.4)	1.0 (5.3)	5.0 (27.8)	0.099
Previous fall, n (%)	5.0 (22.7)	13.0 (68.4)	5.0 (26.3)	0.006
UPDRS score (1/4), n (%)	3.0 (13.6)	7.0 (36.8)	5.0 (26.3)	0.253
MMSE				
Value (median ± IQR)	29 ± 1	19 ± 7	26 ± 6	<0.001
Score ≤ 24 (%)	0 (0)	15.0 (78.9)	8.0 (42.1)	<0.001
Treatments				
≥4 drugs per day, n (%)	3.0 (13.6)	5.0 (26.3)	2.0 (10.5)	0.003
Psychoactive drugs, n (%)	4.0 (18.2)	12.0 (63.2)	10.0 (52.6)	0.009
Neuroleptics, n (%)	0 (0)	1.0 (5.3)	5.0 (26.3)	0.006
Antidepressants, n (%)	0 (0)	3.0 (15.8)	9.0 (47.4)	<0.001
Benzodiazepins, n (%)	4.0 (18.2)	12.0 (63.2)	4.0 (21.1)	0.006
Anticholinesterase inhibitors, n (%)	0 (0)	2.0 (10.5)	3.0 (15.8)	0.147
Cognitive performance				
Number of figures WBC (mean ± SD)	19.1 ± 3.9	19.2 ± 6.4	17.5 ± 5.5	0.552
Number of figures BC (mean ± SD)	21.6 ± 4.1	18.3 ± 6.3	21.4 ± 8.5	0.168

P-Value: Comparison among three groups based on Fisher's exact test or Kruskal-Wallis ANOVA as appropriate; SD: Standard deviation; UPDRS: based on item 22 of the Unified Parkinson's Disease Scale motor score; MMSE: Mini Mental State Examination; WBC: walking while backward counting; BC: backward counting.

*$P < 0.01$ between AD and bvFTD.

consists of two footswitches providing a continuous measurement of temporal step parameters.[17] This system is a pair of innersoles fitted inside the subject's shoes. Each innersole contains two independent footswitches placed at the heel and the toe, which are linked to a portable data logger worn at the waist. The time was calculated using the first contact which is defined by the activation of the heel sensors and the last contact which corresponds to the time when the toe sensor goes off of walkway. Afterwards, we asked the patients to sit and enumerate as many numbers as possible within the same period of time. Each subject completed one trial for each walking condition. The subjects wore their own footwear. Mean values and coefficients of variation (CV)(CV = (standard deviation / mean) × 100) of step time, stride time, swing time, and stance time for all walking conditions were determined during steady-state walking using the SMTEC® system.[17] For the comparison between bvFTD, AD and healthy controls, we focused on backward counting as dual-tasking.

Statistics

Subjects' characteristics were described using means and standard deviations or frequencies and percentages, as appropriate. The normality of the parameters' distribution was checked with skewness and kurtosis tests before and after applying usual transformations to normalize non-Gaussian variables. First, comparisons between groups were performed using the independent samples *t*-test, the Kruskal-Wallis test, one-way analysis of variance (ANOVA) or Chi-square test, as appropriate. Second, univariate (model 1), bivariate model adjusted on gait speed (model 2) and multivariate (model 3) linear regressions were used to examine the association between CV of stride time (independent variable) and type of dementia (AD versus bvFTD; dependent variable) while taking the subjects' baseline characteristics into account. *P*-values less than 0.05 were considered statistically significant. All statistics were performed using the Stata Statistical Software, version 10.1.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics are summarized in Table 1. Specifically, the bvFTD patient group was significantly younger than the AD patient group ($P < 0.001$) but not than the control group ($P = 0.382$). The bvFTD and the AD patient groups

TABLE 2. *Mean value and standard deviation of stride time parameters under single and dual-task conditions*

Stride time (mean ± SD)	Control (n = 22)	AD (n = 19)	bvFTD (n = 19)	*P*-value
Single task (walking alone)				
Mean Value	1.036 ± 0.100	1.184 ± 0.132*	1.128 ± 0.107**	<0.001
CV	0.017 ± 0.005	0.031 ± 0.012*	0.077 ± 0.082**	<0.001
Dual task (walking and backward counting)				
Mean Value	1.143 ± 0.175	1.355 ± 0.209*	1.314 ± 0.201**	<0.001
CV	0.027 ± 0.009	0.06 ± 0.031*	0.083 ± 0.062**	<0.001

AD, Alzheimer's disease group; bvFTD, behavioural variant of frontotemporal degeneration group; *P*-Value, Comparison among three groups based on Kruskal-Wallis ANOVA as appropriate; CV, coefficient of variation.

*$P < 0.01$ between control and AD.

**$P < 0.01$ between control and bvFTD.

differed in terms of level of education ($P < 0.001$), age ($P < 0.001$) and age at onset of disease ($P < 0.001$), but not for MMSE. The three groups were significantly different regarding the number of previous falls ($P = 0.006$; AD > bvFTD and healthy controls), the number of drugs taken per day ($P = 0.003$), and specifically for psychoactive drugs including neuroleptics ($P = 0.006$; bvFTD > AD and controls), antidepressants ($P < 0.001$; bvFTD > AD and healthy controls), benzodiazepines ($P = 0.006$; AD > healthy controls and bvFTD).

Gait Data

For usual walking, the mean value of stride time was significantly different between the three groups ($P < 0.001$), but there was no difference between the bvFTD and the patients with AD groups ($P = 0.13$). The CV of stride time significantly differed between groups ($P < 0.001$), with a highest variability for the bvFTD patient group (7.7 %) but without significant difference between both demented groups ($P = 0.12$) (Table 2). The mean value of gait speed significantly differed between the three groups ($P = 0.009$), with a slowest gait speed for the AD group (110.6 ± 9.9 cm/s) and a fastest one for the control group (118.5 ± 11.7 cm/s).

While dual-tasking, the mean value of stride time was significant between groups ($P < 0.001$), but not between both demented patients groups ($P = 0.272$). For the CV of stride time, there was a highest value in the patients with bvFTD group (8.3 %) with a significant difference between the three groups ($P < 0.001$) (Table 3). For the mean gait speed, we also observed a significant difference between the three groups ($P = 0.002$), with a slowest speed for the patients with bvFTD group (88.9 ± 10.0 cm/s) and a fastest one for the control group (102.3 ± 12.4 cm/s) (Table 3).

Simple regression showed that patients presenting with AD ($P < 0.001$), bvFTD ($P < 0.001$), taking psychoactive drugs ($P = 0.006$) and poor score at MMSE ($P = 0.026$) were associated with an increase of the CV of stride time during single task (Table 4). In the bivariate regression model adjusted on gait speed, we found the same significant associations. After adjusting for all variables, only bvFTD remains associated with the increase of CV of stride time ($P < 0.001$). Under

TABLE 3. *Mean value of gait speed under single and dual-task conditions*

Gait speed (mean ± SD)	Control (n = 22)	AD (n = 19)	bvFTD (n = 19)	*P*-value
Single task (walking alone)				
Mean gait speed (cm/s)	118.5 ± 11.7	110.6 ± 9.9*	111.8 ± 9.0**	0.009
Dual task (walking and backward counting)				
Mean gait speed (cm/s)	102.3 ± 12.4	89.4 ± 22.5	88.9 ± 10.0**	0.002

AD, Alzheimer's disease group; bvFTD, behavioural variant of frontotemporal degeneration group; *P*-value, Comparison among three groups based on Kruskal-Wallis ANOVA as appropriate; CV, coefficient of variation.

*$P < 0.01$ between control and AD.

**$P < 0.01$ between control and bvFTD.

TABLE 4. *Univariate (model 1), bivariate adjusted on gait speed (model 2) and multivariate linear regressions (model 3) showing the cross-sectional association between CV of stride time during single task (independent variable) and type of dementia (dependant variable) adjusted for subjects' baseline characteristics*

	Model 1 (nonadjusted)			Model 2 (bivariate model adjusted on gait speed)			Model 3 (adjusted on all subjects' baseline characteristics)		
	Coef β	95% CI	*P*	Coef β	95% CI	*P*	Coef β	95% CI	*P*
Control	1.00	–			–		1.00	–	
bvFTD	−3.05	[−4.07;−2.03]	<0.001	−3.21	[−4.26;−2.15]	<0.001	−3.18	[−4.47;−1.90]	<0.001
AD	−2.01	[−3.03;−0.1]	<0.001	−2.19	[−3.26;−1.12]	<0.001	−1.31	[−3.19;0.56]	0.165
Psychoactive drugs	−1.45	[−2.46;−0.43]	0.006	−1.48	[−2.50;−0.46]	0.005	−0.42	[−1.43;0.58]	0.401
MMSE	0.10	[0.01;0.2]	0.026	0.10	[0.01;0.20]	0.031	0.02	[−0.10;0.14]	0.722
Age	−0.01	[−0.07;0.05]	0.721	−0.01	[−0.07;0.05]	0.773	−0.04	[−0.11;0.03]	0.248
Sex	0.08	[−1.02;1.18]	0.885	0.02	[−1.11;1.14]	0.976	0.38	[−0.62;1.37]	0.451
Previous fall	−0.88	[−1.96;0.2]	0.108	−0.85	[−1.95;0.24]	0.125	−0.33	[−1.42;0.75]	0.543
Gait speed	0.01	[−0.03;0.06]	0.575		–		−0.03	[−0.07;0.02]	0.269

Coef β, coefficient β; CI, Confidence interval; $P < 0.05$ was considered statistically significant; bvFTD, behavioral variant of frontotemporal degeneration group; AD, Alzheimer's disease group; MMSE, Mini Mental State Examination.

dual-task, simple regression showed that patients presenting with AD ($P < 0.001$), bvFTD ($P < 0.001$), poor score at the MMSE ($P = 0.003$), gait speed ($P = 0.030$) and taking psychoactive drugs ($P = 0.002$) were associated with an increase in the CV of stride time during dual task (Table 5). In the bivariate regression model adjusted on gait speed, bvFTD ($P < 0.001$), AD ($P = 0.001$) and taking psychoactive drugs ($P = 0.018$) were associated with an increase of CV during dual task. After adjusting for all variables, only bvFTD remains associated with the CV of stride time during dual task ($P < 0.001$).

Performance of Cognitive Task

The AD, the bvFTD, and the healthy control subjects enumerated, respectively, 19.2 ± 6.4, 17.5 ± 5.5, and 19.1 ± 3.9 figures while walking. There was no significant difference between groups ($P = 0.552$). While sitting, they enumerated respectively 18.3 ± 6.3, 21.4 ± 8.5, and 21.6 ± 4.1 without significant difference between groups ($P = 0.168$) (Table 1).

DISCUSSION

We tested the hypothesis that patients with bvFTD would have higher stride-to-stride variability while dual-tasking, than patients with AD and healthy older controls. Stride time, mean value and CV, were significantly increased in both patient groups comparing to healthy controls during single task or walking alone and during dual tasking. After adjusting for confounding variables including gait speed, only the patients with bvFTD group was associated with CV of stride time during single walking task and during dual-tasking. There was no significant difference between the

TABLE 5. *Univariate (model 1), bivariate adjusted on gait speed (model 2) and multivariate linear regressions (model 3) showing the cross-sectional association between CV of stride time during dual task (independent variable) and type of dementia (dependant variable) adjusted for subjects' baseline characteristics*

	Model 1 (nonadjusted)			Model 2 (bivariate model adjusted on gait speed)			Model 3 (adjusted on all subjects' baseline characteristics)		
	Coef β	95% CI	*P*	Coef β	95% CI	*P*	Coef β	95% CI	*P*
Control	1.00	–			–		1.00	–	
bvFTD	−1.87	[−2.75;−1.00]	<0.001	−2.95	[−4.05;−1.86]	<0.001	−2.92	[−4.17;−1.66]	<0.001
AD	−1.88	[−2.75;−1.00]	<0.001	−1.91	[−3.00;−0.83]	0.001	−1.03	[−2.87;0.79]	0.261
Psychoactive drugs	−1.27	[−2.07;−0.47]	0.002	−1.24	[−2.27;−0.22]	0.018	−0.59	[−1.56;0.40]	0.237
MMSE	0.11	[0.04;0.18]	0.003	0.08	[−0.01;0.18]	0.079	0.02	[−0.09;0.14]	0.693
Age	−0.02	[−0.07;0.03]	0.472	−0.01	[−0.06;0.06]	0.916	−0.04	[−0.11;0.03]	0.274
Sex	−0.14	[−1.01;0.74]	0.754	0.01	[−1.06;1.06]	0.998	0.24	[−0.74;1.22]	0.619
Previous fall	−0.56	[−1.44;0.31]	0.200	−0.61	[−1.70;0.48]	0.269	−0.32	[−1.43;0.79]	0.567
Gait speed	0.03	[0.01;0.06]	0.030		–		0.01	[−0.03;0.03]	0.970

Coef β, coefficient β; CI, Confidence interval; $P < 0.05$ was considered statistically significant; bvFTD, behavioural variant of frontotemporal degeneration group; AD, Alzheimer's disease group; MMSE, Mini Mental State Examination.

three groups in terms of cognitive performance, in the single task and in the dual task. These findings show, for the first time, that bvFTD is associated with a gait disorder that can be evidenced by using specific and accurate markers of gait processing.

Gait and Frontal Lobe

Our findings suggest that the patients with bvFTD present increase gait variability even in a single walking task in comparison with healthy controls and patients with AD (Table 4). In 1960, gait apraxia was related to frontal lobe dysfunction in general[18] or more specifically to its medial prefrontal regions.[19] In this line of ideas, a few case studies reported the observation of patients with isolated medial frontal lobe lesions associated with gait apraxia.[20,21] Frontotemporal dementia was associated with bilateral atrophy of the frontal and anterior temporal lobes more than 30 years ago, and recently confirmed using voxel-based morphometry.[22] In comparison with AD, the pattern of atrophy in frontotemporal lobar degeneration is anatomically distinct including a more severe atrophy in medial prefrontal cortex.[23] Thus, the gait variability shown in bvFTD in our study could be related to a specific disturbance of the medial prefrontal cortex.

Dual Tasking and Frontal Lobe

Dual tasking challenges one's ability to allocate attentional ressources toward two tasks performed in parallel. The increased CV under dual tasking confirmed that gait is influenced by the concurrent performance of a cognitive task and, therefore should not be considered as an automatic function. In our study, both patients groups presented worse performance during walking and backward counting than the control group (Table 2). Furthermore, the stride time variability during dual tasking was only associated with the patients with bvFTD group (Table 5). Similar changes in dual-tasking were reported in various conditions associated with executive dysfunction and affecting basal ganglia, frontal regions or their reciprocal connections (frontosubcortical circuits) such as in Parkinson's disease,[24] Huntington's disease,[25] AD[7] mood disorders,[26] and attention deficit hyperactivity disorder.[27] Functional neuroimaging studies have shown that the performance of dual-tasking was associated with activation located in the anterior cingulate cortex and the prefrontal regions[28,29]—a group of brain regions that are essential for executive functions. Since dysexecutive deficits are encountered in AD and bvFTD, and predominantly in the latter,[30] it is not surprising that both patients groups were impaired in dual-tasking, particularly the patients with bvFTD group in our study.

Stride Time Variability and Executive Functions

Among many gait parameters, the one that is the most closely associated with executive functions is stride time variability[5–7] considered as the neural control implied in the maintenance of a steady walking rhythm. This parameter was significantly associated in single and dual tasks after adjusting for all variables only with bvFTD (Tables 4 and 5). This association can be related to the dysexecutive syndrome present in patients with bvFTD, such as difficulty planning and executing motor sequences. Similar results were described in elderly fallers,[31] suggesting that gait stability requires a low variability. Freezing of gait, that presents an extraordinary way of gait variability, was associated with executive dysfunction in patients with high level of gait disorders[32] and with Parkinson's disease.[33]

Study Limitations

A main limitation of our study was that our demented patients did not have autopsy-confirmed diagnoses. Our small sample size also necessitates caution. In addition, the bvFTD patient group presented a higher level of education than the patients with AD group (Tables 1). However, to the best of our knowledge, there are no published data showing a relationship between gait and level of education. Finally, the SMTEC® system provides only the measurement of temporal step parameters contrary to electronic walkway, but this drawback is compensated by its possible use in ambulatory settings; it could be interesting to evaluate in a future study the differences of the spatial features of gait between bvFTD, AD and healthy older subjects.

CONCLUSION

Patients with bvFTD had an increase variability of stride time in comparison with AD patients and healthy controls. Stride time variability during single and dual-tasking could represent a supportive argument for the diagnosis of bvFTD and we would advocate gait assessment in the work-up of dementia. Although the gait variables described in this study require the use of footswitches or others instruments, simple gait assessment during single and dual-tasking can be easily appreciated at bedside. As gait disorders can be evidenced in bvFTD, in demented patients with gait instability, the diagnosis of bvFTD should be considered.

Acknowledgments: Gilles Allali was supported by a grant from the Swiss National Science Foundation (No 33CM30-124115).

Financial Disclosures: All authors have nothing to disclose.

Allali was involved in conception, organization, and execution of the research project; design and review and critique of the statistical analysis; writing of the first draft of the manuscript. Dubois was involved in conception and organization of the research project; review and critique of the statistical analysis; review and critique of the manuscript. Assal was involved in conception of the research project; review and critique of the statistical analysis; review and critique of the manuscript. Lallart was involved in review and critique of the manuscript. de Souza was involved in organization and execution of the research project; review and critique of the manuscript. Bertoux was involved in organization and execution of the research project; review and critique of the manuscript. Annweiler was involved in review and critique of the manuscript. Herrmann was involved in design, execution, and review and critique of the statistical analysis; review and critique of the manusript. Levy was involved in conception and execution of the research project; review and critique of the statistical analysis; review and critique of the manuscript. Beauchet was involved in conception and organization of the research project; design and review and critique of the statistical analysis; review and critique of the manusript.

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2.2 Dual-task related gait changes after CSF tapping: a new way to identify idiopathic normal pressure hydrocephalus

This paper has been published in Journal of Neuroengineering and Rehabilitation 2013:10:117 by Gilles Allali, Magali Laidet, Olivier Beauchet, François R. Herrmann, Frédéric Assal and Stéphane Armand.

Patients with idiopathic normal pressure hydrocephalus (iNPH) present a clinical triad of gait disorders, cognitive disturbances and urinary incontinence associated with enlarged brain ventricles at neuroimaging. The clinical and the radiological presentation of iNPH are unspecific and can be observed in various neurological conditions mimicking iNPH, such as Parkinson's disease or vascular dementia (iNPH mimics). Identifying patients with iNPH from its mimics represents a challenge for clinicians, because this condition can be treated by an invasive neurosurgical treatment consisting on the placement of a shunt. This study aims to improve the clinical identification of patients with iNPH from its mimics by studying the changes of gait parameters before and after CSF tapping between patients with iNPH and mimics. Gait parameters, including gait speed, stride length or stride time have been systematically assessed before and after CSF tapping – a medical procedure simulating the effect of the shunt. In order to increase the sensitivity of the gait measurement, we included a quantification of gait parameters during the realization of a cognitive task (i.e. dual tasking). The study showed the interest of combining a quantification of gait parameters while performing a cognitive task before and after CSF tapping in order to identify patients with iNPH from its mimics.

Allali et al. Journal of NeuroEngineering and Rehabilitation 2013, 10:117
http://www.jneuroengrehab.com/content/10/1/117

JNER JOURNAL OF NEUROENGINEERING AND REHABILITATION

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Dual-task related gait changes after CSF tapping: a new way to identify idiopathic normal pressure hydrocephalus

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Abstract

Background: Gait disturbances found in patients with idiopathic normal pressure hydrocephalus (iNPH) are unspecific to the diagnosis and commonly occur in neurodegenerative or vascular conditions (iNPH-like conditions). This current retrospective pre-post intervention study aims to determine whether changes in quantitative gait parameters during dual task condition differed between iNPH and iNPH-like conditions before and after cerebrospinal fluid (CSF) tapping.

Methods: 49 patients assessed before and after CSF tapping were included in this study (27 with iNPH and 22 with iNPH-like conditions). Gait analysis during single and dual task conditions (walking and backward counting) was performed before and after a CSF spinal tap of 40 ml. Gait parameters were compared between iNPH and iNPH-like conditions patients. Logistic regressions were used to examine the association between iNPH and gait parameters.

Results: Improvements of step width (−9.03 (20.75)% for iNPH group; +0.28 (21.76)% for iNPH-like conditions group), stride length (+7.82 (20.71)% for iNPH group; -0.62 (19.22)% for iNPH-like conditions group), walking speed (+12.20 (29.79)% for iNPH group; +2.38 (32.50)% for iNPH-like conditions group) and stance duration (−1.23 (4.03)% for iNPH group; +0.49 (5.12)% for iNPH-like conditions group) during dual task, after CSF spinal tapping, were significant in patients with iNPH compared to patients with iNPH-like conditions. No between group difference was observed for the single walking task evaluation. The multiple logistic regression revealed that among these four gait parameters, only the improvement in step width was associated with the diagnosis of iNPH.

Conclusion: Dual-task related changes in spatio-temporal gait parameters before and after CSF tapping might be a novel and discriminative method of identifying iNPH patients from other similar conditions.

Keywords: Gait disorders, Idiopathic normal pressure hydrocephalus, Dual tasking, Executive function, Cerebrospinal fluid

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) was first identified by Salomon Hakim in 1957. It is a communicating hydrocephalus characterized by enlarged ventricles visible on brain imagery and its clinical presentation relies on a triad of symptoms affecting gait, cognition and urinary incontinence. Gait difficulties are usually the first symptoms of the disease that appear insidiously between the sixth and eighth decade of life and include an apraxic, glue-footed, magnetic or parkinsonian gait [1]. The uncertainty surrounding diagnosis of iNPH patients is particularly problematic, because symptoms of iNPH are unspecific. Identifying patients with iNPH from other patients with higher level gait disorders, vascular dementia or even Parkinson's disease remains a real challenge for clinicians. If quantitative gait analysis has revealed a decreased stride length, decreased foot-to-foot clearance and a broad-based gait in iNPH patients compared to age-matched healthy controls [2], there is

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an urgent need to find new markers that might better differentiate among closely related gait conditions and aid therapeutic decisions, i.e. neurosurgical shunt placement.

Dual-task related gait changes refer to any modification when walking while simultaneously performing an attention-demanding task and represent an interesting paradigm to assess in parallel, gait and cognitive functions, which are both deficient in iNPH. These changes are related to the capacity to share attention between the two tasks, and strongly depend on executive functions [3]. Cognitive deficits in iNPH typically involve executive functions and are potentially improved after shunt placement [4]. Our recent study demonstrated that the dual-task paradigm was a good marker of gait improvement after cerebrospinal fluid (CSF) tapping in a clinical sample of patients with iNPH [5].

This study aims to compare spatio-temporal gait parameters before and after CSF tapping under single and dual task conditions in patients with iNPH and in patients with other gait disorders mimicking this pathology. Since it is known that spinal tapping improves gait in iNPH, and that dual-tasking better reveals gait improvement, we further hypothesize that patients with iNPH will present with increased gait changes under dual task conditions after CSF tapping in comparison with patients with iNPH-like conditions.

Methods

Participants

A total of 49 patients suspected of iNPH at the Department of Neurology at the Geneva University Hospitals were included in this study: twenty-seven patients fulfilled the iNPH consensus guideline criteria [6] and twenty-two patients presented with an alternative neurological diagnosis (age median (IQR); 77.0 (10.0) years and 74.5 (9.0) years respectively; p-value: 0.62) (Table 1): vascular dementia (five patients), Parkinson's disease (four), primary progressive freezing gait (two), Frontotemporal lobar degeneration (two), depression (two), dementia with Lewy bodies (one), Alzheimer's disease (one), alcoholic dementia (one), HIV dementia (one), progressive supranuclear palsy (one), multiple system atrophy (one) and neurosyphilis (one) (Figure 1). The patients gait was analyzed twice, before and then after CSF tapping of 40 ml [1] (time between CSF tapping and second gait evaluation: 2.10 (1.49) days). Exclusion criteria included: acute medical illness in the past three months, orthopedic or rheumatologic disorders interfering with gait, patients receiving CSF tapping in the 3 months preceding the assessment, a change in the treatment between the two gait assessments, unable to walk a minimum of 15 m without a walking aid and not able to perform the dual task evaluation (walking while backwards counting).

Table 1 Clinical characteristics of subjects (n = 49)

	iNPH (n = 27)	iNPH-like conditions (n = 22)	P-value*
Age (years)	77.0 (10.0)	74.5 (9.0)	0.62
Female, n [%]	10 [37]	6 [27]	0.55
Disease duration (months)	30.0 (36.0) ‡	24.0 (39.0) ≈	0.91
Comorbidities (n)	4.0 (4.0)	5.00 (3.0)	0.15
Treatments (n)	5.0 (3.0)	5.5 (5.0)	0.28
Psychoactives drugs (n)	1.0 (1.0)	1.0 (2.0)	0.50
iNPH grading scale¥ (n)			
Gait disturbance (/4)	2 (0.0)	2 (0.0)	0.76
Cognitive impairment (/4)	2 (1.0)	2 (0.0)	0.20
Urinary disturbance (/4)	2 (2.0)	0 (1.5) ≈	**0.04**

iNPH, idiopathic normal pressure hydrocephalus.
Values are medians (interquartile ranges).
Percentages are indicated in brackets.
‡Based on 24 subjects.
≈Based on 20 subjects.
¥Ranges from 0 to 4, with higher scores indicating worse symptoms [7].
*Comparison based on Mann–Whitney test or Fisher exact test as appropriate.
Significant differences (p-values) are highlighted in bold characters.

Gait disorders, cognitive impairment and urinary disturbance were graded using the iNPH grading scale [7]. The iNPH grading scale is used to separately evaluate the severity of each of the three disorders. The score of each domain ranges from 0 to 4 with higher scores indicating worse symptoms. Among the iNPH patients group, nine patients accepted the surgical procedure (ventriculo-peritoneal shunt).

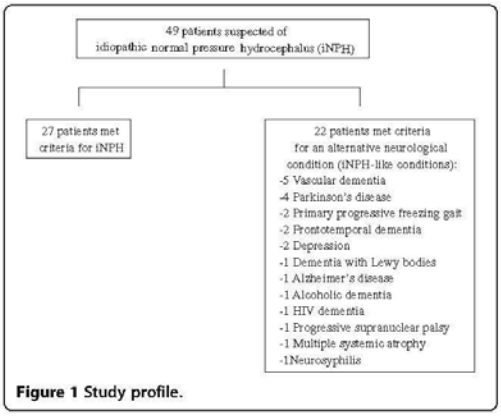

Figure 1 Study profile.

Gait recordings

Synchronized footswitches (AURION ZeroWire, Milan, Italy, sampling rate of 1000 Hz) and a seven-camera opto-electronic system (VICON Mx3+, Vicon Motion Systems, Oxford, UK, sampling rate of 100 Hz) were used. The 3D position of two reflective markers placed on the foot (on both heels and both 2nd metatarsals) and the temporal data of the footswitches were combined to compute gait parameters including walking speed, stride length, stride time, stance duration (measured as the percentage of the gait cycle), step width and step height (maximum distance between the heel marker and the floor during the swing phase on the vertical axis minus the mean position of the heel marker during mid-stance). These gait parameters were assessed whilst walking at a self selected walking speed on a 10-m walkway in single-task and dual-task (backward counting aloud by subtracting serial 1 from 50) conditions in a random order. The number of figures enumerated while walking was taken into account. To compare the inter-subject differences, the number of enumerated figures during the walking time was calculated in minutes. Before testing, a trained evaluator gave standardized verbal instructions on the test procedure. For the dual task condition, patients were asked to walk and to count backwards to the best of their ability without any task prioritization. The difference of gait parameters and cognitive performances between before and after CSF tapping was calculated according to the following formula: [(Performance after CSF tapping – performance before CSF tapping)/(performance before CSF tapping)] × 100.

Statistics

The distribution of gait parameters was not gaussian even after a trial of normalization. The normality of the parameters' distribution was checked with Shapira-Francia tests. Therefore, non-parametric tests were performed and medians, along with interquartile ranges (IQR) were reported. First, between-groups comparisons were performed using Mann–Whitney test, or Fisher exact test, as appropriate. Secondly, univariate (model 1), and multiple logistic regressions (model 2) were used to examine the association between iNPH (independent variable) and gait parameters during dual task conditions. *P*-values less than 0.05 were considered statistically significant. The pseudo R square is to logistic regression what the R square is to linear regression that is the coefficient of determination, which corresponds to the amount of variance explained by the model. All statistics were performed using the Stata Statistical Software, version 12.0.

Standard protocol approvals, registrations, and patient consents

This retrospective study protocol was approved by the ethical committee at Geneva University Hospitals. All subjects gave informed consent according to the ethical standards set forth in the declaration of Helsinki (1983).

Results

Demographic and clinical characteristics are summarized in Table 1. Both groups presented the same clinical characteristics, except in terms of incontinence, which was more severe in the iNPH group (iNPH grading scale [7] incontinence (/4): 2.0 (2.0) and 0.0 (1.5)) (Table 1). Before CSF tapping, no statistical difference between the two groups was observed for any of the measured gait parameters during single and dual task conditions. For the cognitive performance of the dual task, no statistical difference was found between the two groups.

No statistical difference between the two groups was observed for the delta of the gait parameters under single task condition (Table 2). Under dual-task conditions, the delta of the walking speed, stride length, step width and stance duration was significantly improved in the iNPH group, meaning that (i) iNPH patients increased their walking speed between the pre and post- CSF tapping more than the iNPH-like conditions group (+12.20 (29.79) and +2.38 (32.50)% respectively) (Table 2); (ii) iNPH patients increased their stride length between the two evaluations more than the iNPH-like conditions group (+7.82 (20.71) and −0.62 (19.22)% respectively) (Table 2); (iii) iNPH patients decreased their step width between the two evaluations more than the iNPH-like conditions group (−9.03 (20.75) and +0.28 (21.76)% respectively) (Table 2); and iNPH patients decreased their stance duration between the two evaluations more than the iNPH-like conditions group (−1.23 (4.03)% and +0.49 (5.12)% respectively) (Table 2). For the cognitive component of the dual task, the delta of the cognitive task was identical between the two groups.

Under dual-task, univariate (model 1) and multiple logistic regression (model 2) showed that among the gait parameters, only the delta of step width was associated with the group of iNPH (Table 3).

Discussion

In this study, we evaluated the use of quantitative spatio-temporal gait parameters under dual task conditions before and after CSF tapping for the diagnosis of iNPH in patients with a suspicion of iNPH. As hypothesized, the improvement of step width, stride length, walking speed and stance duration whilst walking under dual task conditions after CSF tapping was significantly better in iNPH patients than in iNPH-like conditions. Among these four gait parameters, step width improvement after

Table 2 Clinical performance of subjects (n = 49) and comparison of delta performances¶ between iNPH and iNPH-like conditions

	iNPH (n = 27)		iNPH-like conditions (n = 22)		P-value*
	Pre-LP	Post-LP	Pre-LP	Post-LP	
Single task gait parameters					
Walking speed (m/s)	0.65 (0.37)	0.78 (0.24)	0.66 (0.46)	0.68 (0.42)	
Delta¶ (%)	+11.15 (22.28)		+4.23 (14.82)		0.054
Stride time (s)	1.21 (0.23)	1.19 (0.19)	1.22 (0.20)	1.21 (0.24)	
Delta¶ (%)	−4.09 (15.07)		+0.58 (8.34)		0.278
Stride length (m)	0.88 (0.40)	0.93 (0.28)	0.80 (0.43)	0.80 (0.36)	
Delta¶ (%)	+7.51 (18.67)		+0.20 (10.39)		0.077
Step width (m)	0.10 (0.09)	0.10 (0.05)	0.09 (0.05)	0.10 (0.06)	
Delta¶ (%)	−7.70 (34.12)		+3.54 (43.71)		0.091
Step height (m)	0.17 (0.06)	0.20 (0.06)	0.17 (0.08)	0.18 (0.07)	
Delta¶ (%)	+4.47 (11.21)		+1.36 (9.12)		0.056
Stance duration**	66.70 (3.43)	66.22 (4.60)	66.10 (7.00)	66.41 (6.14)	
Delta¶ (%)	−1.03 (6.69)		−0.32 (7.11)		0.553
Cognitive component					
Backward counting	43.24 (36.82)	52.44 (46.69)	59.81 (42.31)	63.72 (36.65)	
Delta¶ (%)	+15.98 (30.56)		+4.75 (46.28)		0.101
Dual task‡ gait parameters					
Walking speed (m/s)	0.54 (0.39)	0.64 (0.36)	0.46 (0.37)	0.56 (0.32)	
Delta¶ (%)	+12.20 (29.79)		+2.38 (32.50)		**0.044**
Stride time (s)	1.37 (0.30)	1.26 (0.22)	1.34 (0.39)	1.32 (0.31)	
Delta¶ (%)	−6.33 (16.03)		−1.17 (11.47)		0.148
Stride length (m)	0.76 (0.38)	0.83 (0.40)	0.67 (0.45)	0.74 (0.38)	
Delta¶ (%)	+7.82 (20.71)		−0.62 (19.22)		**0.030**
Step width (m)	0.12(0.08)	0.11 (0.08)	0.10 (0.08)	0.09 (0.06)	
Delta¶ (%)	−9.03 (20.75)		+0.28 (21.76)		**0.009**
Step height (m)	0.17 (0.07)	0.18 (0.06)	0.16 (0.07)	0.17 (0.07)	
Delta¶ (%)	+5.20 (10.55)		+0.40 (9.76)		0.051
Stance duration**	68.48 (4.86)	67.16 (5.13)	67.83 (7.72)	68.74 (6.61)	
Delta¶ (%)	−1.23 (4.03)		+0.49 (5.12)		**0.047**
Cognitive component					
Backward counting	45.44 (36.60)	47.44 (42.20)	53.63 (39.23)	61.37 (38.24)	
Delta¶ (%)	+21.02 (53.02)		+0.60 (41.48)		0.294

iNPH, idiopathic normal pressure hydrocephalus.
LP, lumbar puncture.
Backward counting correspond to the number of enumerated figures.
Values are medians (interquartile ranges).
¶Calculated according to the following formula: [(performance after LP − performance before LP)/(performance before LP)] × 100.
*Comparison based on Mann–Whitney test. Significant differences (p-values) are highlighted in bold characters. P-values are based on the comparison of the delta between the iNPH group and the iNPH-like conditions group.
**Stance duration are presented as a percentage of the gait cycle.
‡Gait while backward counting.

Table 3 Univariate (model 1) and multiple logistic regressions (model 2) showing an association between iNPH (independent variable) and gait parameters during delta* of dual task (dependant variable)

	Model 1 (nonadjusted)				Model 2 (adjusted)			
	Odds ratio	95% CI	P-value	r^2	Odds ratio	95% CI	P-value	r^2
Step width	0.95	[0.92; 0.99]	**0.017**	0.104	0.95	[0.91; 0.99]	**0.020**	0.141
Stride length	1.02	[0.99; 1.04]	0.185	0.042	0.97	[0.91; 1.03]	0.318	
Walking speed	1.02	[1.00; 1.04]	0.104	0.059	81.03	[0.25; 25922.77]	0.135	
Stance duration	0.92	[0.83; 1.03]	0.146	0.036	1.01	[0.88; 1.16]	0.901	

iNPH, idiopathic normal pressure hydrocephalus.
CI,Confidence interval.
Significant differences (p-values) are highlighted in bold characters.
*Calculated according to the following formula: [(performance after LP – performance before LP)/(performance before LP)] × 100.
r^2, R square.

CSF tapping during dual task seems to be the most discriminative parameter. Interestingly, the discriminative features of gait parameters between iNPH and iNPH-like conditions were observed only for dual task and not for usual single task gait assessment.

iNPH symptoms and typically gait disorders are not specific, occurring in many neurological conditions, like those presented in the iNPH-like conditions group (i.e. Parkinson's disease, vascular dementia). A previous comparative analysis of gait parameters in individuals with iNPH and Parkinson's disease revealed that the gait pattern of iNPH was clearly distinguishable from that of individuals with Parkinson's disease: this was demonstrated by an improvement in Parkinson's disease due to external cues, and an increased step width in iNPH that was shown to be a critical marker of iNPH [8]. In clinical practice, physicians need to identify iNPH from other undefined medical conditions, tests such as CSF tapping can aid diagnosis, although this is not included in the iNPH consensus guidelines [6]. Interestingly, from a clinical perspective, patients with iNPH have a tendency to fall backwards and as compensation, a broad-based gait is employed by the patients to increase their stability. This specific improvement of stride width after CSF tapping could be due to the combined effect of stability and gait. Previous studies have shown that symptomatic improvements after CSF tapping can increase the likelihood of a favourable response to a shunt [9]. However, Ondo et al. showed that 37.5% of patients with vascular parkinsonism also reported a significant gait improvement after CSF tapping [10]. Ondo et al. evaluated gait improvement two months after spinal fluid removal, assessed by a subjective auto-evaluation, and using a standard single task gait evaluation. Indeed, in a recent retrospective study, none of the patients that underwent an invasive diagnostic procedure for suspected iNPH, and that presented with an alternative neurological diagnosis after shunt placement experienced definite improvement in any symptom three years post neurosurgery [11]. This study of the cognitive component of gait (i.e. dual task) before and after CSF tapping could represent an additional gait marker of iNPH prior to shunting.

Dual-task-related gait changes reflect, in part, the influence of cognitive functions on gait, and in particular, executive functions. Indeed, the ability to dual-task requires an intact capacity to appropriately allocate attention between two tasks performed simultaneously. Pathological interference of a cognitive task while walking has been shown in different neurological conditions, such as Parkinson's disease [12], vascular dementia [13], behavioural variant of frontotemporal dementia [14] and Alzheimer's disease [15]. These conditions share a similar neuropsychological profile with iNPH. As well as gait improvement, previous studies have shown an improvement in executive functioning and attention after shunt placement in iNPH [11,16]. The improvement of gait parameters during dual task (step width, step length, stance duration and walking speed) after CSF tapping showed in iNPH patients indicates a better capacity to specifically allocate attention to gait, and not to the cognitive component of the dual task. The pressure of the distended ventricles on critical cerebral sites in iNPH might be a potential pathophysiological explanation [2]. Following CSF tapping, periventricular regional pressure modification would positively influence the frontosubcortical circuits involved in the dual-task-related gait changes. Simultaneous assessment of gait and cognition using dual-task may better reflect the potential benefits of CSF tapping than a separate evaluation of gait and cognition in iNPH patients.

The main limitations of our study include a lack of autopsy-confirmed diagnosis, a small sample size and the specificity of the exclusion criteria; i.e. patients that were unable to walk without a walking aid. Additionally, adding an older control group would be very interesting to better understand the effect of CSF tapping on gait parameters during dual task in healthy individuals. Finally, the patient's cognitive performances combined

with the dual-task gait approach should be assessed in more detail in a further prospective design study.

Conclusion

Patients with iNPH present with a reduced step width, an increased walking speed, an increased stride length and a decreased stance duration while walking under dual task conditions after CSF tapping in comparison with patients with iNPH-like conditions. The dual task paradigm represents a simple and easy approach to combine the evaluation of gait and cognition simultaneously; both are known to be independently improved by CSF tapping. These results suggest that combining quantitative gait assessment during dual task conditions after CSF tapping could improve the clinical evaluation of patients with a suspicion of iNPH prior to shunting.

Abbreviations

CSF: Cerebrospinal fluid; iNPH: Idiopathic normal pressure hydrocephalus; LP: Lumbar puncture.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

GA has full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: GA and FA; Acquisition of data: ML and SA; Analysis and interpretation of data: GA, ML, OB, FRH, FA, SA; Drafting of the manuscript: GA; Critical revision of the manuscript: ML, OB, FRH, FA, SA; Obtained funding: GA; Statistical expertise: FRH; Administrative, technical and material support: ML and SA; Study supervision: GA and FA. All authors read and approved the final manuscript.

Acknowledgments

The authors thank Charlotte Elsworth for critical review of the manuscript.

Funding

Gilles Allali is supported by a grant from the Geneva University Hospitals (PRD 11-I-3).

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Received: 14 December 2012 Accepted: 17 December 2013
Published: 21 December 2013

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doi:10.1186/1743-0003-10-117
Cite this article as: Allali *et al.*: Dual-task related gait changes after CSF tapping: a new way to identify idiopathic normal pressure hydrocephalus. *Journal of NeuroEngineering and Rehabilitation* 2013 **10**:117.

Chapter 3. Neuroimaging Studies

3.1 Hippocampal volume, early cognitive decline and gait variability

This paper has been published in Experimental Gerontology 2015;61:98-104 by Olivier Beauchet, Cyrille P. Launy, Cédric Annweiler and Gilles Allali.

Following the role of hippocampus in memory and spatial navigation, this study aims to examine the association between hippocampal volume and gait parameters in healthy older adults and in subjects with mild cognitive impairment (MCI) that is a translational state between normal aging and dementia. This cross-sectional study focused on specific gait parameters (mean value and coefficient of variation of stride time) that have been previously suggested as appropriate markers of gait control. The hippocampal volume was measured with a semi-automated software (FreeSurfer). Following our hypothesis, the study showed that healthy older adults and participants with MCI present a different association between hippocampal volume and gait control.

Experimental Gerontology 61 (2015) 98–104

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Hippocampal volume, early cognitive decline and gait variability: Which association?

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ARTICLE INFO

Article history:
Received 25 July 2014
Received in revised form 31 October 2014
Accepted 4 November 2014
Available online 6 November 2014

Section Editor: Christian Humpel

Keywords:
Gait
Hippocampus
Magnetic resonance imaging
Motor control
Older adults
Mild cognitive impairment

ABSTRACT

Background: In contrast to its prominent function in cognition, the involvement of the hippocampus in gait control is still a matter of debate. The present study aimed to examine the association of the hippocampal volume with mean values and coefficients of variation (CoV) of spatio-temporal gait parameters among cognitively healthy individuals (CHI) and patients with mild cognitive impairment (MCI).
Methods: A total of 90 individuals (47 CHI with a mean age of 69.7 ± 3.6 years and 48.9% women, and 43 MCI individuals with a mean age of 70.2 ± 3.7 years and 62.8% women) were included in this cross-sectional study. The hippocampal volume was quantified from a three-dimensional T_1-weighted MRI using semi-automated software. Mean values and CoV of stride time, swing time and stride width were measured at self-selected pace with a 10 m electronic portable walkway (GAITRite®). Age, gender, body mass index, number of drugs daily taken, Mini-Mental State Examination (MMSE) score, history of falls, walking speed and white matter signal-intensity abnormality scoring with Manolio scale were used as covariates.
Results: Patients with MCI had a lower MMSE score ($P < 0.001$), a higher CoV of stride time ($P = 0.013$) and a lower hippocampal volume ($P = 0.007$) compared with CHI. Multiple linear regression models showed that CoV of stride time was specifically associated with higher hippocampal volume among CHI ($P < 0.05$) but not among patients with MCI ($P > 0.650$).
Conclusions: Our findings revealed a positive association between a greater (i.e., better morphological structure) hippocampal volume and a greater (i.e., worse performance) stride time variability among CHI, but not among MCI individuals.

1. Introduction

The hippocampus is a key human brain region involved in memorization and locomotion (Seidler et al., 2010; Scherder et al., 2007; Lithfous et al., 2013). Atrophy of the hippocampus has been related to memory disorders and diagnosis of mild cognitive impairment (MCI), which is a transitional state between normal cognitive functioning and dementia (Fellgiebel & Yakushev, 2011; Leal & Yassa, 2013; Albert et al., 2011). In Alzheimer's disease (AD), the hippocampus constitutes one of the first brain areas affected by neurodegenerative lesions, causing its atrophy, explaining why hippocampal abnormality is considered as a biomarker of Alzheimer (Albert et al., 2011; Dubois et al., 2014). In contrast to its prominent function in cognition, the involvement of the hippocampus in gait control, and thus in the maintenance of gait stability, is still a matter of debate. For instance and when considering the hippocampal volume, Zimmermann et al. reported a non-significant association between hippocampal volume and stride-to-stride variability, whereas other studies showed a significant negative association (Zimmerman et al., 2009; Shimada et al., 2013; Rosso et al., 2014; Annweiler et al., 2014).

Divergence could be due to the studied population and/or the type of spatio-temporal gait parameters examined. Negative results have been found in the unique study that examined both cognitive healthy individuals (CHI) and patients with MCI, whereas all other studies focused on CHI (Zimmerman et al., 2009; Shimada et al., 2013; Rosso et al., 2014; Annweiler et al., 2014). In terms of control of gait, gait variability has been identified as an appropriate biomarker for the measure of the cortical control of gait in normal aging and in patients with dementia (Beauchet et al., 2009a, 2014; Montero-Odasso et al., 2012). Furthermore, higher (i.e., worse) stride time variability (STV) was specifically associated with lower cognitive performance in episodic memory

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http://dx.doi.org/10.1016/j.exger.2014.11.002
0531-5565/

and executive function among older community-dwellers without dementia (Beauchet et al., 2014). This finding was confirmed by a meta-analysis underscoring that higher STV was related to both MCI and dementia (Beauchet et al., 2014). In addition, in terms of gait instability, it has been underscored that the general assumption that variability and stability are negatively correlated cannot be a universal rule. Indeed, higher and lower variability have been reported in younger and older CHI with safe gait, this apparent discrepancy being related to the type of gait parameters examined (Beauchet et al., 2009a, 2014; Montero-Odasso et al., 2012). In particular, lower STV, intermediate swing time variability and higher stride width variability have been associated with safe gait in CHI (Beauchet et al., 2009a). These results were explained by the fact that these spatio-temporal gait parameters reflect different components of gait control (Beauchet et al., 2009a; Montero-Odasso et al., 2012; Beauchet et al., 2013). STV is a marker of the control of rhythmic stepping mechanism, whereas stride width reflects the dynamic postural control, and swing time combines the two previous components of gait control (Beauchet et al., 2009a; Montero-Odasso et al., 2012; Beauchet et al., 2013).

To better understand the relationship between hippocampal volume, early cognitive decline and gait variability, there is a need to examine the association of hippocampal volume with specific gait parameters reflecting the different components of gait control such as stride time, swing time and stride width among CHI and patients with MCI. Because it has been shown that patients with MCI present independently a greater gait variability and a lower hippocampal volume compared to CHI (Albert et al., 2011; Dubois et al., 2014; Zimmerman et al., 2009; Shimada et al., 2013; Rosso et al., 2014; Annweiler et al., 2014), we hypothesized that higher gait variability would be stronger associated with lower hippocampal volume in MCI individuals compared to CHI. We had the opportunity to test this hypothesis in the "Gait and Alzheimer Interactions Tracking" (GAIT) study, which is a cross-sectional study aiming to compare gait characteristics of CHI and patients with MCI and AD, and to examine the association between gait characteristics and brain morphology. The aim of the present study was to examine the association of the hippocampal volume with stride time, swing time and stride width variability among CHI and individuals with any form of MCI (i.e., amnestic or non-amnestic, and single or multiple domains).

2. Material and methods

2.1. Participants

Between November 2009 and July 2010, 90 individuals (47 CHI and 43 MCI individuals) were recruited in the GAIT study, which is an ongoing study. The study procedure has been previously described in detail (Beauchet et al., 2013). Briefly, all participants were referred for the evaluation of memory complaints at the memory clinic of Angers University Hospital, France. The eligibility criteria were: age 65 years and over, ambulatory, an adequate understanding of French, and no acute medical illness in the past month. For the present analysis, exclusion criteria were: dementia, extrapyramidal rigidity of the upper limbs, neurological and psychiatric diseases other than cognitive impairment, severe medical conditions affecting walking, inability to walk 15 min unassisted, or the presence of depressive symptoms defined by a 4-item Geriatric Depression Scale score above 1 (Shah et al., 1997). All participants received a full standardized medical examination, a neuropsychological and gait assessment, and MRI of the brain. The number of drugs taken daily, and the use of psychoactive drugs (i.e., benzodiazepines, antidepressants, or neuroleptics), antidiabetic drugs, antihypertensive drugs and lipid-lowering drugs were recorded. Antidiabetic, antihypertensive and lipid-lowering drugs were combined into a single category of cardiovascular drugs.

2.2. Neuropsychological assessment

A neuropsychological assessment was performed on each participant during a face-to-face examination by a neuropsychologist. The following standardized tests were used to probe several aspects of cognitive function: MMSE (Folstein et al., 1975), Frontal Assessment Battery (FAB) (Dubois et al., 2000), Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog) (Rosen et al., 1984), Trail Making Test (TMT) parts A and B (Brown et al., 1958), French version of the Free and Cued Selective Reminding Test (Grober et al., 1988; Van der Linden et al., 2004), and Instrumental Activities of Daily Living scale (IADL) (Pérès et al., 2006). The diagnosis of MCI was made during multidisciplinary meetings involving geriatricians, neurologists, and neuropsychologists of Angers University Memory Clinic, and was based on the aforementioned neuropsychological tests, physical examination findings, blood tests, and MRI of the brain. MCI was diagnosed according to the criteria detailed by Dubois et al. (2010). Participants with any form of MCI, amnesic or non-amnesic and affecting single or multiple domains, were included in this study. Participants who had normal neuropsychological and functional performances were considered as cognitively healthy.

2.3. Gait assessment

Spatio-temporal gait parameters including stride time, swing time and stride width were recorded at self-selected usual pace using a computerized walkway with embedded pressure sensors (GAITRite® Gold walkway, 972 cm long, active electronic surface area 792 × 610 cm, total 29,952 pressure sensors, scanning frequency 60 Hz, CIR System, Havertown, PA) according to the European guidelines for spatio-temporal gait analysis in older adults (Beauchet et al., 2011; Kressig & Beauchet, 2006). Briefly, the participants were asked to walk at their usual self-selected walking speed in a quiet, well-lit corridor wearing their own footwear. To avoid acceleration and deceleration effects, participants started walking 1 m before reaching the electronic walkway and completed their walk 1 m beyond it. For each parameter, mean value and coefficient of variation (CoV = (standard deviation/mean) × 100) were recorded.

2.4. Hippocampal volume

Imaging of the brain was performed with a 1.5-Tesla MRI scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) using a standard MRI protocol (Dubois et al., 2009) including 3D T_1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) axial images (acquisition matrix = 256 × 256 × 144, FOV = 240 mm × 240 mm × 187 mm, TE/TR/TI = 4.07 ms/2170 ms/1100 ms), and fluid-attenuated inversion recovery (FLAIR) axial images (acquisition matrix = 256 × 192, FOV = 240 mm × 180 mm, slice thickness = 5 mm, slice gap = 0.5 mm, 30 slices, TE/TR/TI = 122 ms/9000 ms/2500 ms).

The volumetric 3D T_1-weighted images were segmented using the FreeSurfer software package (version 5.1.0; 33) to calculate the hippocampal volume. FreeSurfer is a set of tools that automatically segments and labels brain structures based on established processing steps; the technical specifications of these procedures have been described previously (Fischl et al., 2002). Briefly, this processing included removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Jovicich et al., 2006), automated Talairach transformation, segmentation of the sub-cortical white matter and deep gray matter structures (Segonne et al., 2004; Fischl et al., 2004), tessellation of the gray matter/white matter boundary, automated topology correction (Jovicich et al., 2006; Fischl et al., 2001), registration to a spherical atlas (Fischl et al., 1999a), parcellation of the cerebral cortex into units based on gyral and sulcal structures (Segonne et al., 2004; Fischl et al., 1999b), surface inflation and creation of surface-based data (Desikan

et al., 2006). The procedures for the measurement of cortical volume have been validated against histological analysis (Dale et al., 1999) and manual measurements (Rosas et al., 2002; Kuperberg et al., 2003). Freesurfer morphometric procedures have demonstrated good test–retest reliability across scanner manufacturers and across field strengths (Han et al., 2006). Two endpoints were used in the analysis: the absolute hippocampal volume expressed in mm^3, and the ratio of absolute hippocampal volume (mm^3)/total brain volume (mm^3).

2.5. Covariables

Gait variability may be influenced by several clinical variables, which are potential confounders when examining its relationship with the hippocampal volume (Annweiler et al., 2014; Beauchet et al., 2009a, 2014; Montero-Odasso et al., 2012; Beauchet et al., 2011, 2013; Kressig & Beauchet, 2006). The main potential confounders (i.e., age, gender, body mass index, number of drugs daily taken, history of falls in the past year) were recorded using a standardized comprehensive geriatric assessment (Beauchet et al., 2013). Walking speed may also influence gait variability, lower walking speed being associated with higher gait variability (Beauchet et al., 2009b) explaining why it was used as a covariable in the analysis. In our study, walking speed was measured at self-selected usual pace with the GAITRite® system. Lastly, it has been reported that white matter hyperintensities (WMHs) is associated with higher gait variability (Rosano et al., 2007). Therefore, the total extent of white matter signal-intensity abnormality was measured using the semiquantitative visual rating scale devised by Manolio and colleagues (Manolio et al., 1994), with a score ranging from 0 (i.e., best) to 9 (i.e., worst). The inter-rater agreement of this scale is fair (Cohen $\kappa = 0.59$) (Kapeller et al., 2003). A Manolio score >3 was considered as significant WMHs and was used as covariable in the analysis.

2.6. Ethics

Participants in the study were included after having given their written informed consent for research. The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The entire study protocol was approved by Angers local Ethical Committee, France.

2.7. Statistics

The participants' characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. Normality of data distribution was checked using a skewness–kurtosis test. As the number of observations was >40 for each group, no transformations were applied to the variables of interest. For the current analysis, participants were classified into 2 groups, as follows: CHI and patients with MCI. First, between-group comparisons were performed using unpaired *t*-test, Mann–Whitney or Chi-square test, as appropriate. Second, univariate and multiple linear regression analyses were performed to examine the association between spatio-temporal parameters (dependent variables) and the hippocampal volume (independent variables) adjusted on the participants' characteristics. P-values less than 0.05 were considered as statistically significant. All statistics were performed using SPSS (version 15.0; SPSS, Inc., Chicago, IL).

3. Results

Clinical and hippocampal characteristics are presented in Table 1. Patients with MCI had a lower MMSE score ($P < 0.001$), a higher CoV of stride time ($P = 0.013$) and a lower hippocampal volume ($P = 0.007$). There was no significant difference for the other participant's characteristics. Fig. 1 shows T1-weighted MRI images of hippocampus of three characteristic participants: two cognitively healthy individuals (one with a low hippocampal volume (2913 mm^3) and a low CoV of stride time (1.3%) (a) and another one with a high hippocampal volume (4448 mm^3) and a high CoV of stride time (5.8%) (b)) and a patient with MCI with a low hippocampal volume (2751 mm^3) and a high CoV of stride time (4.9%) (c). Multiple linear regression models showed that CoV of stride time was specifically associated with a higher hippocampal volume among CHI ($P = 0.007$ for the absolute value and $P = 0.047$ for the ratio), but not among MCI individuals (Table 2). This association was not significant for absolute volume and ratio without adjustment (respectively, $P = 0.119$ and $P = 0.165$ in CHI, and $P = 0.235$ and $P = 0.825$ in MCI). No other association was reported between spatio-temporal gait parameters and hippocampal volume in both groups.

4. Discussion

This study revealed an unexpected positive association between a greater (i.e., better morphological structure) hippocampal volume and a greater (i.e., worse) STV among CHI, but not among patients with MCI in the studied sample of non-demented older community-dwellers.

Greater gait variability and lower hippocampal volume have been separately reported in patients with MCI (Fellgiebel & Yakushev, 2011; Leal & Yassa, 2013; Albert et al., 2011; Beauchet et al., 2009a, 2014; Montero-Odasso et al., 2012; Beauchet et al., 2013). Furthermore, a significant negative association between greater gait variability and lower hippocampal volume has been also shown in CHI (Albert et al., 2011; Dubois et al., 2014; Zimmerman et al., 2009; Shimada et al., 2013; Rosso et al., 2014; Annweiler et al., 2014). Thus, we hypothesized at first that higher gait variability would be stronger associated with lower hippocampal volume in patients with MCI individuals compared to CHI. However, we did not find this excepted significant association between lower (i.e., worse) hippocampal volume and greater (i.e., worse) STV. The main explanation of this result could be related to the low level of STV observed in our sample of patients with MCI. Even if their mean value of CoV of stride time was higher than CHI, it was still in the normal range (Beauchet et al., 2009a, 2014; Montero-Odasso et al., 2012). Indeed, STV previously reported in patients with MCI was already above 3%, whereas in our study the mean CoV was 2.6% (Beauchet et al., 2009a; Montero-Odasso et al., 2012; Beauchet et al., 2013). In contrast to these previous studies, we focused on a population of patients with MCI with very early cognitive decline that prevents us to observe the suggested association.

The positive association between a greater (i.e., better morphological structure) hippocampal volume and a greater (i.e., worse) STV in CHI highlights the role of the hippocampus in gait control during normal aging. Indeed, it was supported by a recent study that showed the effects of normal aging on the neural substrate of gait control using mental imagery during functional MRI of the brain: hippocampal regions in older adults presented an increased activation in comparison to younger ones in a task requiring a precise control of gait (i.e., walking on surface consisting of cobbles stones) (Allali et al., 2014). This additional hippocampal activation reflects the compensatory mechanism used to maintain a physiological control of gait. During normal aging, both higher and lower STV reflect efficient control of gait and safe gait (Beauchet et al., 2009a; Gabell & Nayak, 1984). Lower STV reflects automatic walking process requiring low attention demands, whereas high STV is in relationship with high demanding walking task like walking on cobble stones (Woollacott & Shumway-Cook, 2002). Our results are in line with the model suggesting that precise gait control requires hippocampal integrity in non-demented older adults. However, recent findings showed a morphological association between lower hippocampal integrity and higher stride length variability, this gait parameter being like STV a biomarker of the rhythmic stepping mechanism (Rosso et al., 2014). In addition, other studies focusing on brain metabolism also found an association between lower levels of hippocampal metabolism and higher stride length variability using proton magnetic

Table 1
Clinical, gait and hippocampal characteristics of participants according to their cognitive status (n = 90).

	Total population (n = 90)	CHI (n = 47)	Patients with MCI (n = 43)	P-value*
Clinical characteristics				
Age, mean ± SD (years)	69.9 ± 3.7	69.7 ± 3.6	70.2 ± 3.7	0.545
Female, n (%)	50 (55.6)	23 (48.9)	27 (62.8)	0.186
BMI (kg/m^2), mean ± SD	25.7 ± 3.7	25.0 ± 3.4	26.4 ± 3.8	0.056
Number of drugs taken daily, mean ± SD	2.3 ± 2.6	2.4 ± 2.5	2.3 ± 2.7	0.844
Use psychoactive drugs[a], n (%)	8 (8.9)	5 (10.6)	3 (7.0)	0.542
Use cardiovascular drugs[b], n (%)	26 (28.9)	14 (29.8)	12 (27.9)	0.844
MMSE score (/30), mean ± SD	28.1 ± 1.6	28.7 ± 1.2	27.4 ± 1.7	**<0.001**
Falls in the past year, n (%)	17 (18.9)	11 (23.4)	6 (14.0)	0.253
Gait characteristics				
Stride time				
Mean, mean ± SD (ms)	1164.1 ± 128.9	1162.9 ± 142.3	1116.5 ± 113.9	0.680
CoV, mean ± SD (%)	2.6 ± 1.2	2.3 ± 1.0	2.9 ± 1.2	**0.013**
Swing time				
Mean, mean ± SD (ms)	419.2 ± 43.8	419.9 ± 46.2	418.6 ± 41.6	0.888
CoV, mean ± SD (%)	3.9 ± 1.6	3.8 ± 1.7	3.9 ± 1.4	0.728
Stride width				
Mean, mean ± SD (cm)	7.5 ± 4.2	6.9 ± 4.6	8.3 ± 3.5	0.136
CoV, mean ± SD (%)	29.2 ± 26.4	26.2 ± 20.6	32.5 ± 31.5	0.426
Walking speed, mean ± SD (cm/s)	112.1 ± 18.3	113.7 ± 20.3	110.2 ± 15.8	0.443
Manolio score[c] (/9) ≥3, n (%)	30 (33.3)	17 (36.2)	13 (30.2)	0.551
Hippocampal volume				
Absolute value, mean ± SD (mm^3)	3707.4 ± 465.7	3819.1 ± 410.5	3585.2 ± 495.7	**0.007**
Relative value[d], mean ± SD	0.35 ± 0.37	0.36 ± 0.36	0.34 ± 0.34	0.060

CHI = cognitively healthy individuals; MCI = mild cognitive impairment; BMI = body mass index; MMSE = Folstein Mini-Mental State Examination; CoV: coefficient of variation; P-value significant (<0.05) indicated in bold.

* Comparison based on unpaired *t*-test, Mann–Whitney or Chi-square test, as appropriate.

[a] Use of benzodiazepines or antidepressants or neuroleptics.

[b] Use of antidiabetic drugs, and/or antihypertensive drugs and/or lipid-lowering drugs.

[c] Semiquantitative rating scale measuring the total extent of white matter signal-intensity abnormality with a score ranging from 0 (absence) to 9 (worst).

[d] Calculated from the formula: absolute hippocampal volume (mm^3)/total brain volume (mm^3).

resonance spectroscopy or positron emission tomography (Zimmerman et al., 2009; Shimada et al., 2013). The fact that the current approach divided the study sample of non-demented older adults on a group of healthy aging and a group of participants with early signs of pathological aging (i.e., MCI) could explain these apparent divergences. So, this association between higher STV and higher hippocampal volume observed in the CHI group leads to the model of a specific role of the hippocampus in the control of gait, and more specifically in the control of the rhythmic stepping mechanism, during normal aging with an alternative role during pathological aging.

Taken together the finding of a nonsignificant association between hippocampal volume and gait variability in patients with MCI, but significant in CHI, is in concordance with a recent study, which reported a tendency to a J-shaped change of the volume of ventricular bodies (an indirect marker of brain atrophy) according to the STV (categorized in tertiles), the lowest volume reported in the intermediate STV tertile (Annweiler et al., 2014). The presence of a compensatory mechanism in CHI, could explain the significant positive association between greater (i.e., worse) STV and increased hippocampal volume among CHI that would be absent in MCI individuals due to the pathological process of MCI. The capacity of focal cerebral plasticity has already been shown in response to environmental demands, especially in spatial navigation: learning the mental atlas of the streets in London, was associated with structural changes in the brain of licensed taxi drivers compared to controls, namely a greater volume of hippocampus (Maguire et al., 2000).

The univariate regression showing no association between CoV of stride time and hippocampal volume is hardly interpretable and has only little meaning as many factors contribute to gait variability. Thus, ignoring these covariables in a univariate model prevents valid conclusions (Annweiler et al., 2014; Beauchet et al., 2009a, 2014; Montero-Odasso et al., 2012; Beauchet et al., 2011, 2013; Kressig & Beauchet, 2006). In contrast, the absence of significant association between mean values of studied spatio-temporal gait parameters while taking into account the effects of covariables is in concordance with previous studies that underscored that stride-to-stride variability, but not mean value, represents a biomarker of the highest (i.e., subcortical and cortical levels) levels of gait control (Beauchet et al., 2009a; Montero-Odasso et al., 2012; Beauchet et al., 2013). Furthermore, we did not show any association with stride-to-stride variability of swing time and stride width. In contrast to stride time, these two gait parameters are related to other components of gait control. Stride width is a marker of dynamic postural control and swing time reflects the dynamic postural control combined to the rhythmic stepping control (Beauchet et al., 2009a). Compared to STV, these two gait parameters are increased in individuals with safe gait (Beauchet et al., 2009a; Brach et al., 2005). From a biomechanical viewpoint, variability is necessary to maintain balance (Brach et al., 2005; Newell & Corcos, 1993), which reflects the ability to adapt limb movement while walking, leading to greater stability (Beauchet et al., 2009a; Montero-Odasso et al., 2012; Beauchet et al., 2013; Brach et al., 2005; Newell & Corcos, 1993). The higher variability of both these gait parameters compared to stride time or stride length is required to a maintain safe gait. Absence of association between swing time and stride width and hippocampal volume could be related to the fact that they both depend on others brain regions. Indeed, it has been shown that the age-related neural correlates for balance control are based on a specific network involving the parietal, frontal and the insular cortical areas in addition to the basal ganglia (Goble et al., 2011).

Although the strength of this study was designed to specifically identify healthy older adults from those with early signs of pathological aging in the relationship between hippocampal volume and gait control, this study is not without limitation. Due to the small number of patients with MCI, a dichotomization of patients with MCI between the amnestic and non-amnestic subtypes was not possible because of a lack of power exposing to invalid results. While this study is the first to demonstrate an association between hippocampal volume and STV in physiological aging, the cross-sectional design does not afford causal inferences. Furthermore, using a longitudinal design, we would be able to determine whether changes in hippocampal volume precipitate higher STV in CHI and MCI patients, or whether worse gait performance precipitate

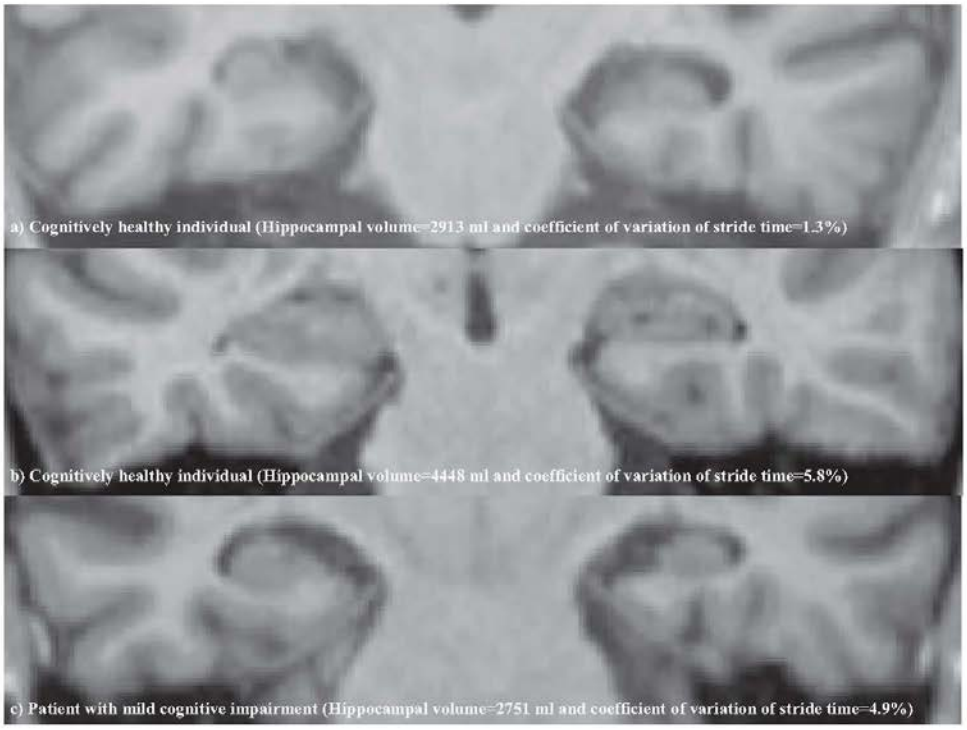

Fig. 1. Coronal T1-weighted MRI images of hippocampus of three characteristic participants (two cognitively healthy individuals a) and b), and one patient with mild cognitive impairment c)).

changes in hippocampal morphology. Finally, the participants included in the GAIT study were referred to our center for the evaluation of a memory complaint. Thus, participants defined as CHI in our study presented the specificity of having a memory complaint, suggesting that the findings of the present study could be generalized to a pre-MCI population.

In conclusion, this study found a specific association between increased hippocampal volume and a greater STV in CHI, but not in patients with MCI. These results suggest that the hippocampus may control the physiology of gait, specifically the rhythmic stepping mechanism, during normal aging, but not during pathological aging. Additional investigations are required to determine which brain regions

Table 2
Multiple linear regression models showing the association between values of spatio-temporal gait parameters (dependent variables) and the hippocampal volume (independent variable) adjusted for clinical characteristics among participants separated on their cognitive status (n = 90).

	Stride time			Swing time			Stride width		
	ß	95% CI	P-value	ß	95% CI	P-value	ß	95% CI	P-value
a) Mean values									
CHI									
Absolute volume	0.000	[0.000;0.000]	0.451	0.000	[0.000;0.000]	0.607	0.002	[−0.002;0.005]	0.378
Relative volume*	15.8	[−39.6;71.3]	0.567	4.8	[−21.3;30.9]	0.711	−1118.8	[−5096.4;2858.8]	0.572
MCI									
Absolute volume	0.000	[0.000;0.000]	0.252	0.000	[0.000;0.000]	0.574	0.000	[−0.002;0.003]	0.873
Relative volume*	23.5	[−38.1;85.0]	0.443	2.0	[−26.7;30.7]	0.808	−368.1	[−3048.2;2312.0]	0.782
b) Coefficients of variation									
CHI									
Absolute volume	**0.001**	[0.000;0.002]	**0.007**	0.000	[−0.001;0.001]	0.882	−0.007	[−0.024;0.010]	0.407
Relative volume*	**758.5**	[11.5;1505.5]	**0.047**	387.8	[−1016.8;1792.3]	0.579	−13572.1	[−32119.1;4974.9]	0.147
MCI									
Absolute volume	0.000	[−0.001;0.001]	0.667	−0.001	[−0.002;0.000]	0.142	0.017	[−0.011;0.044]	0.223
Relative volume*	−133.2	[−1148.9;882.5]	0.791	−604.5	[−1638.1;429.1]	0.243	22130.3	[−5156.5;49417.2]	0.108

CHI = cognitively healthy individuals; MCI = mild cognitive impairment; β: coefficient of regression beta corresponding to an increase or a decrease in value of spatio-temporal gait parameter; all models are adjusted on age, gender, body mass index, number of drugs daily taken, Folstein Mini-Mental State Examination score, history of falls in the past year, walking speed and the total extent of white matter signal-intensity abnormality was measured by Manolio scale; coefficient of regression (ß) and P-value significant (i.e., P < 0.05) indicated in bold.

* Calculated from the formula: absolute hippocampal volume/total brain volume.

are involved in the pathophysiological mechanisms of the stepping mechanisms contributing to the higher gait variability found in the different forms of pathological aging.

Acknowledgments

The authors have listed everyone who contributed significantly to the work in the Acknowledgments section. Permission has been obtained from all persons named in the Acknowledgments section.

- Melinda Beaudenon, MSc, Jennifer Gautier, BS, Romain Simon, MS, and Samuel Thiery, BS, from Angers University Memory Clinic, France, for daily assistance. There was no compensation for this contribution.
- Jean-Yves Tanguy, MD, Anne Pasco-Papon, MD, PhD, Christophe Aube, MD, PhD, from the Department of Radiology, Angers University Hospital, France, for technical support. There was no compensation for this contribution.

Conflict of interest

- **Disclosures**:
  - CA: serves as an unpaid associate editor for Gériatrie, *Psychologie et Neuropsychiatrie du Vieillissement* and for the *Journal of Alzheimer's Disease*. He has no relevant financial interest in this manuscript.
  - OB: serves as an unpaid associate editor for *Gériatrie, Psychologie et Neuropsychiatrie du Vieillissement*. He has no relevant financial interest in this manuscript.
  - GA: serves as an unpaid associate editor for *Scientific World Journal*. He has no relevant financial interest in this manuscript.
- **Funding**:
  - The study was financially supported by the French Ministry of Health (Projet Hospitalier de Recherche Clinique national n° 2009-A00533-54).
  - Gilles Allali is funded by a grant from the Geneva University Hospitals.
  - Software for quantification of brain ventricle volumes was provided my Merge Healthcare (Mississauga, Canada).
  - The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Author contributions

- OB has full access to all of the data in the study, takes responsibility for the data, the analyses and interpretation and has the right to publish any and all data, separate and apart from the attitudes of the sponsor.
- Study concept and design: OB, CA and GA.
- Acquisition of data: OB and CA.
- Analysis and interpretation of data: OB and GA.
- Drafting of the manuscript: OB and GA.
- Critical revision of the manuscript for important intellectual content: CPL and CA.
- Obtained funding: OB.
- Statistical expertise: OB.
- Administrative, technical, or material support: CA and OB.
- Study supervision: GA.

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3.2 The neural basis of age-related changes in motor imagery of gait: an fMRI study

This paper has been published in Journal of Gerontology: Medical Sciences 2014;69(11):1389-1398 by Gilles Allali, Marian van der Meulen, Olivier Beauchet, Sebastian W. Rieger, Patrik Vuilleumier and Frédéric Assal.

This study aimed to describe the age-related changes of the neural substrate of mental imagery of gait. We used a validated gait imagery task (156) to compare the brain activation during functional MRI between healthy young and older adults. The imagery task required that the subjects imagine themselves while walking on easy and difficult paths. We showed an increased activation in healthy older adults in comparison to the young group in a brain networks involving the prefrontal cortex. Furthermore, the left hippocampus was specifically involved in the elders, when they imagined themselves while walking on the difficult path. According to the compensation hypothesis that suggests that older adults need to increase their brain activation to compensate decline in performance, these findings suggest the major role of executive functions, spatial navigation and memory – these functions are monitored by the same brain regions – in the control of gait in aging.

Journals of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci 2014 November;69(11):1389–1398
doi:10.1093/gerona/glt207

Advance Access publication December 24, 2013

Special Issue: Brain Aging

The Neural Basis of Age-Related Changes in Motor Imagery of Gait: An fMRI Study

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Background. Aging is often associated with modifications of gait. Recent studies have revealed a strong relationship between gait and executive functions in healthy and pathological aging. We hypothesized that modification of gait due to aging may be related to changes in frontal lobe function.

Methods. Fourteen younger (27.0±3.6 years) and 14 older healthy adults (66.0±3.5 years) performed a motor imagery task of gait as well as a matched visual imagery task. Task difficulty was modulated to investigate differential activation for precise control of gait. Task performance was assessed by recording motor imagery latencies, eye movements, and electromyography during functional magnetic resonance imaging scanning.

Results. Our results showed that both healthy older and young adults recruited a network of brain regions comprising the bilateral supplementary motor cortex and primary motor cortex, right prefrontal cortex, and cerebellum, during motor imagery of gait. We observed an age-related increase in brain activity in the right supplementary motor area (BA6), the right orbitofrontal cortex (BA11), and the left dorsolateral frontal cortex (BA10). Activity in the left hippocampus was significantly modulated by task difficulty in the elderly participants. Executive functioning correlated with magnitude of increases in right primary motor cortex (BA4) during the motor imagery task.

Conclusions. Besides demonstrating a general overlap in brain regions recruited in young and older participants, this study shows age-related changes in cerebral activation during mental imagery of gait. Our results underscore the importance of executive function (dorsolateral frontal cortex) and spatial navigation or memory function (hippocampus) in gait control in elderly individuals.

Key Words: Mental imagery—Aging—Gait—Neuroimaging.

Received July 16, 2013; Accepted November 16, 2013

Decision Editor: James Goodwin, PhD

GAIT disorders are very common in the elderly individuals; it is estimated that only 20% of very old individuals walk normally (1–3). Specific age-related changes in spatial and temporal gait parameters have been associated with the risk of falling (4). For example, increased stride time variability predicts incidental falls in older adults. Aging can also result in increased step width variability or stride length variability, highlighting a disturbance in automatic and rhythmic motor control (5). Several neurophysiological factors may play a role in the modulation of gait in aging, from regional muscular atrophy (6) through to the degeneration of particular neurotransmitter systems, like the cholinergic system (7) or dopaminergic system (8). The presence of a gait disorder can be a marker of the future development of disease, like dementia, pathologies disturbing the frontal lobe or the connections between subcortical regions and frontal cortices (9). The frontal lobes are closely related to executive functioning, but also appear crucial for the control of gait (10). Gait disturbances may thus be indicative of subtle preclinical changes in higher order cognitive functioning.

In recent years, this relationship between executive functioning and gait control has received considerable attention (10). Impaired executive functioning has been proposed to underlie gait changes in healthy aging (11), but also in Alzheimer's

disease (12), vascular dementia (13), frontotemporal dementia (14), and Parkinson's disease (15). The role of executive functioning in gait control becomes apparent especially in demanding situations such as dual tasking (ie, walking while performing a cognitive task) or walking on uneven ground (10).

The use of functional neuroimaging techniques has greatly contributed to the understanding of cerebral control of gait in humans. Near-infrared spectroscopy (16), transcranial magnetic stimulation (17), nuclear neuroimaging techniques (18), and more recently electroencephalography (19) allow for direct measures of cerebral activity during actual gait performance. Functional magnetic resonance imaging (fMRI) and positron emission tomography have also been employed to study neural processes associated with gait control, through the use of motor imagery (MI) paradigms. This approach exploits the documented overlap in cerebral regions recruited during mental simulation of a movement and during actual execution of the same movement (20,21). Together, these studies have identified a network associated with MI of gait, comprising bilateral SMA, superior parietal lobules, hippocampus, parahippocampal gyri, pedunculopontine nuclei, and cerebellum (22,23).

The effects of aging on the neural substrate of gait control merits more systematic investigations given the high frequency of gait disturbances in the elderly individuals and its significance for future disease. The modification of quantitative gait parameters and the implication of cognitive functions in gait control in the elderly individuals suggest a specific pattern of brain activation during MI of gait in comparison with young adults. Our aim was therefore to compare brain function in a group of young participants and a group of healthy older adults using fMRI and a validated gait imagery task.

Methods

Participants

Fourteen healthy young participants (4 men/10 women, mean age: 27.0±3.6 years, education: 16.2±2.8 years) and 14 healthy old participants (4 men/10 women, mean age: 66.0±3.5 years, education: 14.6±2.5 years) took part in this study. They were recruited from the community through word of mouth and public advertising. The study was approved by the local ethics committee. All participants gave written informed consent. All participants were right handed, as verified with the Edinburgh Handedness Inventory (EHI, Oldfield, 1971). Young participants obtained a mean score of 85.3±17.6 and elderly participants of 87.1±14.4 (p = nonsignificant). All participants had normal or corrected-to-normal vision and no neurological or orthopedic disturbances. Cognitive functioning of all elderly participants was assessed using a detailed neuropsychological test battery (Table 1) and the young participants were screened for any neurological or medical conditions interfering with brain functioning. All the older participants presented normal performances in the neuropsychological assessment.

Table 1. Demographic Data and Neuropsychological Test Scores of the 14 Healthy Older Participants

	EC
	Mean ± *SD*
Sociodemographic	
Female/male	10/4
Age	66.0±3.5
Education	14.6±2.5
Global measures	
MMSE	29.1±0.9
Mattis	142.9±1.2
Memory	
Buschke—48 items	26.9±3.9
Doors Test A	11.2±1.1
Doors Test B	8.6±1.7
Digit span forwards	5.9±0.7
Attention/executive	
Stroop Test	112.3±16.3
Trail-Making Test A	34.6±5.9
Trail-Making Test B	76.1±20.7
Digit span backwards	4.2±0.7
Language	
Boston Naming A*	31.3±1.9
Boston Naming C*	20.0±0.0
Verbal fluency (category)	33.9±7.4
Verbal fluency (letter)	25.0±6.4
Depression/anxiety	
HAD (depression)	1.4±1.2
HAD (anxiety)	4.4±

Motor Performance and Chronometry Ability

To assess individual participant's motor performance and chronometry ability (CA), we administered two mental chronometry tests, both evaluating performed and imagined times of an action. The first was a version of the Timed "Up and Go" (TUG) test developed by Beauchet and coworkers (24). The initiation, acceleration, deceleration, preparation of turning, and turning component of the TUG are also involved in the "difficult" condition of our fMRI task. The second was the Ten Meter test. Participants completed two trials on both the real and imagined version of both tasks. On the imagined TUG, the experimenter gave the cue to start imagining, and the participant was instructed to pronounce the word "stop" when they had completed the mental task. The Ten Meter test was similar in design to the TUG, but assessed CA while walking in a straight line, similar to the fMRI task (which also involved walking straight for 10 m). All participants performed two trials of the Ten Meter and the TUG and the mean of these two trials were used as outcome.

Individual CA scores were calculated on the basis of the delta time scores on the TUG and Ten Meter test. Delta times were calculated according to the following formula: delta = $[T_{real} - T_{Imag}]/[(T_{real} + T_{Imag})/2]$ (24). CA score was

taken as the positive mean of the two delta times for each participant. The lower the CA score, the smaller the difference between real and imagined performance times, and therefore the higher CA.

fMRI Procedure

Materials.—Participants were scanned during a single fMRI session lasting about 30 minutes. All functional and structural MRI data were acquired on a 3T whole body MRI system (Trio TIM, Siemens, Germany) with a 12-channel head coil at the Brain & Behaviour Laboratory (BBL) of the University of Geneva. Visual stimuli were presented on a projection screen inside the scanner using E-prime (E-prime 1.0, Psychology Software Tools Inc., Pittsburgh, PA). Gaze direction and pupil diameter were logged with an MRI compatible long range eye tracker (EyeTrac 6, Applied Science Laboratories).

Scanning protocol.—Whole-brain functional images were collected using a susceptibility-weighted EPI sequence (TR/TE = 2,100/30 ms; flip angle = 80°; PAT factor = 2; FOV = 205 mm; matrix size = 64 × 64 pixels). Thirty-six transversal slices were acquired sequentially with a 3.2 mm thickness and an interslice gap of 0.64 mm, yielding a voxel size of 3.2 mm isotropic. High-resolution whole-brain anatomical scans were acquired with a T1-weighted, 3D sequence (MPRAGE; TR/TI/TE = 1,900/900/2.27 ms; flip angle = 9°; voxel dimensions = 1 mm isotropic; 256 × 256 × 192 voxels).

fMRI activation task.—Stimuli for the fMRI task consisted of 12 photos, 6 each of 2 different outdoor walkways, located in the garden of the rehabilitation unit of the Geneva University Hospital, each taken from a slightly different perspective, side or angle (Figure 1) that have been described previously (25). Both walkways were about 1 m wide. One walkway had a smooth tarred surface (providing stimuli for the "easy" condition), whereas the other had a surface consisting of cobble stones of between 4 and 30 cm in diameter ("difficult" condition). Participants performed three different tasks on the two kinds of walkways: MI, visual imagery (VI), and a perceptual control (C) condition.

In the MI task, participants were shown the photos of the different walkways with two horizontal lines drawn across them: a grey line at the bottom to indicate the start of the trajectory and a black line at a distance of 10 m (as measured on the actual path). Participants were asked to start imagine walking from the grey line to the black line as soon as the picture appeared. They had to press a button when they imagined that they had reached the red line on the walkway. Focusing on the kinesthetic component of MI, they were instructed to imagine walking as vividly as possible, as if feeling their limbs moving (but without actually moving them), and from a first-person perspective.

In the VI task, participants were presented with the same photos as in the MI task, but this time a black disk (25 cm in diameter) was shown on each photo at the start of the trajectory (on the grey line). Participants were asked to imagine this disk moving from the blue to the red line at a constant speed, similar to walking speed. They pressed a button when they had imagined the disk to arrive at the red line.

In the control task, participants were presented with the same pictures as in the MI task, but in this case, the lines on the walkways were either both grey or both black. Participants were instructed to simply inspect each photograph for a fixed period of time (6 seconds in half of the trials and 10 seconds in the other half). After offset of the picture, participants were cued to press either one button if the lines on the walkway were black or another in case they were blue.

Procedure.—The three different tasks were presented in a block-wise fashion, with two blocks per task, and therefore six blocks in total, that have been described previously (25). All participants received detailed instructions and underwent a training session on all three conditions of the task before the scanning session, until they were confident that they were able to perform the task at the best of their capacities.

Behavioral Data Analysis

For each participant, the mean imagery time for both MI and VI was calculated by averaging the trials for each condition. Imagery time was taken as the time between the onset of the picture and the button press. We used an eye-tracker monitor to check online that all participants kept their eyes open and adhered to the actual task instructions (ie, moved their eyes along the walkways). Moreover, following the procedure by Bakker and coworkers (22), we also verified task adherence by investigating the effect of path surface (ie, task difficulty) for the MI and the VI tasks. As the black disk is not impeded by path surface, task difficulty should have a larger effect on MI than on VI. Therefore, a 2 × 2 repeated-measures analysis of variance (ANOVA) of imagery times was carried out, with task (MI vs VI) and difficulty (easy vs difficult) as within-participant variables.

EMG Recording/Analysis

During the fMRI session, muscle activity of the right leg was recorded to control for overt muscle movements. Muscle activity (EMG) was recorded with a modular data acquisition system (MP150, BIOPAC Systems Inc.), with a sampling rate of 10,000 Hz. A pair of carbon-wired MRI compatible electrodes were placed 5

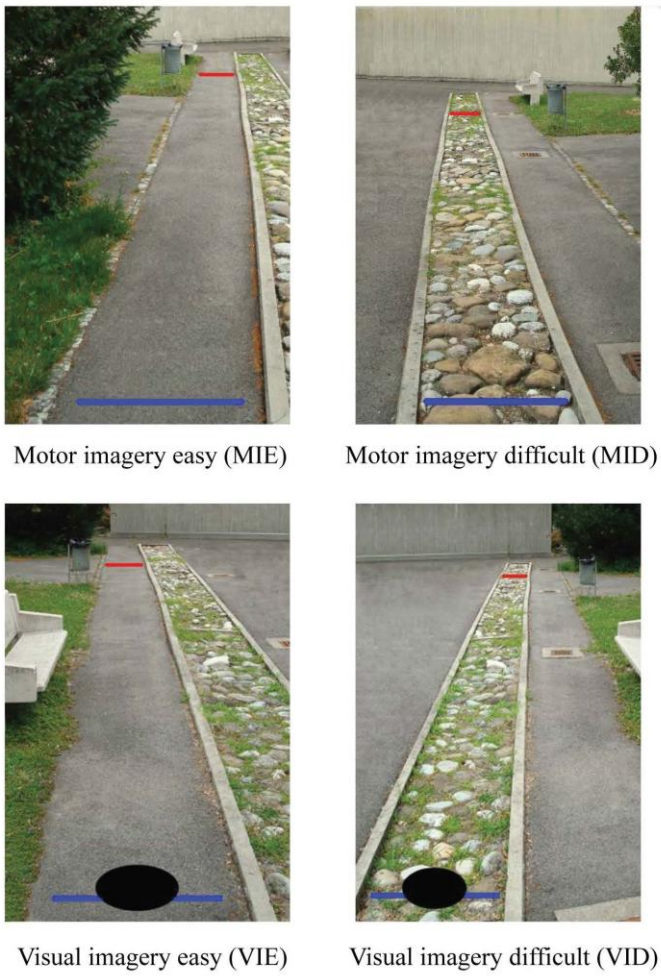

Figure 1.

Functional Data Analysis

First-level analysis.—Functional images were preprocessed and analyzed using standard methods implemented in SPM5 (Wellcome Department of Imaging Neuroscience, London), which have been described previously (25). The experimental conditions were Motor Imagery—Easy (MIE) Motor Imagery—Difficult (MID) Visual Imagery—Easy (VIE) Visual Imagery—Difficult (VID) and Control (C) (Figure 1).

Second-level analysis.—Contrast images obtained in the individual analyses were entered into one flexible factorial design, which included group and condition as main factors, as well as their interaction. The main contrasts of interest were MI > C, probing for activation associated with MI, and MID > MIE, investigating the effect of path surface (ie, task difficulty). MI > VI was also included to investigate the motor specificity of the effects. Imagination times were added as a linear parametric nuisance covariate to make sure that any difference between conditions or groups was not due simply to a difference in time taken to perform the task. CA scores were also added as a second covariate to control for differences between groups in CA. Statistical analyses were performed on a voxel-wise basis across the whole brain, all thresholded at $p < .001$ (uncorrected) with a minimum cluster size of 20 voxels, unless otherwise specified.

Anatomical labels of activated clusters were determined using the xjView toolbox (http://www.alivelearn.net/xjview) and the Anatomy Toolbox version 1.5.

Regression.—To explore whether there were any areas in which activity during gait imagery correlated with executive functioning and according to the previous observations in matter of association between cognitive function and gait (25), we added the Stroop interference score as a linear regressor to the MI > C contrast of our task using the multiple regression option in SPM5. The Stroop interference score refers to the difference in response times related to the suppression of word reading in favor of color naming, which assesses inhibitory control. Walking requires the quick online processing of a flow of information, to adapt motor actions to the environmental conditions and inhibiting the nonrelevant information, which is crucial for gait.

Results

Behavioral Results

Motor performance and CA.—Mean performed (T_{real}) and imagined times (T_{imag}) of the two mental chronometry tests, as well as CA scores, are presented in Table 2. From the table, it can be seen that elderly participants took longer to perform both tasks (significant only for the TUG), indicating a slight reduction in walking speed.

Both groups always imagined doing the tasks faster than they executed them in reality. CA scores differed significantly between groups ($F(1,27) = 7.21$, $p < .012$), indicating that CA was slightly worse in the elderly participants.

fMRI gait imagery task.—Mean imagery latencies during the different conditions of our fMRI task are summarized in Table 3. Responses in the control condition (deciding on the color of the lines) were 100% correct for all participants. A repeated-measure ANOVA with task (MI and VI) and condition (easy and difficult) as within-participant factors revealed that for the young participants, there was a main effect of condition ($F(1,13) = 40.64$, $p < .001$) and an interaction between task and condition ($F(1,13) = 9.40$, $p < .01$), but no main effect of task ($F(1,13) = 1.11$, p = nonsignificant). This indicates that they took longer to perform the difficult than the easy condition for both MI and VI and that the difference between easy and difficult was significantly greater for the MI than for the VI task. For the old participants, there was only a main effect of condition ($F(1,13) = 79.63$, $p < .001$), but no main effect of task ($F(1,13) = 0.23$, p = nonsignificant) and no interaction ($F(1,13) = 0.38$, p = nonsignificant). Therefore, elderly participants showed an equal difference in imagery times between the easy and difficult condition for both the MI and VI tasks. When the two participant groups were collapsed, we found a main effect of condition ($F(1,27) = 106.95$, $p < .001$) and an interaction between tasks and condition ($F(1,27) = 5.59$, $p < .05$).

EMG Results

The mean normalized muscle activity values for MI and VI are presented in Table 4. A repeated-measures ANOVA with task as within-participants factor revealed no difference in EMG values between MI and VI for the young participants ($F(1,13) = 1.47$, p = nonsignificant) nor for the elderly participants ($F(1,13) = 0.87$, p = nonsignificant). There were also no differences between groups for MI ($F(1,27) = 0.002$, p = nonsignificant) nor for VI ($F(1,27) = 1.34$, p = nonsignificant). This indicates that young and old participants presented the same muscle activity during MI and VI and that this muscle activity was similar in both groups.

Imaging Results

Motor imagery effect (MI > C).—For the main contrast MI > C, we found widespread activation in both groups in a network of areas including bilateral supplementary motor area (BA6) extending to midcingulate cortex, superior medial prefrontal cortex, lateral inferior BA4, right inferior prefrontal cortex (incl. BA44/45/47) extending to the insula and right postcentral gyrus, and the cerebellum. When we compared groups directly for this contrast ((MI > C_elderly) > (MI > C_young)), we found stronger activation in elderly participants in the left middle frontal gyrus (BA10), right SMA, and right superior orbitofrontal cortex (BA11). The parameter estimates from these three clusters showed a group difference only for the MI task and not for the VI task, indicating that only imagery for gait (and not imagery for visual movement) in our task is modulated by age (Figure 2 and Supplementary Table 1). There were no clusters that were activated stronger in the young than in the

Table 2. Mean ± *SD* T_{real}, T_{imag}, on the TUG and TM, and Chronometry Ability Scores

	TUG		TM		Chronometry Ability
	T_{real}	T_{imag}	T_{real}	T_{imag}	
Young participants	8.08 ± 0.93*	6.67 ± 1.59	7.59 ± 0.83	6.83 ± 1.18	0.19 ± 0.13*
Old participants	9.33 ± 1.38*	6.64 ± 2.29	7.94 ± 0.84	7.50 ± 2.02	0.33 ± 0.14*

Notes: T_{imag} = imagined performance time; *T*

Table 3. Mean ± *SD* Imagery Times in Seconds

Task	MI		VI	
Condition	Easy	Difficult	Easy	Difficult
Young participants	8.7 ± 2.4	10.5 ± 3.2	8.8 ± 3.1	9.6 ± 3.4
Old participants	9.0 ± 3.0	10.9 ± 3.8	8.9 ± 3.7	10.6 ±

Table 4. Mean ± *SD* EMG Values for the Motor Imagery and Visual Imagery Normalized for the Control Condition

	MI	VI
Young participants	1.05 ± 0.30	0.99 ± 0.28
Old participants	1.05 ± 0.22	1.10 ± 0.16

Notes: MI = motor imagery; VI = visual imagery.

elderly participants. When we compared groups for the contrast MI > VI, using the same threshold as for the contrast MI > C, we did not find any stronger activation in elderly participants.

Correlation of activation with Stroop task.—For the elderly participants, we investigated whether there were any regions that showed a correlation between activation during imagery of gait and behavioral performance on the Stroop test (interference condition). We found a single cluster in the right primary motor cortex (BA4), where activity was tightly and positively correlated with performance on the Stroop (Figure 3 and Supplementary Table 2), indicating that the better executive functioning, the stronger the recruitment of the right primary motor area during MI.

Task difficulty (MID > MIE).—To investigate differential activation for precise control of gait, we looked at the effect of path surface during imagine walking (ie, task difficulty). In the elderly group, we found differential activation for difficult paths (MID > MIE) in bilateral hippocampus, left primary motor cortex (BA4), right insula, left middle and inferior temporal gyrus, and bilateral occipital cortex. For the same contrast, the young participants activated right putamen, bilateral superior temporal gyrus, and bilateral occipital cortex. When we compared the two groups directly, we found stronger activation in the elderly participants in the left hippocampus (Figure 4 and Supplementary Table 3). There were no areas with stronger activation in the young compared with the elderly participants.

Discussion

In this study, we explored the effects of aging on the neural substrate of gait control, using a MI paradigm. We have identified a network of activation in young participants during MI of gait (MI > C), comprising bilateral primary motor cortex and SMA, right prefrontal cortex and cerebellum, which is highly consistent with previous neuroimaging studies on gait imagery (22,26). Elderly participants recruited a network that was similar to that recruited by young participants, but with some critical differences, discussed later.

As predicted, the elderly participants exhibited significantly greater activation than the young participants during MI in two prefrontal regions (left BA10 and right BA11) and the right SMA. The given instruction focusing on the kinesthetic modality of MI could contribute to these results. Indeed, Guillot and coworkers (27) showed that the kinesthetic modality of MI was associated with more activity in motor-associated brain regions. Remarkably, the elderly participants also showed a correlation between activation during imagery of gait and performance on the Stroop test in the right primary motor cortex (BA4). Additionally, they showed stronger activation in some subcortical structures, in particular the substantia nigra and putamen. In the only previous study assessing the effect of aging on the human supraspinal locomotor and postural control by fMRI, although the authors did not assess the cognitive function of their elderly participants, a prominent activation was also observed in the SMA (26). The correlation between activation during imagery of gait and performance on the Stroop test in the right primary motor cortex that we found reinforces the notion of a strong link between executive function and gait.

The frontal lobes are highly susceptible to age-associated changes, including disruption of frontostriatal circuits by diffuse white matter changes, gray matter atrophy (28), and reduction of dopamine activity in the frontal cortex (29). Interestingly, with regard to the greater activation in the orbitofrontal cortex in the elderly participants, previous studies indicate that elderly patients with freezing of gait present a specific hypometabolism in these orbitofrontal regions (30). These metabolic and morphological changes may contribute to deficits in executive functioning as commonly seen in the elderly participants (28,29).

Another main result of this study was a greater activation in the left hippocampus in elderly participants relative to young participants, specifically for the MID > MIE contrast that probed activations associated with the higher order, more precise control of gait. The hippocampus and adjacent regions are well known to be involved in age-related changes in memory and spatial navigation but have also been implicated in gait. In a positron emission tomography study on gait, Malouin and coworkers (23) have shown the involvement of a significant recruitment of the left parahippocampal region during walking. The specific role of the hippocampus/medial temporal lobe in gait may therefore be related to topographical memory (31) and mental navigation (32). Animal models also suggest that the hippocampal formation provides voluntary motor systems with continually updated feedback on environmental conditions (33). Previous studies on anesthetized rats revealed a strong interaction between the hippocampus and the pedoculopontine

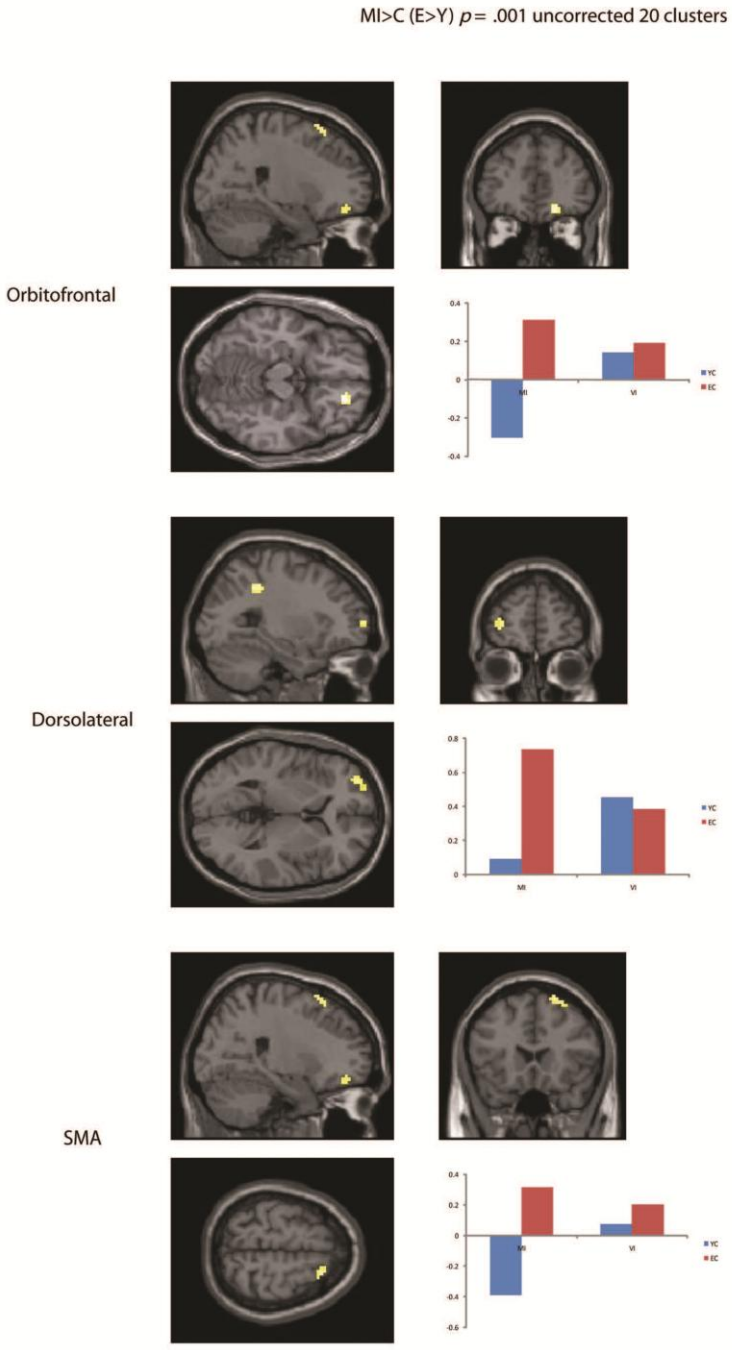
MI>C (E>Y) p = .001 uncorrected 20 clusters
Orbitofrontal
Dorsolateral
SMA
YC
EC

Figure 2.

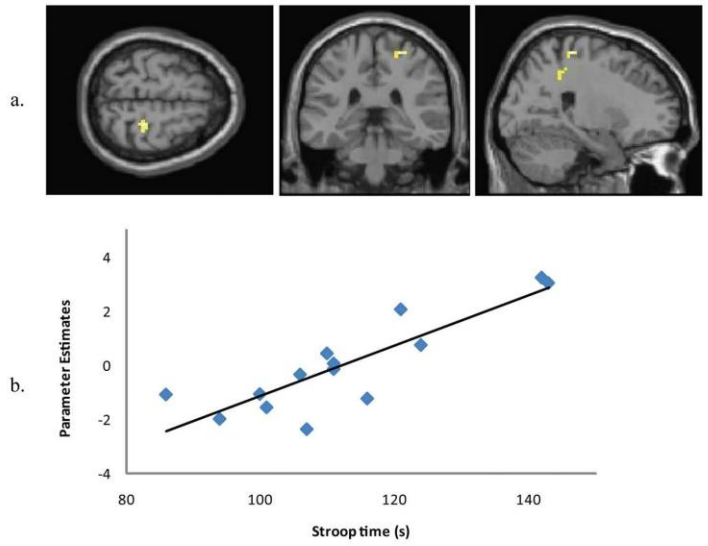

Figure 3. Area that shows a significant positive correlation between activity during motor imagery (a) and performance on the Stroop test (b).

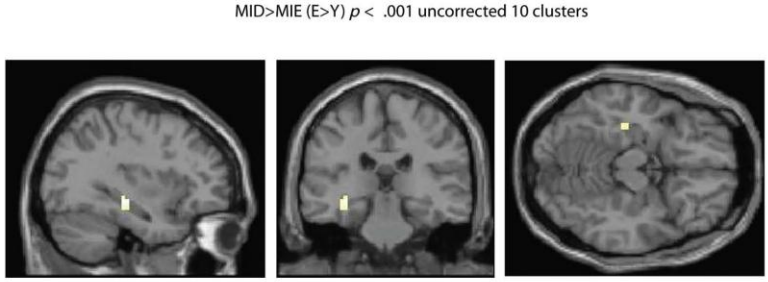

Figure 4.

nucleus mediated by cholinergic input (34). One speculative hypothesis is that the cholinergic pathway reduction due to aging (7) may have contributed to this increased activation in the hippocampus in the elderly participants.

These effects of aging on brain activation during cognitive tasks could be explained by the compensation hypothesis, which holds that aging is associated with a decline in brain function and performance, inducing hyperactivation of specific brain regions as a compensatory mechanism (35). The dedifferentiation hypothesis, according to which older adults tend to present a nonselective recruitment of brain regions relative to young adults (36), could be another explanation. The greater activation in the right SMA (BA6), the right orbitofrontal cortex (BA11), the left dorsolateral frontal cortex (BA10), and the left hippocampus observed in old adults reflects a difficulty in recruiting specialized neural mechanisms (37). Perhaps associated with this inability of selective task-associated cerebral recruitment, the elderly participants may have used different strategies to perform the task. Our behavioral data indicate that the young participants showed a greater modulation of imagination time by task difficulty during the MI task than during the VI task. In contrast, the elderly participants showed an equal modulation by type of path for both tasks. Performance on our task could be regarded as worse in elderly participants than in young participants, given that they fail to show an interaction between task and difficulty. Moreover, like previously observed (38), the motor CA of our elderly participants was worse than that of the young participants, as evidenced by a larger discrepancy between performed and imagined times

on the two mental chronometry tests. Finally, the increased left hippocampal activation seen for the MID > MIE contrast in the elderly participants relative to young participants suggests that the navigational aspect of walking on cobble stones may have been more challenging to them than to young participants. Therefore, the additional cortical and subcortical areas recruited in older adults may constitute a compensatory mechanism in an attempt to achieve normal performance levels on the MI task, in the light of reduced imagery performance and ability.

As a study limitation, it should be noted that most of the activations were obtained with a standard strict threshold of $p < .001$ at the voxel level, with a cluster threshold of $k > 20$. This combination of threshold and cluster criteria selects reliable effects when changes in BOLD (Blood-oxygen-level depedent) have relatively weak amplitudes and imprecise onsets as for mental imagery or other purely internal (non-sensory) mental events (39). Importantly, all activations reported were selective and concerned areas well known to be involved in MI of gait. Furthermore, we found a significant correlation in the right primary motor cortex, prefrontal cortex, and an independent cognitive measure (Stroop test). So this suggests that our effects were reliable and task related.

Conclusion

We have demonstrated that aging results in an increased activation during imagery of gait in the prefrontal cortex (specifically, in the left MFG [BA10] and right superior OFC [BA11]) and the right SMA, with additional increases in left hippocampal activation during more precise gait control. In addition, executive functioning of our elderly participants correlated with activity during MI of gait in the right primary motor cortex. These findings emphasize the age-related modification of brain functioning and the important role of executive function in the control of gait in healthy human participants. Future studies should investigate how these neural circuits are modified in pathologies affecting gait control, such as primary progressive gait apraxia, and further help to guide and assess neurorehabilitation techniques.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

Funding

G.A. was supported by « la Bourse d'encouragement de la Société Suisse de Neurologie », M.v.d.M. and F.A. by a grant from the Société Académique de Genève (NAC 08-025), and P.V. by a grant from the Société Académique de Genève (Fonds Forename).

Acknowledgments

We thank Cecile Ledenrey for her contribution to the neuropsychological assessments. We are grateful to the participants for their cooperation.

Conflict of Interest

The authors report no conflicts of interest.

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39.

3.3 The role of prefrontal cortex during postural control in Parkinsonian syndromes: a functional near-infrared spectroscopy study

This paper has been published in Brain Research 2016;1633:126-138 by Jeannette R. Mahoney, Roee Holtzer, Meltem Izzetoglu, Vance Zemon, Joe Verghese and Gilles Allali.

Patients with parkinsonian syndromes and older adults with mild parkinsonian signs present disturbed gait control that is associated with adverse clinical outcomes, such as falls or disability. The study aims to compare the neural substrate involved in postural control in healthy older adults, patients with mild parkinsonian signs and patients with parkinsonian syndrome. We used the functional near-infrared spectroscopy (fNIRS) to investigate the online prefrontal activation during a postural task. This study showed that patients with parkinsonian syndrome need to increase their prefrontal oxygenation to maintain the postural task. This study highlights the compensatory role of the prefrontal cortex in patients with parkinsonian syndrome.

BRAIN RESEARCH 1633 (2016) 126–138

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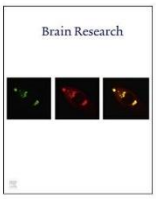

Research report

The role of prefrontal cortex during postural control in Parkinsonian syndromes a functional near-infrared spectroscopy study

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ARTICLE INFO

Article history:
Accepted 30 October 2015
Available online 6 November 2015

Keywords:
Parkinsonian syndromes
Prefrontal cortex
Aging
Postural control
Functional near infrared spectroscopy

ABSTRACT

Postural instability represents a main source of disability in Parkinsonian syndromes and its pathophysiology is poorly understood. Indirect probes (i.e., mental imagery) of brain involvement support the role of prefrontal cortex as a key cortical region for postural control in older adults with and without Parkinsonian syndromes. Using functional near infrared spectroscopy (fNIRs) as a direct online cortical probe, this study aimed to compare neural activation patterns in prefrontal cortex, postural stability, and their respective interactions, in (1) patients with Parkinsonian syndromes; (2) those with mild parkinsonian signs; (3) and healthy older adults. Among 269 non-demented older adults (76.41±6.70 years, 56% women), 26 individuals presented with Parkinsonian syndromes (Unified Parkinson's disease rating scale (UPDRS): 11.08±3.60), 117 had mild parkinsonian signs (UPDRS: 3.21±2.49), and 126 individuals were included as a healthy control group. Participants were asked to stand upright and count silently for ten seconds while changes in oxygenated hemoglobin levels over prefrontal cortex were measured using fNIRs. We simultaneously evaluated postural stability with center of pressure velocity data recorded on an instrumented walkway. Compared to healthy controls and patients with mild parkinsonian signs, patients with Parkinsonian syndromes demonstrated significantly higher prefrontal oxygenation levels to maintain postural stability. The pattern of brain activation and postural control of participants with mild parkinsonian signs were similar to that of normal controls. These findings highlight the online role of the prefrontal cortex in postural control in patients with Parkinsonian syndromes and afford the opportunity to improve therapeutic options for postural instability.

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http://dx.doi.org/10.1016/j.brainres.2015.10.053
0006-8993/

1. Introduction

Postural instability represents a main limitation of older adults with Parkinson's disease (PD; Post et al., 2007; Muslimovic et al., 2008) as it contributes to falls (Kerr et al., 2010; Johnson et al., 2013), gait disorders (Chastan et al., 2009), disability (Muslimovic et al., 2008) and death (Auyeung et al., 2012; Cilia et al., 2014). Postural control mechanisms depend on sensory information received from the visual, proprioceptive, and vestibular systems as well as appropriate motor outputs. As postural conditions become more challenging (e.g., standing on a narrow support, unipedal stance, or even dual-tasking), regions including the prefrontal cortex (PFC; Mihara et al., 2008) and parietal lobes (Mihara et al., 2008; Huang and Hwang, 2013) become progressively more involved in its monitoring. An increase in cortical involvement has been demonstrated in normal aging (Zwergal et al., 2012; Sullivan et al., 2009), especially during challenging conditions (Goble et al., 2011). However, the conclusions of these studies demonstrating the cortical involvement on postural control have been limited by small sample sizes and do not include patients with Parkinsonian syndromes (PS). Studying the online neural correlates of postural control represents a technical challenge. Most previous studies examining postural control have employed indirect methods such as mental imagery of standing (Zwergal et al., 2012; Malouin et al., 2003; Jahn et al., 2004), virtual reality (Basso Moro et al., 2014; Ferrari et al., 2014) or even simulated active balance during supine position (Karim et al., 2014) instead of measuring activity online during actual standing. Findings from these studies employing indirect methods to assess cortical postural control suggest that the prefrontal cortex plays a critical role in healthy younger adults (Basso Moro et al., 2014; Ferrari et al., 2014) and in patients with neurological conditions like stroke (Fujimoto et al., 2014). However, in order to better understand the mechanism of postural instability in healthy older adults and in patients with PS, direct online cortical measurement in the prefrontal regions during upright standing is needed. Functional near-infrared spectroscopy (fNIRs) is a non-invasive neuroimaging technique that enables the direct measurement of cerebral activity in the prefrontal regions during standing, and helps circumvent the limitations of other neuroimaging methods to measure or assess prefrontal activity directly during task performance (Basso Moro et al., 2014; Fujimoto et al., 2014; Karim et al., 2013a).

The current study addressed the knowledge gap regarding online prefrontal neural correlates of postural control in PS. Studying PS patients not only has clinical relevance as it a common neurodegenerative condition in aging but also contrasting this disease group with individuals with normal aging and mild parkinsonian signs provides insights to aging effects on prefrontal postural control mechanisms. Oxygenated hemoglobin activation in the prefrontal areas was measured directly using fNIRs during upright standing in non-demented older adults. Specifically, we compared brain activation patterns in the PFC during postural performance, in patients with PS, to participants with mild parkinsonian signs (MPS) – transitional state between normal aging and Parkinsonian syndromes – and to healthy older participants without any MPS. Based on the role of the PFC in postural control in neurological conditions (Fujimoto et al., 2014; Mihara et al., 2012) and the neural inefficiency hypothesis which posits that greater brain activation is required to perform equal or worse behavioral performance (Holtzer et al., 2009), we hypothesize that patients with PS would demonstrate greater prefrontal activation and worse postural stability throughout the postural control task, compared to both healthy older adults and individuals with MPS.

2. Results

2.1. Demographics

A total of 269 non-demented adults age 65 and older were included in the current study (mean age: 76.41±6.70 years, 56% women). All participants were considered to be non-demented as determined by their AD8 scores (Galvin et al., 2005) and consensus diagnostic case conference (Holtzer et al., 2008). Additionally, participants were relatively healthy and cognitively intact as determined by their overall global health status score (GHS; 1.15±1.11) and overall cognitive functioning standard score on the Repeatable Battery for Assessment of Neuropsychological Status (RBANS; 92±12). All participants were categorized into one of three groups: MPS, PS, or healthy control (i.e., normal). As in our previous studies (Allali et al., 2014a; Mahoney et al., 2014), MPS were systematically ascertained in participants by the study clinician using the motor evaluation portion (Part III) of the original version of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn and Elton, 1987). MPS diagnosis was based on the presence of any one of the four cardinal features (bradykinesia, rigidity, rest tremor, or postural instability and gait disturbance, regardless of its severity (see Section 4 for specific details). For a diagnosis of PS, we applied the United Kingdom Parkinson's disease society brain bank clinical diagnostic criteria (Hughes et al., 1992) where presence of moderate to severe bradykinesia was required in addition to the presence of one additional cardinal feature. All other participants without presence of any cardinal features constituted the normal group. Of the 269 participants, 126 were considered normal, 117 presented with MPS, and 26 were diagnosed with PS.

Baseline characteristics of the sample are provided in Table 1 for each of the three diagnostic groups. Bradykinesia and rigidity were present in all PS patients, whereas PIGD was present in 50% and tremor in 15%. Within the MPS group, rigidity was the most common MPS domain (37%), followed by bradykinesia (23%), PIGD (19%), and tremor (6%). Participants in the control group were significantly younger than those in both the MPS and PS groups; as well, individuals in the MPS group were significantly younger than those in the PS group. Compared to healthy normal adults, those with MPS had significantly lower performance on the RBANS and those with PS endorsed significantly more symptoms of depression.

Oxygenated hemoglobin (HbO_2) data recorded from 16 fNIRs channels were used to characterize changes in

Table 1 – Sample characteristics.

		Normal (n=126)	MPS (n=117)	PS (n=26)
Demographics[#]	Age (years)[˙]	74.41 (6.12)	77.50 (6.72)	81.23 (5.93)
	Education (years)	14.44 (3.00)	14.36 (3.08)	13.81 (2.40)
	% Female	55.00	57.00	58.00
	% Caucasian	89.00	83.00	96.00
	GHS score (0–10)	0.99 (0.97)	1.26 (1.26)	1.39 (0.94)
	GDS score (0–30)[\wideha]	4.12 (3.14)	4.90 (4.04)	6.15 (3.88)
	RBANS total standard score (55–145)[¥]	93.75 (11.10)	89.82 (12.85)	91.04 (11.12)
MPS Domains[#]	Bradykinesia (% present)	0.00	31.00	100.00
	Rigidity (% present)	0.00	63.00	100.00
	Tremor (% present)	0.00	9.00	15.00
	PIGD (% present)	0.00	32.00	50.00
	MPS severity score (0–36)	0.00 (0.00)	3.21 (2.49)	11.08 (3.60)
fNIRS[#]	Mean HbO_2 value	0.03 (0.21)	0.07 (0.21)	0.05 (0.27)
Balance[#]	COP velocity (cm/s)	1.51 (3.14)	1.56 (1.92)	2.82 (7.45)

Abbreviations: MPS=mild parkinsonian signs; PS=parkinsonian syndrome; PIGD=postural instability and gait disturbances; GHS=global health score; GDS=geriatric depression scale; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; HbO_2=oxygenated hemoglobin averaged across 16 channels and 8 second recording time; COP=Center of pressure average across 8 second recording time.

[#] Mean (SD) unless otherwise noted.

[˙] Group differences in demographics: significant difference at the $p<0.01$ for all group comparisons (normal vs. MPS, normal vs. PS, & MPS vs. PS).

[\wideha] Group differences in demographics: significant difference at the $p<0.01$ for normal vs. PS.

[¥] Group differences in demographics: significant differences at the $p<0.01$ for normal vs. MPS.

activation over prefrontal cortex during the postural control task. Here, relative changes in the concentrations of HbO_2 were obtained by comparing the measurements made during the first two seconds to those made during the remaining eight seconds of our ten-second postural control task. Sampling interval of fNIRs activity was set at 500 ms, which afforded 16 time points during the eight-second task. In terms of overall HbO_2 values averaged across all time points and channels, healthy controls demonstrated significantly less oxygenated hemoglobin levels compared to both individuals with MPS ($p=0.04$) and patients with PS ($p<0.001$).

Postural control assessments were conducted on an instrumented walkway that utilizes ProtoKinetics Movement Analysis Software (PKMAS; Zenometrics, LLC; Peekskill, NY) and the center of pressure (COP) velocity (cm/s) was used a proxy for postural control and sway while participants were ask to stand and count silently in numerical order. In terms of postural stability (i.e., overall COP velocity (cm/s; averaged across all time points), healthy controls and individuals with MPS demonstrated similar levels of sway ($p=0.81$) that were significantly less than patients with PS ($p<0.001$).

2.2. *Linear mixed effects model results*

Three separate linear mixed effects models (LMEMs), each adjusted for age, gender, and ethnicity were used to examine the main effects of group, time and HbO_2, as well as their second- and third-order interaction effects. All LMEMs employed a first-order autoregressive covariance type and a random intercept that was included to allow for variability across individuals (i.e., subject was treated as a random effect). The advantage of the linear mixed effects model is that the heterogeneity and correlation of repeated measures under different conditions are taken into account (Laird and Ware, 1982). A preliminary LMEM model to test a main effect of lateralization reports no main effect of HbO_2 by hemisphere or interaction with the group status.

Our first LMEM aimed to test the hypothesis that patients with PS would demonstrate greater prefrontal activation throughout the postural control task compared to healthy older adults. This model examined the effect of group status (MPS, PS, and normal), time (8 s), and their interaction on averaged HbO_2 activation levels during the postural control task. Results indicated no main effect of group status ($p=0.17$) on overall level of prefrontal activation; however there was a significant overall effect of time ($p<0.01$). Further, there were significant differences in prefrontal activation levels between controls and individuals with MPS during the second half of the task (i.e., seconds 5.5–8) relative to the prefrontal activation at 0.5 s (Table 2). Similarly, there were significant differences in prefrontal activation levels between controls and patients with PS from seconds 6 to 8 relative to the prefrontal activation at 0.5 s. In fact, the differences in prefrontal activation between controls and patients with PS ($\beta=0.08$) was nearly twice as large as the differences in prefrontal activation between controls and participants with MPS ($\beta=0.04$). These specific effects reveal that compared to controls, individuals with MPS, and more specifically PS demonstrate a need for significantly greater HbO_2 activation (relative HbO_2 activation at the first time point) in prefrontal regions in order to successfully complete this postural control task (see Fig. 1 – Panel A).

Our second LMEM model tested the hypothesis that patients with PS would demonstrate greater postural instability

Table 2 – Linear mixed effect model of mean HbO_2 with the following predictors: (1) group; (2) time; and (3) group × time[a].

	Parameter	Estimate	Std. error	df	t	Sig.	95% confidence interval	
							Lower bound	Upper bound
(1)	Control vs. MPS	0.01	0.02	795.69	0.24	0.81	−0.04	0.05
	Control vs. PS	−0.02	0.04	784.09	−0.55	0.58	−0.10	0.06
(2)	Time: 0.5 vs. 1.0	0.00	0.02	2260.27	0.08	0.94	−0.04	0.04
	Time: 0.5 vs. 1.5	0.00	0.02	2409.06	0.15	0.88	−0.03	0.04
	Time: 0.5 vs. 2.0	0.00	0.02	2573.27	0.23	0.82	−0.03	0.04
	Time: 0.5 vs. 2.5	0.01	0.02	2753.28	0.32	0.75	−0.03	0.04
	Time: 0.5 vs. 3.0	0.01	0.02	2948.54	0.43	0.67	−0.03	0.04
	Time: 0.5 vs. 3.5	0.01	0.02	3157.09	0.56	0.57	−0.02	0.04
	Time: 0.5 vs. 4.0	0.01	0.02	3374.89	0.75	0.46	−0.02	0.05
	Time: 0.5 vs. 4.5	0.02	0.02	3594.97	0.99	0.32	−0.02	0.05
	Time: 0.5 vs. 5.0	0.02	0.02	3806.79	1.32	0.19	−0.01	0.05
	Time: 0.5 vs. 5.5	0.03	0.01	3995.93	1.77	0.08	0.00	0.05
	Time: 0.5 vs. 6.0	**0.03**	**0.01**	**4144.73**	**2.36**	**0.02**	**0.01**	**0.06**
	Time: 0.5 vs. 6.5	**0.04**	**0.01**	**4234.39**	**3.18**	**<0.01**	**0.02**	**0.06**
	Time: 0.5 vs. 7.0	**0.05**	**0.01**	**4248.54**	**4.35**	**<0.01**	**0.03**	**0.07**
	Time: 0.5 vs. 7.5	**0.06**	**0.01**	**4177.48**	**6.21**	**<0.01**	**0.04**	**0.07**
	Time: 0.5 vs. 8.0	**0.07**	**0.01**	**4021.58**	**10.07**	**<0.01**	**0.05**	**0.08**
(3)	[Time: 0.5 vs. 1.0]*[Control vs. MPS]	0.00	0.03	2260.27	0.17	0.86	−0.05	0.06
	[Time: 0.5 vs. 1.5]*[Control vs. MPS]	0.01	0.03	2409.06	0.36	0.72	−0.04	0.06
	[Time: 0.5 vs. 2.0]*[Control vs. MPS]	0.01	0.03	2573.27	0.55	0.58	−0.04	0.07
	[Time: 0.5 vs. 2.5]*[Control vs. MPS]	0.02	0.03	2753.28	0.75	0.45	−0.03	0.07
	[Time: 0.5 vs. 3.0]*[Control vs. MPS]	0.02	0.03	2948.54	0.95	0.34	−0.03	0.07
	[Time: 0.5 vs. 3.5]*[Control vs. MPS]	0.03	0.02	3157.09	1.16	0.25	−0.02	0.08
	[Time: 0.5 vs. 4.0]*[Control vs. MPS]	0.03	0.02	3374.89	1.36	0.17	−0.01	0.08
	[Time: 0.5 vs. 4.5]*[Control vs. MPS]	0.04	0.02	3594.97	1.57	0.12	−0.01	0.08
	[Time: 0.5 vs. 5.0]*[Control vs. MPS]	0.04	0.02	3806.79	1.78	0.07	0.00	0.08
	[Time: 0.5 vs. 5.5]*[Control vs. MPS]	**0.04**	**0.02**	**3995.93**	**2.00**	**0.04**	**0.00**	**0.08**
	[Time: 0.5 vs. 6.0]*[Control vs. MPS]	**0.04**	**0.02**	**4144.73**	**2.24**	**0.03**	**0.01**	**0.08**
	[Time: 0.5 vs. 6.5]*[Control vs. MPS]	**0.04**	**0.02**	**4234.39**	**2.51**	**0.01**	**0.01**	**0.08**
	[Time: 0.5 vs. 7.0]*[Control vs. MPS]	**0.04**	**0.02**	**4248.54**	**2.86**	**<0.01**	**0.01**	**0.08**
	[Time: 0.5 vs. 7.5]*[Control vs. MPS]	**0.04**	**0.01**	**4177.48**	**3.39**	**<0.01**	**0.02**	**0.07**
	[Time: 0.5 vs. 8.0]*[Control vs. MPS]	**0.04**	**0.01**	**4021.58**	**4.57**	**<0.01**	**0.02**	**0.06**
	[Time: 0.5 vs. 1.0]*[Control vs. PS]	0.00	0.05	2260.27	−0.02	0.98	−0.09	0.09
	[Time: 0.5 vs. 1.5]*[Control vs. PS]	0.00	0.05	2409.06	−0.01	0.99	−0.09	0.09
	[Time: 0.5 vs. 2.0]*[Control vs. PS]	0.00	0.04	2573.27	0.05	0.96	−0.09	0.09
	[Time: 0.5 vs. 2.5]*[Control vs. PS]	0.01	0.04	2753.28	0.16	0.88	−0.08	0.09
	[Time: 0.5 vs. 3.0]*[Control vs. PS]	0.01	0.04	2948.54	0.31	0.76	−0.07	0.10
	[Time: 0.5 vs. 3.5]*[Control vs. PS]	0.02	0.04	3157.09	0.51	0.61	−0.06	0.10
	[Time: 0.5 vs. 4.0]*[Control vs. PS]	0.03	0.04	3374.89	0.75	0.45	−0.05	0.11
	[Time: 0.5 vs. 4.5]*[Control vs. PS]	0.04	0.04	3594.97	1.03	0.30	−0.04	0.12
	[Time: 0.5 vs. 5.0]*[Control vs. PS]	0.05	0.04	3806.79	1.35	0.18	−0.02	0.12
	[Time: 0.5 vs. 5.5]*[Control vs. PS]	0.06	0.04	3995.93	1.70	0.09	−0.01	0.13
	[Time: 0.5 vs. 6.0]*[Control vs. PS]	**0.07**	**0.03**	**4144.73**	**2.07**	**0.04**	**0.00**	**0.13**
	[Time: 0.5 vs. 6.5]*[Control vs. PS]	**0.07**	**0.03**	**4234.39**	**2.50**	**0.01**	**0.02**	**0.13**
	[Time: 0.5 vs. 7.0]*[Control vs. PS]	**0.08**	**0.03**	**4248.54**	**2.99**	**<0.01**	**0.03**	**0.13**
	[Time: 0.5 vs. 7.5]*[Control vs. PS]	**0.08**	**0.02**	**4177.48**	**3.69**	**<0.01**	**0.04**	**0.12**
	[Time: 0.5 vs. 8.0]*[Control vs. PS]	**0.08**	**0.02**	**4021.58**	**5.08**	**<0.01**	**0.05**	**0.11**

[a] Adjusted for age, gender, and ethnicity.

throughout the task compared to healthy older adults. This model examined the effect of group status (MPS, PS, and normal), time (8 s), and their interaction on COP velocity. Results indicated a main effect of group status on overall COP velocity ($p<0.01$), but no significant effect of time ($p=0.44$). The main effect of group status was primarily driven by the difference in overall COP velocity between controls and patients with PS ($p<0.01$; Table 3). The overall group status × time interaction was not significant ($p=0.68$), but there were significant differences between controls and patients with PS at 5.5 s. This effect reveals that patients with PS demonstrated significantly more postural instability (increased COP velocity specifically at the beginning of the task) during the postural control task compared to controls (see Fig. 1 – Panel B),

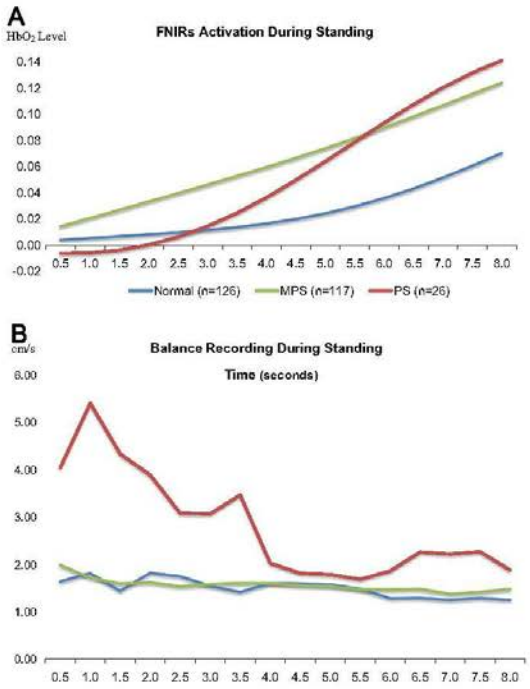

Fig. 1 – (A) Averaged oxygenated hemoglobin (HbO_2) levels across 16 consecutive seconds for normal controls (blue trace), individuals with MPS (green trace), and individuals with PS (red trace). (B) Averaged COP velocity across 16 consecutive seconds for normal controls (blue trace), individuals with MPS (green trace), and individuals with PS (red trace). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

relative to the first 0.5 s. There were no significant main effects or interactions between healthy controls and individuals with MPS for this analysis.

Finally, the last LMEM was designed to test the neural inefficiency hypothesis (Holtzer et al., 2009) and determine whether group status moderated the relationship between level of HbO_2 activation and postural control (Table 4). Here, in order to examine the effect of time on postural control, we compared the mean HbO_2 activation levels acquired during the first and second halves of the recording period. The actual model consisted of a three-level group (MPS, PS, and normal) and a two level time period (first 4 s vs. second 4 s). Overall, there was a main effect of group ($p=0.03$), time ($p<0.01$), and level of HbO_2 activation ($p<0.01$). The group × time × HbO_2 activation interaction was significant ($p<0.01$) and suggested that compared to patients with PS, healthy controls and individuals with MPS require less HbO_2 activation to perform similar levels of postural stability in the second half of the postural control task, compared to the first half. In terms of the two-level interactions, the time period × HbO_2 activation interaction, group × HbO_2 activation interaction, and group × time period interaction were all significant at the $p<0.01$ level; note that these interactions are explained by the above three level interaction. Taken together, these results suggest that group status does indeed moderate the relationship between PFC activation levels and postural stability performance in older adults with PS compared to healthy controls.

3. Discussion

In this study, we tested, in a large group of non-demented older adults, the hypothesis that patients with Parkinsonian syndromes require increased prefrontal activation to maintain an upright standing position in comparison to healthy older adults. The main finding demonstrated that indeed patients with PS required increased prefrontal oxygenation in comparison to both healthy older adults and individuals with MPS in order to maintain postural control. In fact, prefrontal activation between controls and patients with PS was nearly twice as large as the difference in prefrontal activation between controls and participants with MPS. By increasing their prefrontal oxygenation levels, patients with PS were able to improve their postural control (by decreasing their COP velocity) towards the latter part of the task.

3.1. *The role of prefrontal cortex in postural control*

The increased activation in the prefrontal cortex required by patients with Parkinsonian syndromes highlights the role of this region in postural control. In young and middle-aged

Table 3 – Linear mixed effect model of mean COP velocity[a] with the following predictors: (1) group; (2) time; (3) Group x time[b].

	Parameter	Estimate	Std. error	df	t	Sig.	95% confidence interval	
							Lower bound	Upper bound
1)	Control vs. MPS	0.04	0.08	1875.69	0.53	0.60	−0.12	0.20
	Control vs. PS	**0.46**	**0.14**	**1854.75**	**3.41**	**<0.01**	**0.20**	**0.73**
2)	Time: 0.5 vs. 1.0	0.04	0.08	1938.67	0.56	0.58	−0.11	0.20
	Time: 0.5 vs. 1.5	0.02	0.08	1951.40	0.26	0.80	−0.13	0.17
	Time: 0.5 vs. 2.0	−0.02	0.08	1970.08	−0.23	0.82	−0.17	0.14
	Time: 0.5 vs. 2.5	0.04	0.08	1997.40	0.50	0.61	−0.11	0.19
	Time: 0.5 vs. 3.0	0.02	0.08	2037.25	0.32	0.75	−0.13	0.18
	Time: 0.5 vs. 3.5	−0.03	0.08	2095.29	−0.35	0.73	−0.18	0.13
	Time: 0.5 vs. 4.0	−0.05	0.08	2179.71	−0.63	0.53	−0.20	0.10
	Time: 0.5 vs. 4.5	−0.08	0.08	2302.49	−1.10	0.27	−0.24	0.07
	Time: 0.5 vs. 5.0	0.01	0.08	2480.94	0.12	0.90	−0.14	0.16
	Time: 0.5 vs. 5.5	0.04	0.08	2738.86	0.50	0.62	−0.11	0.19
	Time: 0.5 vs. 6.0	−0.10	0.07	3103.44	−1.37	0.17	−0.25	0.04
	Time: 0.5 vs. 6.5	−0.08	0.07	3581.95	−1.08	0.28	−0.22	0.06
	Time: 0.5 vs. 7.0	−0.10	0.07	4075.94	−1.49	0.14	−0.23	0.03
	Time: 0.5 vs. 7.5	−0.05	0.06	4231.16	−0.76	0.45	−0.16	0.07
	Time: 0.5 vs. 8.0	−0.08	0.05	3630.88	−1.61	0.11	−0.17	0.02
3)	[Time: 0.5 vs. 1.0]*[Control vs. MPS]	−0.03	0.11	1938.67	−0.27	0.78	−0.25	0.19
	[Time: 0.5 vs. 1.5]*[Control vs. MPS]	0.02	0.11	1951.40	0.15	0.88	−0.20	0.24
	[Time: 0.5 vs. 2.0]*[Control vs. MPS]	0.09	0.11	1970.08	0.79	0.43	−0.13	0.31
	[Time: 0.5 vs. 2.5]*[Control vs. MPS]	0.01	0.11	1997.40	0.11	0.91	−0.21	0.23
	[Time: 0.5 vs. 3.0]*[Control vs. MPS]	0.08	0.11	2037.25	0.70	0.48	−0.14	0.30
	[Time: 0.5 vs. 3.5]*[Control vs. MPS]	0.12	0.11	2095.29	1.03	0.30	−0.10	0.34
	[Time: 0.5 vs. 4.0]*[Control vs. MPS]	0.13	0.11	2179.71	1.20	0.23	−0.08	0.35
	[Time: 0.5 vs. 4.5]*[Control vs. MPS]	0.10	0.11	2302.49	0.94	0.35	−0.11	0.32
	[Time: 0.5 vs. 5.0]*[Control vs. MPS]	0.05	0.11	2480.94	0.41	0.68	−0.17	0.26
	[Time: 0.5 vs. 5.5]*[Control vs. MPS]	−0.06	0.11	2738.86	−0.56	0.57	−0.28	0.15
	[Time: 0.5 vs. 6.0]*[Control vs. MPS]	0.11	0.11	3103.44	1.04	0.30	−0.10	0.32
	[Time: 0.5 vs. 6.5]*[Control vs. MPS]	0.09	0.10	3581.95	0.90	0.37	−0.11	0.30
	[Time: 0.5 vs. 7.0]*[Control vs. MPS]	0.06	0.10	4075.94	0.61	0.54	−0.13	0.25
	[Time: 0.5 vs. 7.5]*[Control vs. MPS]	0.02	0.09	4231.16	0.27	0.79	−0.15	0.19
	[Time: 0.5 vs. 8.0]*[Control vs. MPS]	0.07	0.07	3630.88	0.98	0.33	−0.07	0.20
	[Time: 0.5 vs. 1.0]*[Control vs. PS]	−0.19	0.19	1938.67	−0.99	0.32	−0.56	0.18
	[Time: 0.5 vs. 1.5]*[Control vs. PS]	−0.20	0.19	1951.40	−1.06	0.29	−0.57	0.17
	[Time: 0.5 vs. 2.0]*[Control vs. PS]	−0.17	0.19	1970.08	−0.90	0.37	−0.54	0.20
	[Time: 0.5 vs. 2.5]*[Control vs. PS]	−0.15	0.19	1997.40	−0.82	0.41	−0.52	0.22
	[Time: 0.5 vs. 3.0]*[Control vs. PS]	−0.09	0.19	2037.25	−0.49	0.63	−0.46	0.28
	[Time: 0.5 vs. 3.5]*[Control vs. PS]	−0.10	0.19	2095.29	−0.53	0.60	−0.47	0.27
	[Time: 0.5 vs. 4.0]*[Control vs. PS]	−0.23	0.19	2179.71	−1.21	0.23	−0.59	0.14
	[Time: 0.5 vs. 4.5]*[Control vs. PS]	−0.19	0.19	2302.49	−1.03	0.30	−0.56	0.17
	[Time: 0.5 vs. 5.0]*[Control vs. PS]	−0.25	0.19	2480.94	−1.35	0.18	−0.61	0.11
	[Time: 0.5 vs. 5.5]*[Control vs. PS]	**−0.40**	**0.18**	**2738.86**	**−2.20**	**0.03**	**−0.76**	**−0.04**
	[Time: 0.5 vs. 6.0]*[Control vs. PS]	−0.11	0.18	3103.44	−0.60	0.55	−0.46	0.24
	[Time: 0.5 vs. 6.5]*[Control vs. PS]	−0.13	0.17	3581.95	−0.74	0.46	−0.47	0.21
	[Time: 0.5 vs. 7.0]*[Control vs. PS]	−0.03	0.16	4075.94	−0.17	0.86	−0.35	0.29
	[Time: 0.5 vs. 7.5]*[Control vs. PS]	−0.16	0.15	4231.16	−1.09	0.28	−0.45	0.13
	[Time: 0.5 vs. 8.0]*[Control vs. PS]	−0.15	0.11	3630.88	−1.28	0.20	−0.37	0.08

[a] Natural log (COP velocity).
[b] Adjusted for age, gender, and ethnicity.

healthy adults, the cerebellum, especially the vermis, but also the visual associative cortex are mainly activated during an upright standing task (Ouchi et al., 2001, 1999). However, mental imagery studies of locomotion (i.e. gait) in aging have demonstrated the role of the prefrontal cortex using different neuroimaging methods (Holtzer et al., 2014a) like functional MRI (Allali et al., 2014b; Blumen et al., 2014) or PET-Scan (la Fougere et al., 2010). However, few studies address this issue in older adults with PS using direct online assessments of prefrontal brain regions (Maillet et al., 2014; Thevathasan et al., 2012). In the PS population, extracortical regions, like the pedunculopontine nucleus (Thevathasan et al., 2012) or

Table 4 – Linear mixed effect model of mean COP velocity[a] with the following predictors: (1) group; (2) time period; (3) HbO_2; (4) time × group; (5) time × HbO_2; (6) HbO_2 × group; and (7) HbO_2 × time × group[b].

	Parameter	Estimate	Std. error	df	t	Sig.	95% confidence interval	
							Lower bound	Upper bound
(1)	PS vs. MPS	−0.29	0.08	317.29	−3.87	<0.01	−0.44	−0.14
	PS vs. control	−0.39	0.08	297.47	−5.18	<0.01	−0.54	−0.24
(2)	[Time period 1 vs. 2][c]	−0.46	0.08	161.88	−5.79	<0.01	−0.62	−0.31
(3)	HbO_2	−0.77	0.17	288.18	−4.48	<0.01	−1.11	−0.43
(4)	[Time period 1 vs. 2]*[PS vs. MPS]	0.35	0.09	159.56	4.02	<0.01	0.18	0.53
	[Time period 1 vs. 2]*[PS vs. control]	0.44	0.09	156.86	5.08	<0.01	0.27	0.61
(5)	[Time period 1 vs. 2]*[HbO_2]	1.62	0.19	309.81	8.48	<0.01	1.24	1.99
(6)	[HbO_2]*[PS vs. MPS]	0.88	0.20	288.55	4.32	<0.01	0.48	1.28
	[HbO_2]*[PS vs. control]	0.86	0.20	288.27	4.25	<0.01	0.46	1.25
(7)	[HbO_2]*[time period 1 vs. 2] * [PS vs. MPS]	−1.10	0.23	298.26	−4.86	<0.01	−1.55	−0.66
	[HbO_2]*[time period 1 vs. 2]*[PS vs. control]	−1.07	0.22	306.31	−4.80	<0.01	−1.51	−0.63

[a] Natural log (COP velocity).
[b] Adjusted for age, gender, and ethnicity.
[c] Time period 1=average of COP velocity over first 8 time points (first half); Time period 2=average of COP velocity over the second 8 time points (second half).

cerebellar regions (Maillet et al., 2014) appear to play a key role in the cerebral networks involved in the control of gait. In terms of postural control, previous studies (Goble et al., 2011; Karim et al., 2013b) showed that older adults recruit cerebral networks involving temporal and prefrontal regions, as well as the subcortical areas. Interestingly, in PD, decreased cholinergic innervations in the pedunculopontine nucleus and in the thalamus, but not in the cortical regions, affect postural control (Muller et al., 2013). The close connection between the pedunculopontine nucleus and the thalamus with the prefrontal cortex (Maillet et al., 2012) could contribute to the explanation of the increased oxygenation of the prefrontal cortex to maintain postural control in patients with PS. Neuropathological studies have reported that older adults with parkinsonian signs not due to PD have specific neuronal loss in the substantia nigra (Ross et al., 2004; Buchman et al., 2012), that projects via the striatum and the thalamus to the prefrontal cortex (Obeso et al., 2008; Krack et al., 2010). The nigral neuronal loss that consecutively affects the cortico-basal ganglia-thalamo-cortical circuits, including the motor circuit, could explain the compensatory need for increased prefrontal activation in patients with PS in order to optimize their postural control. However, in contrast to participants with MPS who were able to maintain a similar postural performance relative to healthy older adults, as suggested by the neural inefficiency model (Holtzer et al., 2009), patients with PS fail to maintain the same postural performance as the healthy controls, although they increased prefrontal activation during the postural task. Interestingly, in regard to the similar postural performance between MPS and healthy older participants, a previous report showed that MPS can be reversible in 38% at a follow-up of 1 year (Mahoney et al., 2014).

Another indirect illustration of the suspected role of the prefrontal cortex in postural control follows the effect of deep brain stimulation on postural control in PD: as subthalamic nucleus and internal globus pallidus stimulations did not improve posture (St. George et al., 2014). Therefore, one could argue that these targets are too deep to affect postural control controlled by cortical regions, especially the prefrontal cortex, as suggested in the present study. Taken together, findings from neuropathological studies in older adults as well as clinical studies in PD could explain the observed role of increased cortical activation in the PFC during a postural control task for individuals with PS.

3.2. *Postural instability in Parkinsonian syndromes*

Although participants with MPS did not show any postural instability during the course of the task, patients with PS were unable to maintain similar postural control to the healthy older participants at the beginning of the task. Poor postural control was previously associated with MPS in older adults (Louis et al., 2006). Unlike the objective quantitative measure of postural control in the present study, this previous report assessed balance by subjective complaints and the use of an assisted device, which could explain the contradictory findings (Louis et al., 2006). Different factors from disease processes to compensatory strategies contribute to postural instability in older adults with PS. In addition to the cholinergic system (Muller et al., 2013), defective adrenergic innervations (Grimbergen et al., 2009) were also suspected to contribute to postural control in neurodegenerative diseases like PD. Other external factors, like cerebrovascular risk factors, especially diabetes (Kotagal et al., 2013), or comorbidities (Williams-Gray et al., 2013) contribute to postural instability in patients with Parkinsonian syndromes. Independent of these factors, the involvement of the frontal lobe on postural control in PD patients has been suggested in many reports (Wang et al., 2012; Jacobs, 2014); however, the current study highlights for the first time, to our knowledge, the online role of prefrontal regions during actual standing in patients with Parkinsonian syndromes.

3.3. Strengths and limitations

Measuring online prefrontal activation using fNIRs during actual standing in a large cohort of non-demented older adults constitutes the main strength of this study. Furthermore, including a transitional state-participants with MPS – adds to the understanding of the involvement of the prefrontal lobe in postural control from the spectrum from normal aging to PS. Co-registration of fNIRs with a standard morphological neuroimaging method would permit the identification of exact brain regions involved in postural control. Future studies should include a longer period of postural control task in order to confirm the present findings. To prevent participants from daydreaming during the postural task, we used a very simple counting task during the recording of the postural control task. However, we cannot exclude the hypothetical contribution (even minimal) of the prefrontal activation by the counting task. Since a validated scale to quantify mild parkinsonian signs in aging does not exist, we used the UPDRS specifically designed for patients with Parkinson's disease and not for older adults in general, as performed in previous studies (Allali et al., 2014a; Louis and Bennett, 2007). Finally, a future longitudinal study, including yearly clinical follow-up, would enable us to make causal inferences and assess if healthy participants with greater prefrontal activation during the postural task will develop Parkinsonian syndromes. Such a longitudinal study could also include a specific assessment of the dopamine responsiveness of participants with Parkinsonian syndrome in regard to the prefrontal activation.

3.4. Conclusions

In conclusion, this study revealed that non-demented older adults with Parkinsonian syndromes require increased prefrontal activation in comparison to healthy older adults and individuals with MPS in order to maintain postural control. These findings afford the opportunity to refine therapeutic options for postural instability in patients with PS.

4. Experimental procedure

4.1. Participants

A total of 405 non-demented adults age 65 and older, recruited in an ongoing cohort study entitled Central Control of Mobility in Aging (CCMA) from June 2011 to January 2014 were included in the current study. The CCMA study aims to determine the cognitive and brain predictors of mobility decline and disability in aging. The study procedures have been previously described (Holtzer et al., 2014b, 2014c, 2015). Briefly, participants enrolled in the CCMA study are non-demented older adults residing in lower Westchester County who have successfully passed a structured telephone-screening interview where verbal assent, medical history, mobility function (Baker et al., 2003) are assessed and dementia is ruled out (Galvin et al., 2005). Exclusion criteria include significant loss of vision and/or hearing, inability to ambulate independently, current or history of neurological or psychiatric disorders, participants on dopaminergic drugs (i.e. levodopa or dopamine agonists) and recent or anticipated medical procedures that may affect mobility. Individuals who passed the telephone interview and agreed to participate in the study were invited to two in-person study visits at our research center, each lasting approximately three hours. During the visits, participants received comprehensive neuropsychological, cognitive, psychological, and mobility assessments as well as a structured neurological examination. Consensus diagnostic case conferences were conducted to assure that participants did not meet criteria for dementia (Holtzer et al., 2008).

Of the 405 participants who completed the in-house evaluations, participants without valid fNIRs recordings ($n=46$), without valid postural control recordings ($n=53$), with idiopathic Parkinson's disease (PD) at baseline ($n=2$), with dementia at baseline ($n=4$), with history of stroke or TIA ($n=27$), prescribed dopamine-blocking agents/neuroleptics ($n=1$), and/or unable to stand without an assistive device during the postural control task ($n=3$) were excluded from this analysis. Following exclusions, 269 non-demented older adults were included in the current analysis (mean age: 76.41 ± 6.70 years, 56% women). The institutional review board of the Albert Einstein College of Medicine approved the experimental procedures and all participants provided written informed consent in accordance with the tenets of the Declaration of Helsinki.

4.2. Clinical assessment

Comprehensive neurological examination included assessment for clinical gait abnormalities (Verghese et al., 2002), mild parkinsonian signs (MPS), and medical illnesses. As stated earlier, all participants were categorized into one of three groups: MPS, PS, or healthy control (i.e., normal). As in our previous studies (Allali et al., 2014a; Mahoney et al., 2014), MPS were systematically ascertained in participants by the study clinician using the motor evaluation portion (Part III) of the original version of the Unified Parkinson's Disease Rating Scale (UPDRS; (Fahn and Elton, 1987)). Accordingly, clinician ratings (0–4) within 4 core domains were recorded: (1) bradykinesia in extremities and body (UPDRS items 23-26 and 31); (2) rigidity in extremities and neck (UPDRS item 22); (3) rest tremor in extremities (UPDRS item 20); and (4) postural instability and gait disturbance (PIGD) (UPDRS items 29-30); where scores greater than zero in any one of these domains suggest the presence of MPS. Consistent with our previous work on MPS (Allali et al., 2014a; Mahoney et al., 2014), we diagnosed MPS based on the presence of any one of the four cardinal features of MPS regardless of its severity (1–4 points). This approach has shown good internal consistency (Allali et al., 2014a; Mahoney et al., 2014). Although more conservative methods have been employed by other investigators (Louis et al., 2004, 2005), we employed a sensitive definition in an effort to identify early markers of MPS. Participants with MPS can present one or more abnormal scores in the 4 core domains of the UPDRS, as long as they did not meet the clinical criteria of parkinsonism defined by the United Kingdom Parkinson's disease society brain bank clinical diagnostic criteria (Hughes et al., 1992). We applied the United Kingdom

Parkinson's disease society brain bank clinical diagnostic criteria (Hughes et al., 1992) to define PS, where presence of bradykinesia (≥2 points) was required in addition to the presence of one additional core feature (rigidity, tremor, or PIGD). All other participants without presence of bradykinesia, rigidity, tremor, or PIGD constituted the healthy control group.

4.3. *fNIRs acquisition during the postural control task*

fNIRs Imager 1000 (fNIRs Devices, LLC, Potomac, MD) was used to monitor changes in hemodynamic activity in the prefrontal cortex (specifically oxygenated hemoglobin levels) of participants during the ten-second postural control task, where participants were asked to stand upright, fixate on the wall directly in front of them, and count silently in their head, as previously described (Holtzer et al., 2015). The counting task, a very simple task, was strategically included to ensure that all participants were engaged in the same task while standing and not just daydreaming. Participants were not asked to complete a complex task, like reciting alternate letters, during standing.

The fNIRs system consists of a flexible circuit board (102 gr) that is placed on each participant's forehead using standard procedures, a control box for data acquisition and a computer for data collection and storage. The system collects data at a sampling rate of 2 Hz. The fNIRs sensor consists of four LED light sources and ten photodetectors with a source-detector separation of 2.5 cm (see Fig. 2A). This configuration forms 16 channels of recording. The light sources on the sensor (Epitex Inc. type L4 × 730/4 × 805/4 × 850-40Q96-I) contain three built-in LEDs with peak wavelengths at 730, 805, and 850 nm, with an overall outer diameter of 9.2±0.2 mm. The photodetectors (Bur Brown, type OPT101) are monolithic photodiodes with a single-supply transimpedance amplifier. Light sources and detectors are built on a flexible printed circuit board that is covered in silicone for sealing, durability, comfort and hygiene (see Fig. 2B). Light levels are individually calibrated based on skin color to ensure valid fNIRs recordings between 700 and 3500 nm. The flexibility of the sensor permits components to move and adapt to the various contours of the participants' foreheads, such that the sensor elements maintain an orthogonal orientation to the skin surface, which ultimately improves light coupling efficiency and signal strength. Minimal migration of sensors was assured by placement of a firm band around each participant's head (see Fig. 2). There is a standard sensor placement procedure followed in all of our studies. The fNIRs is placed on the forehead so that the horizontal axis is centered on the midline of the head, and the vertical axis is centered right above the eyebrows, such that according to the international 10–20 system FP1 and FP2 locations are approximately positioned in-line with the lower row of channels (Ayaz et al., 2006). Given the sensitivity of the fNIRs recording device, the lighting in the test room was reduced such that the mean illumination of the forehead was approximately 150 lux, which is about one-third of typical office lighting.

4.3.1. *Preprocessing and hemodynamic signal extraction*

First, data from each of the 16 fNIRs channels were carefully inspected and recordings were removed from analysis if saturation or dark-current conditions were identified. The raw intensity measurements at 730 and 850 nm that were not saturated or at dark-current levels were then low-pass filtered with a finite impulse response filter that had a

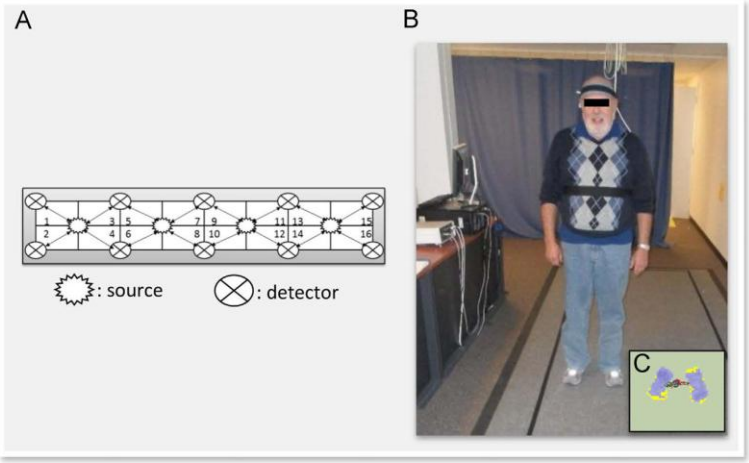

Fig. 2 – (A) The fNIRs sensor with 4 light sources and 16 light detectors (i.e., channels; see also Holtzer et al. (2015, 2011)) and their approximate placement over prefrontal cortex. (B) This panel depicts a participant wearing the fNIRs sensor while standing on the PKMAS instrumented walkway. (C) This panel shows the participants' footprints with varying levels of pressure (violet). The red and green dots in between the feet represent the center of mass and center of pressure values respectively at a given time point. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cut-off frequency of 0.14 Hz to eliminate possible contamination from respiration and heart rate signals as well as any unwanted high-frequency noise (Izzetoglu et al., 2010). Oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (Hb), oxygenation or oxygen index (HbO_2–Hb) and total hemoglobin (HbO_2+Hb) signals can be calculated from the artifact-removed raw intensity measurements at 730 and 850 nm using the modified Beer–Lambert law for each channel (see Boas et al., 2002). In the current experiment, only HbO_2 values were used to characterize changes in the prefrontal cortex during the postural control task, given that they have been found to be more reliable and less sensitive to movement-related changes in cerebral blood flow (Harada et al., 2009). The use of a single index for task-related hemodynamic changes also reduces the number of comparisons, and thus the probability of increased Type I error.

Baseline corrections over a wide range of 1–15 s have been used in previous fNIRs studies (Csibra et al., 2004; Izzetoglu et al., 2007). In the current study, relative changes in the concentrations of HbO_2 were obtained by comparing the measurements made during the first 2 s to those made during the remaining 8 s of our 10 s postural task. Given that the time for a peak hemodynamic response during a motor task is typically ~6 s post stimulus, with an onset delay of about 2 s (Jasdzewski et al., 2003), and the fact that we are specifically investigating the time window of 2–10 s post stimulation, we are confident that we captured the peak hemodynamic response in the current dataset. The sampling interval of fNIRs activity was set at 500 ms, which afforded 16 time points during the eight-second postural stability task.

4.3.2. *fNIRs data collection during the postural control task*

Individual mean HbO_2 data were extracted separately for each of the 16 channels during a synchronized eight-second recording of concurrent fNIRs and postural activation data. A central "hub" computer with E-Prime 2.0 software was used to send synchronized triggers to both the fNIRs system (via serial port) and the Zenometrics quantitative gait system (via parallel port). The fNIRs acquisition software (COBI Studio) accepted numerical triggers from E-prime. The gait acquisition software (PKMAS) accepted TTL (transistor–transistor-logic; 5 V) pulses (square waves) that indicated the beginning and end of each recording.

4.4. *Postural recordings*

Postural control assessments were conducted by a research assistant (blinded to the group status) via an instrumented walkway that utilizes ProtoKinetics Movement Analysis Software (PKMAS) (Zenometrics, LLC; Peekskill, NY). The postural measure was collected simultaneously with fNIRs recordings. Quantitative measures collected on this instrumented walkway are based on location and mathematical parameters between footfalls (i.e., geometric arrangement, spatial and temporal relationship, relative pressures). As in previous studies in both aging and Parkinsonian syndromes (Muller et al., 2013; Mancini et al., 2012; Eikema et al., 2013), the center of pressure (COP) velocity (cm/s), a proxy for postural control and sway, was the criterion measure (see Fig. 2C for pressure sensor data). COP velocity, as a measure of the mean speed of the COP, represents a highly reliable parameter of postural control in healthy older adults (Lin et al., 2008; Moghadam et al., 2011), as well as in patients with neurological conditions (Gray et al., 2014; Tamburella et al., 2014). In line with the fNIRs data, the sampling interval of the COP velocity during the eight-second recording was set at 500 ms. Testing was conducted in a quiet room and participants wore comfortable footwear with the fNIRs sensor attached to their forehead.

4.5. *Additional testing procedures*

As in our previous studies, global health status (GHS; range 0–10) was obtained from dichotomous rating (presence or absence) of medical illnesses including: diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, PD, chronic obstructive pulmonary disease, angina, and myocardial infarction (Verghese et al., 2007). Global cognitive status was assessed using the RBANS total score. The RBANS, a brief cognitive test with alternate forms, measures immediate and delayed memory, attention, language, and visuospatial abilities, which also provides a total index score (Duff et al., 2008). Additionally, depression was measured using the Geriatric Depression Scale (GDS) in which a cutoff score > 9 was used to define the presence of any depression symptomology from mild to severe (Yesavage et al., 1982).

4.6. Statistics

Descriptive statistics (M and SD) were calculated for each of the three (control, MPS, and PS) groups. Data were inspected graphically, as well as with descriptive statistics, and model assumptions (e.g., normality) were formally tested. Log transformation of COP velocity was performed to achieve normality and variance stabilization of differences across participants. All statistical analyses were run using IBM's Statistical Package for the Social Sciences (SPSS), Version 20.0 (Corp., 2011).

As stated earlier, three separate linear mixed effects models (LMEMs), each adjusted for age, gender, and ethnicity were used to examine the main effects of group, time and HbO_2, as well as their second- and third-order interaction effects. As previously noted, fNIRs light levels are individually calibrated to ensure valid recordings; however, ethnicity was included as a covariate in each of our statistical models as a means of adjusting for skin color, where individuals with darker skin required increased levels.

The first LMEM was designed to test the hypothesis that patients with PS would demonstrate greater prefrontal activation throughout the postural control task compared to healthy older adults; it examined the effect of group status, time, and their interaction on averaged HbO_2 activation levels (criterion variable) during the postural control task. To identify the contributors to postural control and determine whether participants with PS would demonstrate greater postural instability throughout the task compared to healthy older adults, a second LMEM examined the effect of group status, time, and their interaction on COP velocity (criterion variable). Both models consisted of a three-level group (control, MPS, and PS) and a 16-level time variable.

To test the neural inefficiency hypothesis (Holtzer et al., 2009) we employed a final LMEM to examine the effects of group status, time, averaged HbO_2 activation level over first and second time periods, and their interactions on averaged COP velocity. This final LMEM was designed to determine whether the relation between group status and postural control throughout the task is moderated by HbO_2 activation level. Here, in order to examine the effect of time on postural control, we compared the mean HbO_2 activation levels acquired during the first and second halves of the recording period. The actual model consisted of a three-level group (control, MPS, and PS) and a two level time period (first vs. second half). All three LMEMs employed a first-order autoregressive covariance type and a random intercept that was included to allow for variability across individuals (i.e., subject was treated as a random effect). The advantage of the linear mixed effects model is that the heterogeneity and correlation of repeated measures under different conditions are taken into account (Laird and Ware, 1982).

Finally, to assess the effect of lateralization, we conducted a separate LMEM to determine whether participants demonstrated lateralized (right vs. left hemisphere) prefrontal activation (averaged across time and channels) during our postural control task.

Funding

This study was supported by funds from the National Institutes of Health, National Institute on Aging (R01AG036921-01A1 & R01AG044007-01A1). Gilles Allali was supported by a Grant from the Resnick Gerontology Center, Albert Einstein College of Medicine, Yeshiva University and the Geneva University Hospitals.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

Special thanks to the CCMA research assistants and clinicians for their assistance with data collection and to Constantin Trantzas (Zenometrics, LLC) for his assistance.

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3.4 Dopaminergic denervation is not necessary to induce gait disorders in atypical parkinsonian syndrome

This paper has been published in Journal of Neurological Sciences 2015;351(1-2):127-132 by Gilles Allali, Valentina Garibotto, Ismini C. Mainta, Stephane Armand, Richard Camicioli, Osman Ratib, Habib Zaidi, François R. Herrmann and Frédéric Assal.

This study investigates the role of the nigrostriatal pathway on quantitative gait parameters in patients with parkinsonian syndrome. In order to avoid the interference of dopaminergic and anti-dopaminergic drugs, this investigation excludes patients with Parkinson's disease and also any patients treated by dopaminergic or anti-dopaminergic drugs. Based on the observation of the dopa-resistive gait disorders in parkinsonian syndrome and the major role of the prefrontal cortex in gait control, we hypothesized that the nigrostriatal pathway will not have a major role in gait disorders in parkinsonian syndromes. Comparing the gait parameters between patients with normal and abnormal nigrostriatal pathway (assessed by the [^{123}I]FP-CIT SPECT), we showed that quantitative gait parameters, including gait speed, stride length and stride time, were similar between both groups. This study suggests that non-dopaminergic pathways play a major role in gait disorders in patients with parkinsonian syndromes. By instance, non-dopaminergic drugs should be considered for treating gait disorders in parkinsonian syndromes.

Journal of the Neurological Sciences 351 (2015) 127–132

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Dopaminergic denervation is not necessary to induce gait disorders in atypical parkinsonian syndrome

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ARTICLE INFO

Article history:
Received 24 November 2014
Received in revised form 3 February 2015
Accepted 26 February 2015
Available online 7 March 2015

Keywords:
Gait disorders
Parkinsonian syndromes
Neuroimaging
Nigrostriatal pathways
[123I]FP-CIT SPECT
Dual task

ABSTRACT

Background: Gait impairment is common in parkinsonian syndromes but not specific to striatonigral dysfunction. The relationship between the dopaminergic system and gait parameters is poorly understood. This cross-sectional study aimed to determine if gait measures are related to the striatal dopamine transporters distribution using [^{123}I]FP-CIT SPECT in patients with parkinsonian syndromes.

Materials and methods: Twenty-four patients with gait impairment and parkinsonian syndromes without Parkinson's disease (mean age: 73.6 ± 8.2 years) were included in this study. Gait analysis during single- and dual-task condition (walking and backwards counting) and [^{123}I]FP-CIT SPECT were performed within 3 months of each other. Patients were visually categorized as having normal ($n = 14$) or abnormal ($n = 10$) [^{123}I]FP-CIT SPECT. In addition, a volume-of-interest-based analysis of uptake ratios (caudate and putamen) relative to the occipital cortex and a voxelwise analysis using SPM8 were also performed.

Results: Patients with parkinsonian syndromes and abnormal [^{123}I]FP-CIT SPECT did not significantly differ in terms of spatiotemporal gait parameters from those with normal [^{123}I]FP-CIT SPECT. Moreover, after correction for multiple comparisons, we did not observe any association between regional uptake ratio and spatiotemporal gait parameters for single and dual tasking. Finally, none of these parameters showed a significant association with voxelwise [^{123}I]FP-CIT uptake.

Conclusions: Dopaminergic denervation, as measured by [^{123}I]FP-CIT SPECT, is not necessary to induce alterations of spatiotemporal gait parameters during single and dual task in patients presenting with atypical parkinsonian syndromes.

1. Introduction

Parkinsonism is very prevalent in neurodegenerative diseases and increases markedly with age affecting up to 52 % of people over age 85 years [1]. Gait disorders are common in parkinsonian syndrome (PS) but may be caused by other central or peripheral nervous system disorders [2,3]. Like other axial parkinsonian signs, gait disorders respond poorly to dopaminergic treatments in Parkinson's disease (PD), suggesting the implication of extra-dopaminergic lesions [4]. Positron emission tomography (PET) or single photon emission computerized tomography (SPECT) with ligands that label specific components of the dopaminergic nerve terminal can examine the role of the dopaminergic system in gait disorders. In healthy adults, dopaminergic physiology influences certain aspects of gait independent of age-related changes [5]. While previous data suggest a correlation between gait and ^{123}I labelled -2b-carbomethoxy-3b-(4-iodophenyl)-N-(3-fluoropropyl)nortropane ([^{123}I]FP-CIT) binding in PD [6,7], no study have looked for an association between quantitative gait parameters and [^{123}I]FP-CIT binding in patients with PS without PD. The aim of this study was to search for an association between the striatal dopamine transporters distribution using [^{123}I]FP-CIT SPECT and

Abbreviations: PS, Parkinsonian syndrome; PD, Parkinson's disease; PET, Positron emission tomography; SPECT, Single photon emission computerized tomography; [^{123}I]FP-CIT, ^{123}I labelled-2b-carbomethoxy-3b-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane; CV, Coefficient of variation; VOI, Voxel of interest; SPM, Statistical parametric mapping.

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http://dx.doi.org/10.1016/j.jns.2015.02.051
0022-510X/

quantitative gait parameters during walking at self selected speed and walking while backward counting in patients with PS without PD. We compared spatiotemporal gait parameters in patients with normal and pathological [^{123}I]FP-CIT SPECT, and we determined if there was an association between gait parameters and regional and voxelwise [^{123}I]FP-CIT distribution. We recruited only non-PD patients to be able to study a range of dopamine denervation in a distinct pattern from the classical PD picture.

2. Materials and methods

2.1. Patients

Twenty-four consecutive patients (7 women and 17 men) referred to the Department of Neurology at the Geneva University Hospitals with gait disorders and PS without PD who underwent a spatiotemporal gait analysis and a [^{123}I]FP-CIT SPECT with a maximum interval of 3 months were retrospectively included in this study. Patients were mobile and walked independently. All underwent a neurological and general examination by board-certified neurologists, confirming the presence of PS and that gait disorders were due solely to a central neurological disturbance (i.e., cerebellar, spinal, peripheral nervous system and systemic causes were excluded). The UK brain bank criteria were applied to define parkinsonian syndrome [8]. Mean age ± SD was 73.6 ± 8.2 years and was not statistically different between women and men (72.0 ± 3.1 and 74.2 ± 9.5 respectively; $p = 0.55$). Mean duration of gait difficulties was 22.3 ± 28.6 months. At the time of the study, all patients were drug naïve for neuroleptic and anti-parkinsonian medication or other medications affecting the dopaminergic system. Exclusion criteria included acute medical illness in the past 3 months, orthopedic or rheumatologic disorders interfering with gait, patient unable to walk a minimum of 15 m without a walking aid and not able to perform the dual-task evaluation (walking while backward counting). Patients were categorized as having normal ($n = 14$) or abnormal ($n = 10$) [^{123}I]FP-CIT SPECT. The categorization was performed independently by two expert readers (VG and ICM) who were blind to neurological diagnosis. The dichotomization in normal/abnormal imaging was based on visual assessment, supported by BRASS™ automated functional brain analysis software (Hermes BRASS software, Nuclear Diagnostics AB, Sweden). Briefly, BRASS fits and compares patients' images to a 3D reference template [9]. The data of 14 healthy controls are included in the software and provide a normal reference. For all abnormal cases, there was agreement of the visual interpretation by expert readers (V.G; I.C.M.) and of the automated analysis, i.e., [^{123}I]FP-CIT binding was below 2 standard deviation of the normative samples in at least one striatal region. The etiologies of the PS in the normal and the abnormal [^{123}I]FP-CIT SPECT groups are displayed in Table 1 and was performed after completion of clinical work-up, including morphological brain imaging and clinical follow-up. All patients had morphological brain imaging by CT or MR within 6 months from [^{123}I]FP-CIT SPECT data acquisition, which could assess the presence of vascular lesions involving the basal ganglia. In one patient a vascular lesion in the left caudate and putamen was associated with a significantly reduced [^{123}I]FP-CIT uptake on the same side. This retrospective study protocol was approved by the ethics committee of the Geneva University Hospitals.

2.2. [^{123}I]FP-CIT SPECT data acquisition

All patients received about 185 MBq of [^{123}I]FP-CIT by slow intravenous injection. Thyroid uptake was blocked before the scan by administration of Lugol solution (5 drops 5% KI administered before and 4 h after injection). SPECT data acquisition started 4 h after administration of the tracer. The scans were acquired on a triple-head gamma-camera (Toshiba Medical Systems, Tokyo, Japan) equipped with xfan-beam, low-energy, high-resolution collimators. In all cases, the head was fixed in a head-holder to minimize motion artefacts. Acquisition parameters included step-and-shoot mode over 30 min. Sixty projection angles were taken over 360 degrees and a 128 × 128 matrix was used. Reconstruction was performed by filtered backprojection using a Shepp and Logan filter, prefiltered by a fourth order Butterworth filter. The triple-energy window method was used for scatter compensation whereas a uniform Chang attenuation correction was used to compensate for photon attenuation using a uniform attenuation coefficient of 0.15 cm^{-1}.

2.3. Gait recordings

Gait recordings have been previously described in more details [10,11]. Briefly, synchronized footswitches (AURION ZeroWire, Milan, Italy, sampling rate of 1000 Hz) and a seven-camera opto-electronic system (VICON Mx3+, Vicon Motion Systems, Oxford, UK, sampling rate of 100 Hz) were used for gait analysis. The 3D position of two reflective markers placed on the foot (on both heels and both 2nd metatarsals) and the temporal data of the footswitches were combined

Table 1
Clinical characteristics of subjects ($n = 24$).

	Normal [^{123}I]FP-CIT SPECT ($n = 14$)	Abnormal [^{123}I]FP-CIT SPECT ($n = 10$)	P-value[a]
Age (years)	75.8 ± 5.5	70.5 ± 10.4	0.46
Female (%)	42.9	10	0.09
Disease duration (months)	17.4 ± 13.3	29.2 ± 41.8	0.72
Comorbidities (n)	3.6 ± 1.3	2.8 ± 2.9	0.27
Treatments (n)	4.5 ± 2.6	3.7 ± 2.2	0.44
Psychoactive drugs (n)	1.0 ± 1.0	0.8 ± 1.0	0.57
Clinical diagnosis (n)			0.52
iNPH	2	3	
AD	1	0	
bvFTD	2	0	
PSP	0	1	
MSA	1	1	
MCI	1	0	
Vascular dementia	2	0	
CBD	1	2	
Progressive gait apraxia	1	1	
AD and iNPH	2	1	
PSP with subcortical leucoencephalopathy	0	1	
Mixed dementia (vascular dementia and AD)	1	0	

iNPH: idiopathic normal pressure hydrocephalus; AD: Alzheimer's disease; bvFTD: behavioral variant of frontotemporal degeneration; PSP: progressive supranuclear palsy; MSA: multiple system atrophy; MCI: mild cognitive impairment; CBD: corticobasal degeneration.
[a] Comparison based on Mann–Whitney test or Fisher exact test as appropriate.

to compute gait parameters including walking speed, stride length, cadence, stride time, step width and step height. These gait parameters were assessed during comfortable speed locomotion on a 10-m walkway in single-task and dual-task (backward counting aloud by subtracting serial 1 from 50) conditions in a random order. Before testing, a trained evaluator gave standardized verbal instructions on the test procedure. For dual-tasking, patients were asked to walk and to count backwards at the best of their capacity without any task prioritization.

2.4. Statistical analysis

Subjects' characteristics were described using means and standard deviations or frequencies and percentages, as appropriate. Comparisons between groups of subjects were performed using the Mann–Whitney test and chi-square test as appropriate. Spearman's correlation coefficients were used to assess relationships between outcomes. After correction for multiple comparisons according to Bonferroni, *P*-values less than 0.0125 were considered statistically significant (each gait parameters were correlated with 4 striatal regions—right/left caudate and right/left putamen). Post hoc power analysis with an alpha set at 0.05 and a power set at 80% were applied to compute the number of patients needed by group to reach a significant *P*-value when comparing the mean of the two groups using an unpaired *t* test. All statistics were performed using the Stata Statistical Software, version 12.1.

2.4.1. Volume-of-interest (VOI) analysis

[^{123}I]FP-CIT SPECT images were quantitatively analyzed using BRASS™, as mentioned earlier. This analysis takes the tomographic data, spatially registers them to a template in a standard space, and finds the count concentration in striatal (Cs) and background occipital (Cb) volumes-of-interest (an example is provided in Fig. 1). Using the activity concentrations in the volumes of interest, striatal uptake ratios defined as [(Cs − Cb)/Cb] of specific tracer binding are calculated. The template VOI sets were predefined in the BRASS software [12,13]. Uptake ratios measured for the caudate and the putamen, for the left and right hemisphere, relative to occipital activity, were taken as input variables.

2.4.2. Voxelwise statistical parametric mapping (SPM) analysis

In order to identify possible focal changes of [^{123}I]FP-CIT binding in subregions of the basal ganglia, we also performed a voxelwise SPM analysis. We obtained a customized [^{123}I]FP-CIT template, adopting the method validated by Kas et al. [14]. In brief, we first obtained a customized template on a subgroup of patients for whom a 3D T1 MRI was available. The MR images were spatially normalized to the reference space by the unified segmentation-normalization approach, as implemented in SPM8, which provides better and more reliable matching to a standard template than the commonly used alternatives [15]. Normalization parameters were then applied to the coregistered [^{123}I]FP-CIT images. These images were averaged, as previously described, in order to obtain a customized template, and subsequently all individual [^{123}I]FP-CIT images were spatially normalized to the template and smoothed with a Gaussian kernel of 10 mm full width at half maximum, as previously validated [14]. The spatial normalization was successful also in the cases showing radiological features of normal pressure hydrocephalus, as previously reported [16]. The customized template and exemplary individual normalized images are shown in Fig. 2. In Fig. 3, a normalized image of a patient with normal [^{123}I]FP-CIT SPECT and a patient with pathological [^{123}I]FP-CIT SPECT were illustrated. Linear regression analyses between parametric images and age and spatiotemporal gait parameters, limited to the striata by applying a binary mask, were performed, adopting activity normalization for the mean counts measured in the occipital cortex. *P*-values lower than 0.05 were considered statistically significant.

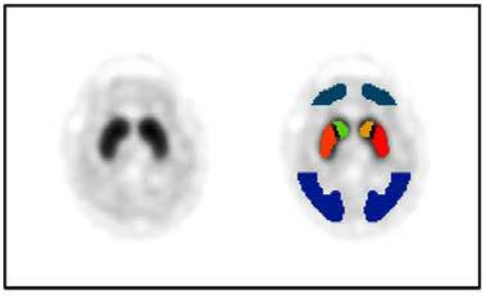

Fig. 1. The figure shows an example of a normal [^{123}I]FP-CIT SPECT study: on the left, the image, spatially normalized, on the right, the volume-of-interest (VOI) map of caudate, putamen, frontal and occipital regions implemented in the BRASS software, overlaid on the normalized image.

3. Results

Demographic and clinical characteristics are summarized in Table 1. Patients with normal and abnormal [^{123}I]FP-CIT SPECT were well matched in terms of demographics and baseline characteristics. Striatal uptake ratio was decreased in the abnormal [^{123}I]FP-CIT SPECT group. The normal and abnormal [^{123}I]FP-CIT SPECT groups showed the same spatiotemporal gait parameters without any differences in term of walking speed, stride and step time, stride and step length, step width and heel height for mean values, coefficients of variation and standard deviations of each parameter (Table 2).

Post hoc power analysis shows the large number of patients that would be needed to reach statistical significance for all gait parameters with the exception of step width for both tasks and step width CV for the dual task.

After correction for multiple comparisons, we did not observe any correlation between striatal uptake ratios and age or spatiotemporal gait parameters for single and dual task (Table 3).

Voxelwise analyses showed an inverse correlation between age and [^{123}I]FP-CIT relative uptake, normalized to the occipital uptake, bilaterally in the medial caudate confirming previous data [17,18]. This was introduced as confounding variable in all linear regression analyses with spatiotemporal gait parameters. No significant association was found between any spatiotemporal gait parameter in single and dual task and [^{123}I]FP-CIT relative uptake in the 24 patients, as well as in each individual group (i.e., patients with normal [^{123}I]FP-CIT SPECT and with abnormal [^{123}I]FP-CIT SPECT).

4. Discussion

In the current study, we evaluated the relationship between the dopaminergic system and spatiotemporal gait parameters in patients with various atypical PS using dopamine transporter distribution and availability with [^{123}I]FP-CIT SPECT. Spatiotemporal gait parameters during single and dual walking task were similar in the patients with normal and abnormal [^{123}I]FP-CIT SPECT. Furthermore, [^{123}I]FP-CIT relative uptakes were not associated with any spatiotemporal gait parameters in single and dual tasking. These data suggest that the dopaminergic denervation is not necessary to alter gait parameters in atypical PS.

Several studies have investigated the relationship between [^{123}I]FP-CIT binding and parkinsonian motor impairment. In normal aging, the nigrostriatal denervation presents an average age-related decline of 5.5% per decade [18]. This physiological denervation may contribute to the common occurrence of subtle parkinsonian motor symptoms with aging [19]. Our study confirms this inverse correlation between age and [123I]FP-CIT striatal uptake. This relationship between [^{123}I]FP-CIT

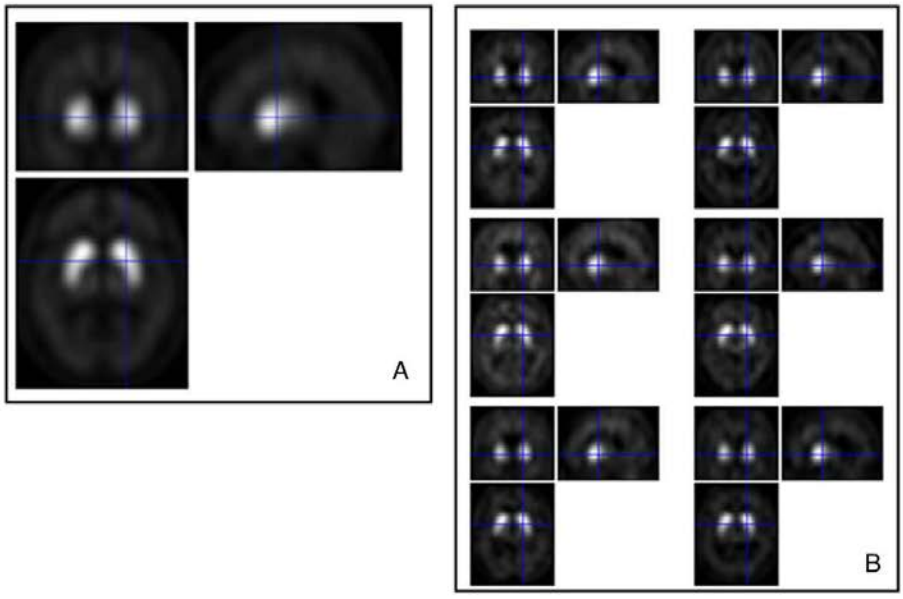

Fig. 2. The figure shows the customized [^{123}I]FP-CIT template obtained (panel A) and 6 examples of individual [^{123}I]FP-CIT SPECT images spatially normalized to the template (panel B).

binding and motor impairment has been mainly studied in the model of PD. Bradykinesia shows a significant inverse correlation with striatal [^{123}I]FP-CIT binding [4,6,7]. Some studies found also the same inverse correlation for rigidity [6,20]. For gait disorders, some previous reports suggested that in PD, progressive supranuclear palsy and multiple systemic atrophy, gait and posture signs correlate with [^{123}I]FP-CIT binding [7,21]. However, cholinergic but not dopaminergic denervation was associated with the measure of gait speed in non-demented PD patients, suggesting a close relationship between the control of gait and the cholinergic system [22]. These apparent contradictory results may be related to the methods used to assess gait. Except for the Bohnen's study [22], whose the results are in line with our study, the assessment of gait in the previous studies was performed on the items of the Unified Parkinson's Disease Rating Scale (UPDRS), which is a clinical scale designed to follow the longitudinal course of PD. Gait is only assessed using a 5 point scale ranging from normal gait to impaired

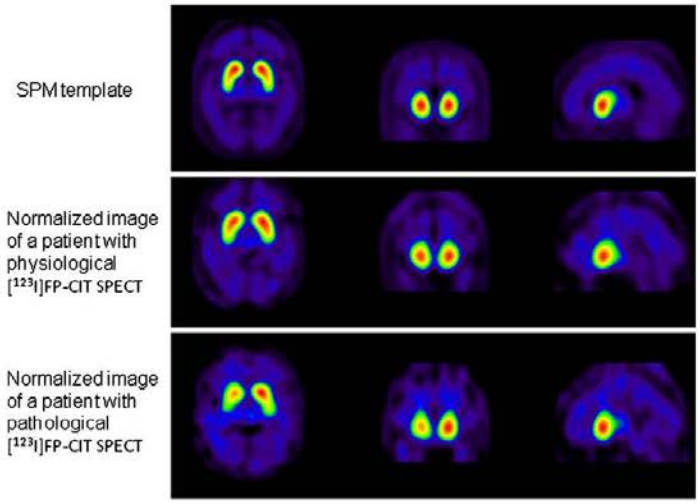

Fig. 3. The figure shows the normalized image of two patients on the SPM template (first raw): one with a physiological [^{123}I]FP-CIT SPECT (second raw) and one with a pathological [^{123}I] FP-CIT SPECT (third raw).

Table 2
Gait performance of subjects ($n = 24$) and comparison between normal and abnormal [^{123}I]FP-CIT SPECT.

	Normal ($n = 14$)	Abnormal ($n = 10$)	*P*-value[a]	Power *N*[b]
Single task				
Gait speed (m/s)	0.68 ± 0.29	0.73 ± 0.38	0.81	583
Stride time (s)	1.28 ± 0.21	1.27 ± 0.28	0.60	23478
CV (%)	3.73 ± 1.96	3.57 ± 2.44	0.60	3120
Stride length (m)	0.82 ± 0.31	0.85 ± 0.37	0.86	1900
CV (%)	7.25 ± 6.52	5.21 ± 4.91	0.24	126
Step width (m)	0.09 ± 0.04	0.12 ± 0.05	0.27	51
CV (%)	31.2 ± 23.6	18.5 ± 12.1	0.20	35
Step height (m)	0.16 ± 0.05	0.18 ± 0.06	0.38	108
CV (%)	6.42 ± 4.63	6.96 ± 6.60	0.91	1785
Dual task[c]				
Gait speed (m/s)	0.53 ± 0.26	0.57 ± 0.32	0.81	877
Stride time (s)	1.47 ± 0.30	1.41 ± 0.38	0.73	494
CV (%)	6.80 ± 3.60	6.30 ± 3.93	0.56	889
Stride length (m)	0.73 ± 0.32	0.72 ± 0.35	0.95	16410
CV (%)	9.32 ± 7.88	9.54 ± 6.64	0.68	17792
Step width (m)	0.11 ± 0.04	0.11 ± 0.05	0.81	3319
CV (%)	24.4 ± 16.5	16.7 ± 8.23	0.32	46
Step height (m)	0.15 ± 0.05	0.16 ± 0.06	0.64	234
CV (%)	9.16 ± 6.65	7.95 ± 7.59	0.52	547

CV: coefficient of variation (=100 x standard deviation/mean).
[a] Comparison based on Mann–Whitney test.
[b] Power *N* indicates the number of patients needed by group to reach a significant *P*-value with an alpha set at 0.05 and a power set at 80%.
[c] Gait while backward counting.

mobility. In the present study, we compared quantitative spatiotemporal gait parameters with [^{123}I]FP-CIT binding.

Positron emission tomography has been used to determine the cerebral regions involving during mental imagery of walking. Malouin et al. [23] showed that the involvement of multiple cortical regions involving supplementary motor area was required during the imagination of gait. Recently, brain networks activated during mental imagery of gait were studied using functional MRI (fMRI). Converging results showed that networks involving bilateral primary motor cortex, supplemental motor area, prefrontal regions and cerebellum are recruited during mental imagery of gait [24–27]. Others functional imaging techniques, such as near-infrared spectroscopy, were also used to highlight the role of the prefrontal regions in the preparation and execution of actual walking [28,29]. These converging results suggest that a cortical network is implicated in the imagery of walking and not the basal ganglia. This cortical network involved in mental imagery of gait could in part explain this absence of association between gait parameters and [^{123}I]FP-CIT binding. Cortical pathology occurs in all parkinsonian disorders, including PD and likely contributes to gait impairment [30].

With these results, we cannot exclude that [^{123}I]FP-CIT binding plays a role in motor impairment when the nigrostriatal pathway is involved, given that our population includes patients with mixed etiologies: however, our data are in line with previous evidence showing that gait is modulated by an extended network and that the basal ganglia dopaminergic dysfunction is not associated with distinctive features. The strength of our study was that we used a transnosological and not a diagnostic-based approach in patients with gait impairment and various atypical PS affecting the nigrostriatal pathways and the cerebral cortex.

The main limitation of our study was that our patients did not have autopsy-confirmed diagnoses. Our relatively small sample size also necessitates caution, but the study is relatively underpowered only for step width for both tasks and step width CV for the dual task. Our data provide information to plan future studies. However, to the best of our knowledge, there are no previous published data showing a relationship between spatiotemporal gait parameters and [^{123}I]FP-CIT uptake.

5. Conclusion

In patients with atypical PS, dopaminergic denervation, assessed by [^{123}I]FP-CIT binding, was not necessary to alter spatiotemporal gait

Table 3
Correlations[a] between gait parameters and [^{123}I]FP-CIT SPECT normalized striatal binding in all participants ($n = 24$), in abnormal [^{123}I]FP-CIT SPECT ($n = 10$), and normal [^{123}I]FP-CIT SPECT ($n = 14$).

	All participants ($n = 24$)				Abnormal [^{123}I]FP-CIT SPECT ($n = 10$)				Normal [^{123}I]FP-CIT SPECT ($n = 14$)			
	Right caudate	Left caudate	Right putamen	Left putamen	Right caudate	Left caudate	Right putamen	Left putamen	Right caudate	Left caudate	Right putamen	Left putamen
Single task												
Gait speed	−0.22	−0.07	−0.32	−0.30	−0.44	−0.15	−0.62	−0.48	−0.07	0.09	0.03	−0.15
Stride time	0.10	0.08	0.24	0.28	−0.08	−0.03	0.22	0.19	0.14	0.05	0.03	0.14
CV	0.13	−0.16	0.12	0.09	0.10	−0.12	0.30	0.19	0.20	−0.16	0.09	0.10
Stride length	−0.23	−0.06	−0.26	−0.24	−0.59	−0.31	−0.62	−0.52	−0.09	0.14	0.10	−0.09
CV	0.33	0.10	0.15	0.20	0.59	0.20	0.46	0.24	0.12	−0.09	−0.20	−0.01
Step width	−0.25	−0.35	−0.26	−0.13	−0.26	−0.25	−0.18	−0.21	−0.08	−0.24	−0.23	0.07
CV	0.14	0.22	0.15	0.09	0.21	0.33	−0.09	0.27	−0.05	0.06	0.18	−0.16
Step height	−0.31	−0.18	−0.41**	−0.38	−0.46	−0.21	−0.59	−0.48	−0.19	0.00	−0.08	−0.22
CV	0.11	0.03	0.13	0.17	−0.03	−0.07	0.19	0.12	0.24	0.02	0.06	0.23
Dual task[b]												
Gait speed	−0.10	0.03	−0.17	−0.22	−0.30	−0.07	−0.69**	−0.36	0.13	0.30	0.29	−0.02
Stride time	−0.24	−0.15	−0.02	0.01	−0.25	−0.13	0.15	−0.07	−0.56**	−0.42	−0.29	0.01
CV	−0.03	−0.19	−0.06	0.01	−0.12	−0.29	−0.03	−0.29	−0.34	−0.41	−0.27	−0.12
Stride length	−0.15	0.01	−0.21	−0.21	−0.50	−0.24	−0.69**	−0.47	0.01	0.15	0.08	−0.15
CV	−0.04	−0.11	0.02	0.10	0.07	−0.19	0.14	0.07	0.00	−0.02	0.05	0.31
Step width	−0.07	−0.27	−0.08	0.01	0.03	−0.03	−0.02	−0.06	−0.28	−0.53	−0.40	−0.17
CV	0.11	0.31	0.13	0.07	−0.67**	−0.29	−0.66**	−0.62	0.31	0.49	0.53	0.31
Step height	−0.26	−0.11	−0.33	−0.31	−0.42	−0.12	−0.72**	−0.39	−0.10	0.06	0.02	−0.21
CV	0.10	−0.05	0.27	0.25	0.38	0.02	0.67**	0.31	−0.26	−0.32	−0.11	0.04

[a] Spearman correlation coefficient.
[b] Gait while backward counting.
* Significant correlation after correction for multiple comparisons ($p < 0.0125$).
** Significant correlation without correction for multiple comparisons ($p < 0.05$).
CV: coefficient of variation (=100 x standard deviation/mean).

parameters in single and in dual tasking. In addition to the understanding of the neural basis of gait disorders, these findings suggest a non-dopaminergic approach to improve gait disorders in patients with atypical parkinsonian syndromes. A further approach needs to examine the role of the dopaminergic system with spatiotemporal gait parameters in patients with de novo PD naive for anti-parkinsonian therapy.

Funding

Gilles Allali was supported by the Geneva University Hospitals (PRD 11-I-3 and PRD 12-2013-I) and the Baasch-Medicus Foundation. Frédéric Assal was supported by the Société Académique de Genève (Fonds Cognitive Memory NAC 08-025) and the Swiss National Science Foundation (grant no. 320030-138163/1). The sponsors have no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflict of interest

None.

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Chapter 4. Discussion

4.1 Summary of the study findings.

Determining the neural correlates of neurological gait disorders represents a real challenge, which explains why we used a combined approach of behavioral studies with different neuroimaging methods. In Chapter 2, which focused on behavioral studies, we reported the interest of measuring quantitative gait parameters in well-determined degenerative and reversible neurological conditions. This approach has been extensively used with the quantification of gait parameters in Parkinson's disease (157-161), Alzheimer's disease (28, 29, 162, 163) or other dementias (23, 63, 64). Here, by comparing the gait patterns of patients with frontotemporal dementia and Alzheimer's disease, we verified the hypothesis of the major role of executive function on gait control: patients with the behavioral variant of frontotemporal dementia – the hallmark of this dementia is the presence of major dysexecutive syndrome (155) - demonstrated an increase in gait instability in comparison to patients with Alzheimer's disease (23). After demonstrating the major role of executive function on gait, especially with the dual-task paradigm (63, 64), we applied these findings for improving the identification of idiopathic normal pressure hydrocephalus – a reversible condition combining gait and cognitive deficits – from neurological conditions presenting with similar symptoms. We found that the quantification of gait parameters during dual tasking before and after CSF tapping improves the identification of idiopathic normal pressure hydrocephalus from similar neurological conditions (164).

The combined approach of the different neuroimaging methods to study the neural substrate of neurological gait disorders presented here aimed to overcome the limitations of each individual technique. The comparison of brain activation during mental imagery of gait between younger and older adults using fMRI demonstrated the involvement of a common neuronal network across aging, and highlighted the major of role of the dorsolateral part of the frontal lobe and the hippocampus specifically recruited by

older adults (28). The hippocampus - playing a major role in memory and spatial navigation and representing a brain region specifically affected in Alzheimer's disease (165, 166) – has been the focus of the structural study that compared the association of hippocampal volume and gait control between physiological and pathological aging. In normal aging, but not pathological, we reported an association between hippocampal volume and gait control (98).

The influence of pathological aging, such as patients with parkinsonian syndrome, has been the focus of the two last neuroimaging studies. In the first report, we assessed the role of the nigrostriatal pathway, using the [^{123}I]FP-CIT SPECT, on spatio-temporal gait parameters. Following the hypothesis of the major role of the prefrontal cortex in gait control and although the basal ganglia play an important role in locomotion (86, 167), we showed that the dopaminergic denervation was not necessary to induce gait disorders (148). Then, as postural instability plays a major role in gait disorders in patients with parkinsonian syndrome, we compared the online involvement of the prefrontal cortex – key region for gait control – on postural control between healthy older adults, individuals with mild parkinsonian signs and patients with parkinsonian syndrome by using functional near-infrared spectroscopy. In this last study, we found that patients with parkinsonian syndrome need to increase more their prefrontal oxygenation in comparison to healthy older adults or individuals with mild parkinsonian signs in order to maintain postural stability (168).

4.2 Clinical Applications

Combining studies focusing on aging and neurological condition, we found a widespread brain network including cortical (prefrontal and hippocampal regions) and subcortical regions that is consistent with the literature. Some authors suggest that a direct and an indirect pathways combined this complex interplay between the spinal cord, the brainstem, the basal ganglia, the cerebellum and the cortical regions in the gait control (169). The direct pathway involves the primary motor cortex, the cerebellum and the spinal cord, whereas the indirect pathway is mainly modulated by the prefrontal cortex and the basal ganglia. This top-down regulation is directly involved in behavioral studies using the dual-task paradigm. Different

explanations have been suggested to understand this extended brain networks involved in aging and in neurological conditions: the compensation, inefficiency and dedifferentiation hypotheses (85). However, none of them has been demonstrated yet.

These findings can be applied for diagnosis improvement of neurological conditions affecting gait; and pharmacological and non-pharmacological interventions for neurological gait disorders (Table 3).

Different classifications of gait disorders have been proposed as reviewed in Chapter 1. A hierarchical approach combining clinical and quantitative gait profiles has been demonstrated more specific to identify bad clinical outcomes (8). Based on the theoretical models suggesting that gait is controlled by specific brain regions and cognitive domains, we showed that gait parameters by themselves can be used as a surrogate diagnostic biomarker of specific neurological conditions, such as frontotemporal dementia or iNPH (23, 164). Beside the identification of specific neurological disorders, the use of gait disorders has been also suggested as an appropriate marker for identifying older adults at risk of dementia (5, 44). However, if gait disorders and cognitive deficits are frequently associated, and that gait disorders may start several years before dementia from neurodegenerative or vascular origins(5), the specificity of clinical gait abnormalities or quantitative gait parameters is still matter of debate: a recent systematic literature search that identifies 20 longitudinal studies focusing on the relationship between walking and development of cognitive decline conclude that we still need future studies examining the specificity and the accuracy of gait parameters to predict future cognitive decline(170). Interestingly, a second recent review article includes nine longitudinal studies, where gait was considered as a predictor of cognitive decline. The authors of this last review article concluded that gait can be considered as a robust predictor of cognitive decline (171). However, we should be aware that if the observation of gait patterns that leads to the classification of clinical gait abnormalities relies on the experience of the physicians and is subject to an unavoidable inter-rater reliability, the objective and accurate quantitative gait analysis presents also some limitations: even if some experts suggested some consensus guidelines for gait analysis (172), the variability of the various systems (i.e. instrumented walkway, accelerometer, 3d motion analysis); the

absence of general consensus on how measuring gait, especially in dual-task condition (i.e. how to deal when the dual-task interference leads to gait arrest); or the absence of consensus on how performing the dual task leads to various methodological approaches that contribute to produce various findings. Finally, associating the dual-task paradigm or mental imagery of gait to usual gait parameters has been also demonstrated as interesting clinical markers of specific neurological conditions or good predictors of adverse clinical outcomes, such as dementia or falls (25, 69, 173-175).

The second main clinical application of the neural substrate of gait control concerns the treatment of neurological gait disorders. Treating gait disturbances should not only focused on the symptom, but also should also include the management of its adverse consequences, such as falls or behavioral avoidance (i.e. fear of falling). Different therapeutic approaches have been suggested for treating gait disorders that include rehabilitation strategies, pharmacological treatments, non-invasive brain stimulation or deep brain stimulation. Various internal and external factors contributing to gait disorders influence the choice of treatment strategy. The underlying neurological pathology, the presence of cognitive deficits or the associated medical conditions will all contribute to select an appropriate treatment that aims not only to improve walking ability, but also to decrease the resulting disability. The complexity of the treatment strategy needs also to include the comorbidities that negatively affect gait, such as fear of falling, depression or orthostatic hypotension. However, the current model of the neural substrate of gait control has contributed to use new therapeutic strategies that help clinicians in their choice. For example, this major role of the executive and the attentional system on gait control has contributed to focus on pharmacological treatment that improves attention, such as methylphenidate or acetylcholinesterase inhibitors. Improving the efficiency of the attention has also been the focus of rehabilitative interventions that improve the management of dual tasking, such as dance interventions (9, 176, 177) or cognitive remediation (178). Brain modulation that includes non-invasive and deep brain stimulation also contributes to the improvement of gait disorders in appropriate neurological conditions, such as Parkinson's disease (159, 160, 179-183). The pedunculopontine nucleus has recently been identified as an

interesting target for treating gait disorders in patients with Parkinson's disease. Although results are contrasting for improving gait disorders (184-188), one aim of this new target is to activate the cholinergic neurons of this nucleus to improve gait and other axial symptoms, such as balance (167).

Table 3. Clinical applications of the brain networks involved in gait control for the diagnosis and the treatments of neurological gait disorders (personal contribution)

Clinical applications	Domains	Examples
Diagnosis	Improving diagnosis of neurological conditions	Alzheimer versus non-Alzheimer dementias (5, 37) iNPH versus mimics (164) PD versus non-PD parkinsonian syndromes (167)
	Using of new transitional syndromes to better identify subjects at risk of bad clinical outcomes	Motoric cognitive risk syndrome (44-46)
	Using mental imagery of gait for assessing cognitive functioning	Imagined TUG in dementia, multiple sclerosis, or schizophrenia (189-191)
Treatment	Rehabilitative interventions	Physical exercises in normal aging or in neurological disease (i.e. PD) (192, 193); Dance therapy (i.e. Tango, Salsa) in normal aging or in neurological disease (i.e. AD, PD) (176, 194-196); Tai Chi in normal aging or PD (197-199);
	Pharmacological treatments for gait disorders	Acetylcholinesterase inhibitors or Memantine in AD (28, 29); Methylphenidate or Amantadine in PD (31, 200-204); Fampridine in Multiple sclerosis (205);
	Non-invasive brain stimulation	TMS and tDCS in stroke (206-209); TMS and tDCS in PD (210-214); TMS in vascular parkinsonism (215); TMS in Multiple sclerosis (216); TMS in spinal cord injury (217);
	Deep brain stimulation	PPN stimulation in PD (167)

PD: Parkinson's disease, iNPH: idiopathic normal pressure hydrocephalus, TUG: timed up and go, TMS: transcranial magnetic stimulation, tDCS: transcranial direct current stimulation, PPN: pedunculopontine nucleus

4.3 Future directions

Our current knowledge on the neural substrate of gait control opens new promising research fields. Future research should explore the "gait signature" of the different neurological conditions. Following the

methods developed in a recent meta-analysis aiming to describe the gait phenotype of healthy older adults, patients with MCI and Alzheimer's disease (25), future analyses comparing the various quantitative gait parameters in different neurological condition would lead to a better understanding of neurological gait disorders. The identification of a specific "gait signature" of neurological conditions would contribute to improve the strategy of the diagnostic process that will take into account the complexity of the comorbid conditions affecting older adults (218).

With the recent advances in neurosciences, especially in neuroimaging methods, including new neuroimaging modalities will improve our knowledge of the physiopathological mechanisms underlying neurological gait disorders. For example, non-invasive functional MRI methods without the need of experimental tasks called resting-state fMRI allow access to the brain regions functionally connected (219). Resting-state fMRI represents an appropriate method to understand the interconnecting brain networks involved in gait control, as suggested by recent preliminary reports (126, 220, 221). Future studies should also include new neuroimaging methods that are able to study grey and white matter brain structures as well as biochemical pathways that are specifically affected in neurological conditions with gait disturbances. Furthermore, the new neuroimaging techniques will benefit from the progress of the methods of gait quantification (222) that now include more portable devices that allow a long term monitoring of gait in the patient's own environment and not in "artificial" movement analysis laboratories (223, 224). These new approaches should also include the influence of the environment on the subject's performances (225).

In terms of therapeutic approach, to test the changes of brain networks modulates by pharamocological or non-pharmacological interventions, randomized controlled clinical trials focusing on gait are required. These clinical trials should include patients from different neurological conditions and not focus only on patients with prototypical Parkinson's disease. They should also measure gait with an appropriate quantification of gait parameters and not only with a rough clinical scale. Finally, these clinical

interventions should benefit from the new advances in neuroimaging methods to measure the neural mechanisms behind the clinical improvements.

4.5 Conclusion

Behavioral studies and multimodal neuroimaging methods to study the neural correlates of gait disorders have demonstrated an extended brain network involving the prefrontal cortex and subcortical structures. These brain structures are specifically affected by various neurodegenerative and vascular mechanisms, explaining the complexity of the physiopathological processes of neurological gait disorders. The increasing focus on these brain mechanisms offers a unique opportunity to improve the diagnosis of neurological disorders and to study new therapeutic options for treating gait disorders. The new advances in neuroscientific methods combined with the technological development of systems for gait quantification will contribute to enhance our knowledge of neurological gait disorders.

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