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Brain activation changes during locomotion in middle-aged to older adults with multiple sclerosis

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ABSTRACT

Mobility and cognitive impairments are common in persons with multiple sclerosis (MS), and are expected to worsen with increasing age. However, no studies, to date, in part due to limitations of conventional neuroimaging methods, have examined changes in brain activation patterns during active locomotion in older patients with MS. This study used functional Near Infrared Spectroscopy (fNIRS) to evaluate real-time neural activation differences in the pre-frontal cortex (PFC) between middle-aged to older adults with MS and healthy controls during single (Normal Walk; NW) and dual-task (Walking While Talking; WWT) locomotion tasks. Eight middle-aged to older adults with MS and eight healthy controls underwent fNIRS recording while performing the NW and WWT tasks with an fNIRS cap consisting of 16 optodes positioned over the forehead. The MS group had greater elevations in PFC oxygenation levels during WWT compared to NW than healthy controls. There was no walking performance difference between groups during locomotion. These findings suggest that middle-aged to older individuals with MS might be able to achieve similar levels of performance through the use of increased brain activation. This study is the first to investigate brain activation changes during the performance of simple and divided-attention locomotion tasks in MS using fNIRS.

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disease characterized by diffuse axonal damage and brain atrophy that arises from demyelination and neurodegeneration in the central nervous system [1–3]. Mobility impairments are one of the clinical hallmarks of MS [4] and often present as reduced walking performance that compromises independence. Mobility typically worsens with disease progression [5]. Furthermore, 40–65% of individuals with MS suffer from cognitive deficits, such as decreased working memory, attention, processing speed, information processing efficiency, and executive function [6], which often worsen with disease progression [7].

Though MS is usually diagnosed between the ages of 20 and 50 years, there are growing concerns as the peak prevalence of MS shifts into older age groups [8]. Indeed, declines in mobility and cognition associated with both aging and MS pathology might co-occur [9]. Declines in performance when walking while carrying out a concurrent cognitive task (i.e., dual-task walking) in persons with MS have been associated with increased fall risk [10]. Furthermore, similar to aging [11], attention and executive function have been shown to be crucial for the cognitive control of mobility in persons with MS [12,13], particularly when dual-tasking. Given the interrelation between mobility and cognitive function as we age [14] and in younger adults with MS [13], dual-task methodology provides a testbed for evaluating the cognitive control of mobility in older adults with MS through the use of divided attention tasks.

Evidence suggests that cortical reorganization may explain the limited relationship between actual tissue degradation and actual physical and cognitive deficits, which are the clinical expressions associated with MS, particularly at the earliest stages of the disease [15,16]. The remapping of cortical areas that control cognitive and motor functioning are seen as evidence for adaptive compensatory mechanisms in the PFC of persons with MS. Compensatory cortical activation is characterized by increased cortical activation in the PFC during cognitive tasks, which serves to compensate for widespread tissue damage, thus reducing the expected clinical effects in the early stages of MS [17]. Therefore,

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if similar cognitive performances are observed during dual-task conditions in persons with and without MS, increased PFC activation in those with MS compared to healthy controls would be expected, based on the compensatory cortical activation theory. Alternatively, increased PFC activation in persons with MS if associated with decreased gait performance would be consistent with the neural efficiency model [18]. Lower performing individuals would be expected to demonstrate increased PFC activation levels in comparison to higher performing individuals, but demonstrate decreased modulation as the task difficulty is increased, based on the neural efficiency model [18]. However, research concerning cognitive control of mobility in MS has been relatively scarce [9]. Additionally, partly due to the limitations of conventional neuroimaging methods, no studies thus far have examined changes in brain activation patterns during active locomotion in patients with MS.

Functional near-infrared spectroscopy (fNIRS) is an emerging neuroimaging technique for evaluating cortical activation during walking and cognitive tasks. Results from fNIRS studies indicate increased activation in the pre-frontal cortex (PFC) during walking while talking (WWT) compared with walking alone in older adults [19,20]. This parallels findings from functional magnetic resonance imaging (fMRI) research whereby increased BOLD activation levels in the PFC were observed for imagined WWT compared to imagined walking alone [21]. However, fNIRS has several advantages over fMRI in that fNIRS provides a non-invasive and low-cost measure of changes in cortical oxygenated hemoglobin (HbO_2) levels that may be better able to handle motion artifacts [22]. This is important considering that persons with MS who have cognitive impairments tend to move more than healthy controls in an fMRI scanner [23]. Further, the use of fNIRS allows for continuous recordings of hemodynamic responses in the PFC while performing natural movements such as walking [19,20], while fMRI requires that there is no movement as well as a supine position. Lastly, using fNIRS during actual locomotion tasks we may be better able to capture online brain activity during dual task paradigms, given that normal aging is associated with deficits in mental imagery proficiency [24].

The present study investigated the levels of PFC activation during gait under single and dual-task conditions in community-dwelling older adults with and without MS using fNIRS. This study focused on the PFC due to its role in coordinating attentional resources while dual-tasking [11,25]. We hypothesized that in comparison to healthy controls, persons with MS would exhibit a greater increase in PFC oxygenation levels during walking while talking (WWT) compared to normal walking (NW). Consistent with principles of neurovascular coupling [26], and prior observations in older adults [20], elevated HbO_2 levels are expected across all tasks relative to baseline. However, due to diffuse axonal damage in the central nervous system in persons with MS, we expected the efficiency of PFC activation to be deteriorated in comparison to healthy controls and lead to greater increases in PFC activation during WWT. Changes in HbO_2 levels across the PFC were further measured to examine if additional areas of the PFC are recruited in MS when compared to healthy controls, to compare with expected results from compensatory cortical activation theory. We further assessed the effect of MS on the cognitive control of gait function via changes in gait speed in NW and WWT tasks. Finally, we explored the relationship between disability in older adults with MS and the change in HbO_2 levels from NW to WWT.

2. Materials and methods

2.1. Participants

Participants were recruited from the local community and from previous MS studies at the University of Illinois at Urbana-Champaign. Participants consisted of a convenience sample of 8 community-dwelling individuals with MS (6 females) and 8 healthy controls that were recruited to be within a similar age range (HOA, 6 females) (Mean ± SD age: individuals with MS, 57 ± 5 years, range: 49–62 years; controls, 61 ± 4 years, range: 53–67 years; $p = 0.07$). A structured telephone interview was administered to potential participants to obtain verbal consent, assess medical history, and rule out dementia using the Telephone Interview for Cognitive Status (TICS-M) [27]. The inclusion criteria for individuals with MS included a definite diagnosis of MS that was confirmed in writing by the patient's neurologist, relapse-free for the past 30 days and had mild to moderate disability, as evaluated by the Kurtzke Expanded Disability Status Scale (EDSS, range = 1–6) [28], no cardiovascular conditions, and a TICS-M score ≥ 18. The EDSS was evaluated through a neurological examination that was administered by a Neurostatus-certified examiner. HOA were included in the study if they had no physical disabilities, neurological diseases, or cardiovascular conditions, and a TICS-M score ≥ 18. All participants were 45 years of age or older, had no lower limb injury within the last 6 months, were medically stable, and had normal or corrected to normal vision. No participants were left-handed [29] or had any neurological disease in addition to MS for the individuals with MS. Characteristics of the individuals are given in Table 1. This study was approved by the Institutional Review Board of the University of Illinois at Urbana-Champaign, and participants provided written informed consent.

2.2. Walking protocol

Reliability and validity of this walking paradigm has been established in prior studies involving older adults [30,31]. For the NW condition, participants were asked to walk at their "normal pace" for three consecutive loops around an instrumented walkway, 14 ft long and 4 ft wide, (Zenometrics, LLC; Peekskill, NY) in a quiet room. In the WWT condition, participants were asked to walk at their normal pace while reciting alternate letters of the alphabet starting with the letter 'B'. Participants were specifically instructed to pay equal attention to their walking and talking, as previously described in studies of older adults [31,32] and persons with MS [12]. For both conditions, participants wore comfortable footwear. Participants walked a set distance with the start and end points clearly demarcated. Participants were allowed to walk with or without an assistive device during the walking protocol. There was one MS participant that used a cane during the walking protocol and no HOA. However, no significant difference in the prevalence of use of an assistive device was found between groups ($p = 1.0$). During all trials, participants wore a ceiling mounted harness to ensure safety in the event of a slip, trip, or stumble (i.e., fall prevention). One researcher followed 1 m behind the participant and recorded the distance traveled (m) using a measuring wheel (Stanley MW50, New Briton, CT), as described in prior studies [33,34]. The actual walking speed (m/s) was then calculated by dividing the distance traveled by the time elapsed from the start to the stop of three consecutive loops. During the WWT condition, performance on the talking task was also assessed using the number of correct utterances per second, so as to normalize for the differences in time elapsed from the start to the stop of the WWT condition.

Table 1
Mean (SD) cohort characteristics.

Mean (SD) characteristics			
	MS (n = 8)	HOA (n = 8)	*p* Value
Age (years)	57 (5)	61 (4)	0.07
Height (cm)	170 (9)	170 (11)	0.98
Weight (kg)	69 (10)	76 (18)	0.35
Higher education (years)	4 (3)	5 (3)	0.68
RBANS (Index score)	97 (15)	110 (12)	0.07

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MS = Multiple sclerosis; HOA = Healthy older adult.