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ORIGINAL RESEARCH

Cognitive-Motor Related Brain Activity During Walking: Differences Between Men and Women With Multiple Sclerosis

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Abstract

Objective: To determine if sex differences in glucose uptake, a marker of brain activity, are present in brain regions that facilitate walking performance in persons with multiple sclerosis (MS).

Design: Cross-sectional, observational pilot.

Setting: University laboratory.

Participants: Positron emission tomography with fluorine-18-labeled deoxyglucose (FDG) was performed on persons with MS and healthy controls (4 men and 4 women per group; N = 16) after a 15-minute walking test.

Interventions: Not applicable.

Main Outcome Measure: Brain activity was quantified as the mean standardized uptake value (SUV).

Results: The mean SUV was significantly lower in the thalamus ($P = .029$) and cerebellum ($P = .029$) for men with MS compared with women with MS, but not for the prefrontal ($P = .057$) or frontal ($P = .057$) cortices. Similar nonsignificant trends were found for healthy controls. No mean SUV group × sex interaction effects were found between the MS and healthy control groups (all $P > .05$).

Conclusions: To our knowledge, this is the first study of brain activity sex differences based on FDG uptake in persons with MS during walking. Significantly less FDG uptake in the thalamus and cerebellum brain regions important for walking performance was found in men with MS compared with women with MS; however, these comparisons were not significantly different in the healthy control group. No differences in FDG uptake were found between the MS and healthy control groups in any of the brain regions examined. Results from this study provide pilot data for larger studies aimed at identifying underlying mechanisms responsible for accelerated disability in men with MS.

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Multiple sclerosis (MS) is a chronic, demyelinating degenerative disease of the central nervous system. Although women present with greater disease activity at a younger age and during earlier phases of the disease, overall disability and disease progression are accelerated in men, advancing with age and disease duration.[1] Secondary to their aggressive advancement of physical disability, men with MS are considerably less physically active[2] and present with higher rates of falls.[3,4]

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Effective physical activity (eg, walking) is essential to daily living and requires cognitive and motor interaction to achieve coordinated and automated walking performance. Disability among those with MS has largely been evaluated on walking; however, cognition as it pertains to daily physical tasks, cognitive-motor function (eg, mental attention, processing), is paramount to safe and efficient walking. Cognitive impairment affects up to 70% of persons with MS, beginning early in the disease process,[5] and worsening with disease duration and progression.[6] Impaired cognition in MS leads to restricted work and social activities and participation, resulting in poorer quality of life.[7] Persons with MS present with different aspects of cognitive dysfunction, most frequently observed as limitations in processing speed, sustained attention, and visuospatial perception.[8] Multiple cortical and subcortical brain structures, including the thalamus, cerebellum, and prefrontal and frontal cortices are responsible for proper performance and long-term preservation of these cognitive-motor domains. Moreover, men with MS consistently present with greater cognitive impairments that are associated with altered functioning in multiple brain regions,[9] including the thalamus.[10] Previously, positron emission tomography (PET) neuroimaging has been implemented to quantify resting-state glucose uptake and metabolism in multiple cortical and subcortical brain structures among persons with MS.[11,12]

Recommendations have been made to implement neuroimaging to identify biomarkers that may play important roles in cognitive behavior.[13] Recent studies have found functional attenuation of the thalamus, cerebellum, and prefrontal and frontal cortices in persons with MS during cognitive task performance and resting states.[14-18] However, to our knowledge, no prior studies have compared brain activity in regions responsible for cognitive-motor function based on sex during or after a walking task, leaving the reasons for distinct sex differences among persons with MS poorly understood.

The purpose of our study was to compare fluorine-18-labeled deoxyglucose (FDG), a glucose analogue PET tracer, uptake in brain regions that are important for sustained walking performance in men and women with MS and healthy controls after walking. Because men with MS present with greater disability in cognition and walking, we hypothesized that men with MS would present with significantly less FDG uptake in the thalamus, cerebellum, and prefrontal and frontal cortices brain regions compared with women with MS and that the sex differences in those with MS would be greater compared with healthy participants. Our efforts are further supported by a recent topical review on sex differences in MS, which concluded that the lack of sex-related neuroimaging comparisons on this topic is a significant gap in research.[19]

Methods

Participants and procedures

The pilot study was a cross-sectional, observational design. Eight participants with MS (4 men, 4 women) were recruited through advertisements through a local MS center, and 8 healthy control participants (4 men, 4 women) were recruited by advertisement on a local medical campus. A local scientific ethics committee, guided by the ethical principles for human subject research and in accordance with the U.S. Department of Health and Human Services policy and regulations (45 CFR 46), approved this study. All participants gave written informed consent prior to their participation in the study. Participants with MS had confirmed diagnosis of MS, no changes in disease status 3 months prior to the study, and no greater than mild spasticity in the legs; were between 18 to 55 years of age; and were able to walk 15 minutes without assistance. Participants with MS completed the Patient Determined Disease Steps Scale[a] to determine disability level. The healthy control participants were without neurologic or musculoskeletal disorders. All participants reported performing $\leq$2 to 4d/wk of no greater than moderate level of exercise. After completion of informed consent, all participants underwent the same experiment protocol to decrease variability and bias. The experiment began with each participant walking on a treadmill at a self-selected speed for 15 minutes. Two minutes after walking started, they were injected with approximately equal to 321.9MBq of FDG into an antecubital vein. On completion of treadmill walking, participants underwent PET imaging. PET images were subsequently converted into standardized uptake value (SUV) parametric images using a voxel by voxel calculation with the formula SUV_{mean}=activity (Bq/mL^3)/(injected activity [MBq]/body weight [kg]), where SUV_{mean} is the mean SUV. SUV parametric images were then normalized to a tracer specific template into Montreal Neurological Institute space similar to Tuulari et al.[20] Images were smoothed at 10-mm full width at half maximum. The mean SUV of regions of interest within the automatic anatomic labeling template[21] were extracted from the SUV parametric images using the MarsBaR toolkit[b] within the Statistical Parametric Mapping 8 toolbox[c] for MATLAB R2014a.[d] Consent and all aspects of the experiment were performed in a university medical campus laboratory. Power and sample size estimates were not performed for this pilot study because no prior preliminary data or study results were available. The methodology of this study has been reported previously.[22-25]

List of abbreviations:

FDG fluorine-18-labeled deoxyglucose
MS multiple sclerosis
PET positron emission tomography
SUV standardized uptake value

Data analysis

Data, including the regions of interest, analysis was conducted using the nonparametric Mann-Whitney *U* test for within-group characteristics and sex differences. To compare mean SUVs between the groups based on sex (group $\times$ sex), an adjusted rank transformation was implemented as a nonparametric test of interaction.[26] All tests were 2-tailed, using .05 as the level of statistical significance. Mean and SD, median and range, and nonparametric standard effect size index (Cohen *r*) were calculated. Cohen *r* interpretations are as follows: large effect was 0.5, medium effect was 0.3, and small effect was 0.1.[27]

Results

Participant characteristics

Participant demographics and characteristics for the MS group are detailed in table 1, where age, MS diagnosis duration, disability level, and self-selected speed walk were similar between men and