Journal of the Neurological Sciences 354 (2015) 33–36

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Pallidal and caudate volumes correlate with walking function in multiple sclerosis ☆

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ARTICLE INFO

Article history:
Received 17 February 2015
Received in revised form 23 April 2015
Accepted 24 April 2015
Available online 1 May 2015

Keywords:
Multiple sclerosis
Walking
Thalamus
Basal ganglia
MRI
Imaging

ABSTRACT

Background: Walking dysfunction is common in multiple sclerosis (MS). The thalamus and basal ganglia seemingly have important associations with walking performance. The contribution of these subcortical gray matter (SGM) structures for walking dysfunction is poorly understood in MS.
Purpose: This study examined associations among volumes of the thalamus and basal ganglia with walking outcomes in MS.
Method: We enrolled 61 MS patients who underwent brain MRI and completed the 6-minute walk (6 MW) and timed 25-foot walk (T25FW). Volumes of the thalamus, caudate, putamen, and pallidum as well as whole-brain white matter (WM) and gray matter (GM) were calculated from 3D T1-weighted structural brain images. We examined associations using bivariate correlations (r) and partial correlations (pr) that controlled for age, MS clinical course, and whole-brain WM and GM volumes. We further performed hierarchical linear regression (HLR) for identifying the strongest SGM correlate of walking performance.
Results: The 6 MW and T25FW correlated significantly with volumes of the thalamus (r's = .382 & .383), caudate (r's = .388 & .416), pallidum (r's = .457 & .457), and putamen (r's = .258 & .293) in bivariate correlations. The 6 MW and T25FW remained significantly correlated with caudate (pr's = .243 & .312) and pallidum (pr's = .321 & .345) volumes in partial correlations. Pallidum volume was the strongest SGM correlate of 6 MW (β = .39) and T25FW (β = .40) performance in HLR.
Conclusion: We provide novel evidence of possible SGM structures, particularly the pallidum and perhaps caudate, as correlates of walking performance in MS.

1. Introduction

Walking is one of the most valued functions among persons with multiple sclerosis (MS) [1,2], and upwards of 75% of persons with this disease report mobility and walking problems [3,4]. The dysfunction of walking is present early in MS [4] and worsens with disease and disability progression [5–7].

To date, there has been limited research on subcortical gray matter (SGM) pathology as correlates of walking dysfunction in MS [4,7,8]. The thalamus and basal ganglia nuclei, in particular, represent SGM structures within the central nervous system that are important for motor control [9] and demonstrate atrophy in MS [10]. We focused on these nuclei considering the importance of the cortico-striato-pallido-thalamo-cortical circuit for controlling motor function [11]. Atrophy of the thalamus and basal ganglia nuclei of the caudate, putamen, and pallidum further has been associated with walking speed and motor function in older adults [12,13], yet such associations are poorly understood in MS.

This study examined associations among volumes of the thalamus and basal ganglia nuclei with walking performance in persons with MS. We expected that volumes of thalamic and basal ganglia nuclei would be associated with walking outcomes, and that the associations would be independent of age, MS clinical course, and whole-brain white matter (WM) and gray matter (GM) volumes. We further explored the SGM structures most strongly associated with walking performance in MS.

☆ Disclosures: This paper was supported, in part, by grants from the National Multiple Sclerosis Society (RG 4491A3/1, IL 0003, IL 0011).
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http://dx.doi.org/10.1016/j.jns.2015.04.041
0022-510X/

2. Methods

2.1. Participants

The methods for this study were approved by an IRB, and all participants provided written informed consent. We enrolled 63 patients with clinically definite MS [14]. The sample was primarily female (n = 47, 77%) with a mean age of 50.0 (SD = 9.1) years, and the clinical course was relapsing–remitting MS (RRMS) in 46 patients (75%) and progressive (either primary or secondary) in the other 15 patients (25%). The mean disease duration of those with MS was 11.4 (SD = 8.3) years, and the median Expanded Disability Status Scale score was 5.5 (IQR = 3.0). All participants with MS were receiving an ongoing disease modifying therapy, but none were currently receiving short-course medications for ongoing relapse.

2.2. Walking performance

We included two walking performance outcomes based on psychometric criteria outlined in recent reviews [4,7,15], and the outcomes were administered by personnel who were not involved in the MRI acquisition or analyses.

6 MW. The six-minute walk (6 MW) was included as a measure of walking endurance and administered according to standardized instructions for persons with MS [5,16]. Participants were instructed to walk as fast and as far as possible for 6 min in a single 75-foot long corridor with 180° turns marked by plastic cones. One experimenter followed approximately 3 ft behind the participant with a measuring wheel (Stanley MW50, New Briton, CT) and recorded the total distance traveled in feet.

T25FW. The timed 25-foot walk (T25FW) was administered as a measure of walking speed [17]. Briefly, participants underwent two trials of walking as fast as possible over a 25-foot course. The primary outcome of the T25FW was mean walking speed (ft/s) over the two trials (i.e., T25FW speed). This outcome measure is more normally distributed than the mean T25FW time [18].

2.3. MRI acquisition and analysis of SGM structures

The MRI acquisition and analysis was conducted by personnel who were not involved in the administration of walking measures. Using a whole body Siemens Trio 3 Tesla MRI scanner (Erlangen, Germany), we acquired high-resolution 3D T1-weighted structural brain images using an MPRAGE sequence with the following parameters: 23 cm FOV, 256 × 256 × 192 matrix size with 0.9 mm isotropic resolution, echo time (TE)/repetition time (TR)/inversion time (TI) of 2.32/1900/900 ms, flip angle of 9°, GRAPPA accelerated factor of 2 with 24 reference lines. We then extracted the brain and excluded the skull by deleting non-brain tissue from our T1 whole-brain images using the Brain Extraction Tool [19] from FMRIB's Software Library. We used bias field correction in order to ensure accurate brain extraction. Next, we segmented the 3D T1 image into 3 tissue types, white matter, gray matter, and cerebrospinal fluid, using FMRIB's Automated Segmentation Tool [20] from FMRIB's Software Library. Using the 3D T1 images, we calculated volumes of the right and left thalami and basal ganglia nuclei using FMRIB's Integrated Registration and Segmentation Tool-algorithm [21]. This segments the T1 images into subcortical structures and measures the volumes. We computed a volume scaling factor by linear registration of the skull and brain masks using FSL's flirt, and extracting scaling parameters from the resulting affine transformation matrix, as is done in FSL's SIENAX [22–24]. We further computed whole-brain WM and GM volumes using SIENAX. We then normalized all volumes based on intracranial volume by multiplication with this volume scaling factor, and then normalized right and left volumes were averaged for inclusion as composites in the statistical analyses. This was based on strong correlations between right and left volumes (e.g., thalami: $r = .93$, $p < .0001$) and reducing possible inflated error rates with multiple comparisons. We further note that this has been undertaken in other research on SGM volumes in MS [10].

2.4. Procedures

The protocols for data collection were administered on two separate days separated by no more than a week. The participants initially completed the walking outcomes on the first day. There was a 15-minute period of seated rest between the walking assessments. The participants then underwent an MRI within seven days of the first testing session.

2.5. Data analysis

The data were analyzed in SPSS Statistics version 22.0 for Mac OS X operating system. Descriptive statistics were provided as mean ± standard deviation, unless otherwise noted. We examined the associations among 6 MW, T25FW, and thalamic, basal ganglia, and whole-brain WM and GM volumes using Pearson product-moment correlation coefficients (r). We then examined the associations among 6 MW, T25FW, and thalamic and basal ganglia volumes controlling for age (yrs), clinical course (0 = RRMS, 1 = secondary/primary progressive MS), and whole-brain WM and GM volumes using partial correlation coefficients (pr). The final analysis involved hierarchical linear regression models that explored the SGM structure most strongly associated with walking performance. We regressed walking outcomes on age (yrs), clinical course (0 = RRMS, 1 = secondary/primary progressive MS), and whole-brain WM and GM volumes using direct entry in Step 1, and thalamus and basal ganglia volumes were entered in Step 2 using a forward stepwise technique (entrance criterion of $p < .05$ and exit criterion of $p = .10$). This permitted an exploration of the strongest SGM predictors of walking performance over-and-beyond whole-brain WM and GM volumes.

3. Results

3.1. Descriptive statistics for walking and MRI outcomes

The mean values for the 6 MW and T25FW were 1109 ± 637 ft and 3.7 ± 2.0 ft/s, respectively. The mean composite values for the thalamus, caudate, pallidum, and putamen volumes were 8562 ± 1193 mm^3, 3931 ± 721 mm^3, 1845 ± 292 mm^3, and 5154 ± 883 mm^3, respectively. The mean values for whole-brain WM and GM volumes were 719,443 ± 61,191 mm^3 and 669,709 ± 51,398 mm^3, respectively.

3.2. Bivariate correlations among walking and MRI outcomes

The bivariate correlations among walking and MRI outcomes are provided in Table 1. The 6 MW and T25FW were significantly correlated with composite volumes of the thalamus, caudate, pallidum, and putamen. Both the 6 MW and T25FW were significantly associated with whole-brain WM volume, whereas only 6 MW was associated with whole-brain GM volume. Volumes of the thalamus, caudate, pallidum, and putamen were associated with whole-brain WM and GM volumes.

3.3. Partial correlations among walking and SGM outcomes

The bivariate correlations among walking and SGM outcomes are provided in Table 2. The 6 MW and T25FW remained significant correlates of caudate and pallidum volumes, when controlling for age, MS clinical course, and whole-brain WM and GM volumes. Of note, the strength of the correlations was attenuated, as expected, considering the covariation between SGM and whole-brain structural volumes. The 6 MW and T25FW did not significantly correlate with thalamus and putamen volumes, when controlling for age, MS clinical course, and whole-brain WM and GM volumes.