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Altered brain activation in complex walking conditions in patients with Parkinson's disease

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ABSTRACT

Introduction: Behavioral studies suggest that deficits in cognitive domains and sensory-motor processes associated with Parkinson's disease (PD) impair the ability to walk in complex environments. However, the neural correlates of locomotion in complex environments are still unclear.
Methods: Twenty healthy older adults (mean age 69.7 ± 1.3 yrs) and 20 patients with PD (mean age 72.9 ± 1.6 yrs; disease duration: 6.8 ± 1.3 yrs; $UPDRS_{III}$: 29.8 ± 2.4) were asked to imagine themselves walking while in the MRI scanner. Three imagined walking tasks, i.e., usual walking, obstacle negotiation, and navigation were performed. Watching the same virtual scenes without imagining walking served as control tasks. Whole brain analyses were used.
Results: Compared to usual walking, both groups had increased activation during obstacle negotiation in middle occipital gyrus (MOG) (pFWEcorr<0.001), middle frontal gyrus (MFG) (pFWEcorr<0.005), and cerebellum (pFWEcorr<0.001). Healthy older adults had higher activation in precuneus and MOG (pFWEcorr<0.023) during navigation, while no differences were observed in patients with PD. Between group comparisons revealed that patients with PD had a significantly higher activation in usual walking and obstacle negotiation (pFWEcorr<0.039) while during navigation task, healthy older adults had higher activation (pFWEcorr<0.047).
Conclusions: Patients with PD require greater activation during imagined usual walking and obstacle negotiation than healthy older adults. This increased activation may reflect a compensatory attempt to overcome inefficient neural activation in patients with PD. This increased activation may reduce the functional reserve needed during more demanding tasks such as during navigation which may contribute to the high prevalence of falls and dual tasking difficulties among patients with PD.

1. Introduction

The ability to walk safely and independently is a fundamental component of daily living activities [1]. This ability requires constant adaptation of one's walking pattern to avoid obstacles and plan the traveled path based on prior and continuously updated information and maps. Meeting these requirements involves high-level cognitive functions such as navigation, divided attention and visual scanning [2]. Deficits in cognitive domains and sensory-motor processes associated with neurodegenerative diseases such as Parkinson's disease (PD) lead to decreased performance when walking in challenging conditions and an increased risk of falls during walking in everyday life environments [1,3]. Behavioral studies show that impairments in cognitive function can be observed in all phases of gait, including motor planning [4], execution [5,6], and ongoing adjustments to the environment [7] and may contribute to the poor walking performance. However, the neural circuits that modulate these changes, specifically in the frontal, parietal, and occipital lobe are poorly understood.

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MRI studies have used motor imagery to explore neural activation associated with walking, as motor imagery has been shown to activate neural networks associated with motor execution, more specifically those associated with motor planning [5,6]. Virtual reality has been proposed as a method to improve motor imagery performance [8]. By using a simulation of a real world, virtual reality allows for the control of content of the imagined task and increases engagement [9,10]. The few studies that used motor imagery of gait and virtual reality observed increased activation in prefrontal regions in patients with PD as compared to healthy older adults [11–13]. This increased activation in patients with PD was shown during usual walking [11] and more complex tasks such as turning [11] and stepping over obstacles [13]. However, changes in activation as a result of different cognitive loads and demands were not assessed. Thus, it is not clear if different types of cognitive load will result in different activation within and between groups.

To elucidate changes in neural activation associated with different cognitive demands, we included imagined usual walking and two complex imagined walking tasks. One was imagined walking while negotiating obstacles which emphasizes motor planning, while the second was imagined walking while navigating to a specific target, which requires visual memory, information processing, and decision making, in addition to motor planning [14,15]. As such, the aims of this study were to investigate the differences in neural areas that are activated during complex walking that possess different cognitive demands and to assess the influence of a neuro-degenerative disease such as Parkinson's disease on these neural circuits. Our hypotheses were that (1) imagined complex walking tasks with different cognitive demands will show altered brain activation as compared to usual walking in frontal, parietal and occipital regions, and (2) patients with PD will have higher brain activation than healthy older adults during all imagined walking tasks.

2. Material and methods

2.1. Participants

A cross sectional study design was employed to compare two groups of subjects: twenty healthy older adults and twenty patients with PD. General inclusion criteria were (1) age > 60 years, (2) able to walk at least 5 min unassisted, and (3) stable medication for the past month. Patients with PD were included if: (1) diagnosed as having idiopathic PD, as defined by the UK Brain Bank criteria, (2) in Hoehn and Yahr stage II-III, and (3) taking anti-Parkinsonian medication. Subjects were excluded if they had: psychiatric comorbidity, Mini Mental State Exam score <24, a history of stroke, traumatic brain injury or other chronic neurological disorders, and any orthopedic problems that may affect their gait [8]. All participants gave their written informed consent prior to participation. The study was approved by local ethical committees and was performed according to the principles of the Declaration of Helsinki.

2.2. Protocol

The protocol included two parts that were conducted in two separate visits: 1) MRI scan and 2) gait and cognitive assessments. Patients with PD performed the two parts of the protocol during their “on” medication state, typically 2 h after intake of the last dose of anti-parkinsonian medication. Prior to the MRI scan subjects underwent preparatory session in which motor imagery of walking in three virtual environments (supplementary 1) was practiced. In addition, motor imagery ability was evaluated based on performance across three measurements tools [16]: (1) Kinesthetic and Visual Imagery Questionnaire (KVIQ), (2) a chronometric test in which the time to complete real and imagined 10 m walking task was compared, and (3) a debriefing questionnaire. During the MRI scan subjects were instructed not to move their legs. Each of the three imagined walking tasks lasted 45 s and was repeated four times. In the first task, the virtual path was clear and subjects were asked to imagine themselves walking at their comfortable speed (“usual walking”). In the second task, the virtual path contained various obstacles and subjects were instructed to imagine themselves walking while stepping over the obstacles (“obstacles negotiation”). In the third task, a map was presented and subjects were asked to plan their route to a specific target marked on the map. Each route included three intersections. After 45 s the map was removed and the subjects were asked to navigate through a virtual path towards the chosen destination. A response box was used to record the subject's choice of path when an intersection was reached (“navigation”). Control tasks of only watching the same virtual scenes, without imagining walking, were conducted to account for brain activation associated with viewing the scenes. Following the fMRI scan subjects were debriefed for their motor imagery performance and their ability to watch the video without imagined walking. The answers were given based on 0 to 10 scale in which 0 represent no difficulty and 10 extreme difficulty to imagine walking.

2.3. Data acquisition

Gait and cognitive tests were conducted to characterize real walking and cognitive abilities. Gait assessments included three walking tasks: (1) usual walking, (2) walking while serially subtracting 3s, and (3) walking while stepping over 5 obstacles at the size of 25 cm width × 10 cm height × 15 cm depth. Gait measurements were obtained from the Zeno Walkway (PKMAS, Portokinetics), a sensorized mat that captured individual footfall data. Each walking task was repeated for 5 times and tempo-spatial measurements of gait were calculated as the average of the 5 trials. The computerized cognitive battery included six tests: (1) Go-NoGo, (2) Non-verbal memory, (3) Color stroop, (4) Catch game, (5) visual spatial processing, and (6) Staged information processing (NeuroTrax: Modiin, Israel). Based on these tests the NeuroTrax software composites indices of six cognitive domains on an IQ-like scale, with 100 representing the estimated population mean normalized for age and education. The cognitive domains include: (1) global cognitive score, (2) memory, (3) executive function, (4) visual spatial, (5) attention, and (6) information processing [17].

Neural brain activation was assessed using a GE 3 T Signa scanner. All images were acquired using a standard eight-channel head coil. For each subject, a structural scan three-dimensional spoiled gradient (3D-SPGR) echo sequence was collected: field of view (FOV) 250 × 250 mm; matrix size 256 × 256; voxel size 0.98 × 0.98 × 1; Repetition Time (TR) 9 msec; Echo Time (TE) 3.6 msec. Functional images were acquired using a single-shot echo-planar T2*-weighted sequence with the following parameters: FOV 200 × 200 mm; matrix size 128 × 128; 39 slices with 3 mm thickness and no gap; TR/TE 3000/35 msec; flip angle 90°. Acquisition orientation obtained from the fourth ventricle plane. The visual stimulus delivery and the response acquisition of the tasks conducted in the scanner were controlled using Presentation software (Neurobehavioral Systems, Albany, USA). Images were projected via an LCD projector (NEC, VT660K) onto a screen positioned in front of the subjects' forehead and viewed through a tilted mirror. Responses such as the decision to turn right or left at intersections were gathered with an MRI-compatible response box (HH-1 × 4L, Current Designs).