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Abstract

Background

Persons with multiple sclerosis (MS) often demonstrate impaired walking performance, and neuroimaging methods such as resting state functional connectivity (RSFC) may support a link between central nervous system damage and disruptions in walking.

Objectives

This study examined associations between RSFC in cortical networks and walking performance in persons with MS.

Methods

29 persons with MS underwent 3-T brain magnetic resonance imaging (MRI) and we computed RSFC among 68 Gy matter regions of interest in the brain. Participants completed the Timed 25-foot Walk as a measure of walking performance. We examined associations using partial Pearson product-moment correlation analyses (*r*), controlling for age.

Results

There were eight cortical brain regions that were significantly associated with the T25FW, including the left parahippocampal gyrus and transverse temporal gyrus, and the right fusiform gyrus, inferior temporal gyrus, lingual gyrus, pericalcarine cortex, superior temporal gyrus, and transverse temporal gyrus.

Conclusions

We provide novel evidence that RSFC can be a valuable tool to monitor the motor and non-motor networks impacted in MS that relate to declines in motor impairment. RSFC may identify critical nodes involved in a range of motor tasks such as walking that can be more sensitive to disruption by MS.

Keywords

Connectivity, Walking, Multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disease characterized by inflammation, demyelination and transection of axons, and neurodegeneration within the central nervous system (CNS) (Trapp and Nave, 2008). Persons with MS often demonstrate impaired walking performance, ostensibly a result of the damage in the CNS (Motl, 2013). Neuroimaging methods can provide a link between focal damage to the CNS and disruptions to walking, and this is an emerging area of literature that has largely focused on regions of interest (Motl et al., 2015) and tracts (Hubbard et al., 2016).

Functional magnetic resonance imaging (fMRI) during the resting state (RS) may be an effective technique for examining the neural correlates of walking performance in MS (Sbardella et al., 2015). This technique temporally correlates spontaneous, low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal that are temporally coherent across anatomically separate brain regions at rest as a measure of functional connectivity (FC) (Ogawa and Lee, 1990, Filippi and Rocca, 2013). Resting state functional connectivity (RSFC) relies on the same BOLD signal mechanism that would present during a task-based fMRI scan, and hence this signal represents neural activity, including neurotransmitter turnover and metabolism (Attwell and Iadecola, 2002). Importantly, RSFC may elucidate the networks involved with walking performance as well as the impact of CNS damage, providing a potential to monitor disease progression or intervention efficacy.

A recent study examined the associations of RSFC at the cortical and subcortical levels with disability and cognitive impairment in persons with MS (Rocca et al., 2017). That study analyzed four cortical hubs, including specific brain regions representing the default mode network (DMN), dorsal attention network (DAN), sensorimotor network, and the visual network; and three subcortical hubs, including specific brain regions representing the cerebellum network, thalamic network, and reward-emotion network. The results indicated that higher disability (i.e., Expanded Disability Status Scale (EDSS) scores) was significantly correlated ($p < 0.05$) with reduced RSFC in the DMN, DAN, and the sensorimotor network (Rocca et al., 2017). Worse performance in the attention, verbal, and visual memory domains of neuropsychological measures (i.e., the Brief Repeatable Battery of Neuropsychological Tests) were significantly correlated with reduced global RSFC in the DMN and DAN and reduced regional RSFC in the cognitive, sensorimotor, cerebellar, and subcortical networks (Rocca et al., 2017). However, other research on RSFC in persons with MS have been somewhat contradictory as some studies demonstrated cognitive impairment to be associated with reduced RSFC (Rocca et al., 2010, Bonavita et al., 2011) in cognitive-related networks, while other studies demonstrate increased RSFC (Hawallek et al., 2011, Faivre et al., 2012).

Previous research in healthy populations has demonstrated that locomotion, or walking, is associated with brain activation in several brain regions, including parietal, parahippocampal, and prefrontal regions that are associated with spatial navigation, memory, and executive function (Hamacher et al., 2015). For example, a study in a sample of healthy older adults examined RSFC and gait velocity in normal walking and dual task (DT; i.e., walking while talking) conditions (Yuan et al., 2015). That study demonstrated gait velocity in both conditions to be significantly and positively associated ($p < 0.05$) with RSFC, such that faster gait velocity was associated with higher RSFC. This was specifically apparent in the sensorimotor (premotor, primary motor, and supplementary motor cortices), visual (primary, secondary, and associative visual cortices), vestibular (insula and the primary and secondary auditory cortices), and left frontal parietal (left posterior parietal association areas, left supplementary motor cortex, left frontal eye field, and left prefrontal association cortex) areas (Yuan et al., 2015). The networks associated with gait velocity in the DT condition demonstrated significantly greater FC in supplementary motor and prefrontal regions, when compared to the normal walking condition (Yuan et al., 2015). In persons with MS, two previous studies demonstrated that corticospinal motor pathway damage, measured using diffusion tensor imaging, was associated with walking performance (Hubbard et al., 2016, Fritz et al., 2017) in persons with MS. However, these studies did not examine the neural correlates of walking performance in persons with MS at the cortical level.

To that end, this novel and exploratory study examined the associations of RSFC in cortical motor and non-motor (i.e., sensory, spatial, and attention) networks with walking performance (i.e., the Timed 25-foot Walk (T25FW)) in participants with MS. By focusing on cortical RSFC, we believe this study will help to identify critical FC nodes involved in MS-related degradations in walking performance. Importantly, cortical nodes identified as critical to walking performance in MS may potentially provide targets to monitor for early responses to behavioral interventions, such as physical activity, for the promotion of improved walking performance.

2. Materials and methods

2.1. Participants

A University Institutional Review Board approved the methods, and participants provided written informed consent. Participants were recruited through targeted advertisements disseminated in central Illinois. The inclusion criteria were confirmed diagnosis of MS, relapse-free within the past 30 days, not taking monthly medications for ongoing relapse, ambulatory with or without an assistive device, between the ages of 18 and 64, being right-handed, and willingness to undergo an MRI. Participants who screened positive for MRI contraindications were excluded from the study. 29 participants satisfied inclusion criteria and were enrolled in

the study. Participants first underwent a neurological examination administered by Neurostatus-certified research personnel for Expanded Disability Status Scale (EDSS) scoring (Kurtzke, 1983), and all participants completed the T25FW and underwent an MRI within 14 days of the initial testing.

2.2. Timed 25-foot walk (T25FW)

The T25FW was administered as a measure of walking speed (Motl et al., 2017). Participants were instructed to walk as quickly and as safely as possible over a 25-ft course on a carpeted surface. One researcher recorded the participant's time (s) over two trials. Scores were averaged and then converted into walking speed (ft/s) in order to normalize the distribution (Hobart et al., 2013).

2.3. MRI acquisition and analysis

High resolution 3D T_1-weighted structural brain images were acquired using a whole-body Siemens Trio 3-T MRI scanner (Erlangen, Germany) using a magnetization prepared, rapid acquisition gradient echo (MPRAGE) sequence and the following parameters: 23 cm field of view, 256 × 256 × 192 matrix size with a 0.9 mm isotropic resolution, echo time (TE)/repetition time (TR)/inversion time (TI) of 2.32/1900/900 ms, flip angle of 9°, and generalized autocalibrating partially parallel acquisitions (GRAPPA) accelerated factor of 2 (Griswold et al., 2002). In addition, RS fMRI data was acquired using a gradient echo, echo planar imaging (EPI) acquisition with the following parameters: 38 slices, 3 mm slice thickness and 10% slice gap, TE/TR of 25 ms/2 s, 92 × 92 matrix size with a 23 cm field of view, parallel imaging using a GRAPPA accelerated factor of 2, and a resulting spatial resolution of 2.5 × 2.5 × 3.3 mm. 300 volumes were collected in the RS acquisition, which lasted for 10 min. Participants were instructed to keep their eyes open during the scan.

2.4. Preprocessing pipeline

DICOM format files acquired from the MRI scanner were first converted into the NIfTI format and then taken through a multi-step pipeline (Chou et al., 2012) relying heavily on FMRIB Software Library (FSL) (Jenkinson et al., 2012, Smith et al., 2004, Woolrich et al., 2009) and the Nipype python module (Gorgolewski et al., 2011). After converting the data to radiological (LAS) orientation, the first four time points of the time series were discarded. Then, the data were algorithmically corrected for slice acquisition timing and then FSL's MCFLIRT tool for motion registration was applied to the functional data (Jenkinson et al., 2002a, b). After registration, the six motion parameters were regressed from the time series. The timewise mean of the functional data was then calculated and used as a reference for FSL's brain extraction tool (BET) to skull strip the dataset (Jenkinson et al., 2002a, b). The functional dataset was then resampled into a 2 mm isotropic analysis space, to minimize interpolation and increase the computational efficiency of the preprocessing pipeline as an alternative to carrying out processing in the structural space. A transformation to this analysis space was then computed for the T_1-weighted sagittal MPRAGE structural image using FSL's Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002a, Jenkinson and Smith, 2001), to be applied to a semi-automated cortical Freesurfer parcellation (Desikan et al., 2006, Fischl et al., 2004) generated from the structural data, as well as white matter (WM) and cerebrospinal fluid (CSF) masks generated using FSL's Automated Segmentation Tool (FAST) (Zhang et al., 2001). The Freesurfer-based parcellation used in this study included manual edits by a trained analyst to correct common tissue misclassifications, according to the methods recommended on the Freesurfer website (Freesurfer Tutorial, 2017). The WM and CSF signals were then regressed from the dataset, and the data were bandpass filtered to remove low frequency motion signals and high frequency noise.

2.5. Generation of connectivity matrices

After preprocessing, the Freesurfer parcellation was applied to the data to extract the average time series for the 68 grey matter (GM) regions of interest in this study and these regions are listed in the Appendix. This method has demonstrated to be both anatomically valid and reliable for subdividing the human cerebral cortex

into standard gyral-based neuroanatomical regions (Desikan et al., 2006). The Pearson correlation coefficient was computed between the mean time series for each region of interest yielding a 68 × 68 connectivity matrix for each participant. Prior to correlation, we identified and removed any data that exhibited motion past a certain threshold, discarding time frames that exceed a frame-wise displacement threshold of 0.5 mm or a DVARS threshold of 0.5% (Power et al., 2012). We then calculated the average RSFC between each region and all 67 other regions as a measure of regional strength (Nelson et al., 2017).

2.6. Statistical analyses

Data analyses were conducted in IBM SPSS Statistics, Version 24 (SPSS, Inc., Chicago, IL). Descriptive statistics are listed in Table 1 as mean (standard deviation, SD), unless otherwise noted (e.g., percentages). The primary analysis estimated the associations between cortical connections of brain regions and the T25FW using partial Pearson product-moment correlations (*r*), controlling for age. We included age as a covariate as previous research has demonstrated a variety of aging-related RSFC changes in the brain (Ferreira and Busatto, 2013). The level of significance was set at $p < 0.05$, after multiple comparisons were corrected for using the Benjamini Hochberg false discovery rate (FDR) correction (Genovese et al., 2002). The magnitude of comparisons was interpreted as small, medium, and large based on values of 0.1, 0.3, and 0.5, respectively (Cohen, 1988).

Table 1. Demographic and clinical characteristics and descriptive statistics for walking performance in persons with MS (n = 29).

Variable	MS (n = 29)
Age	52.3 (8.3)
Sex, % female	100%
MS Type, % RRMS	75%
Disease Duration	17.6 (9.3)
Assistive Device	58.3%
EDSS, mdn (min – max)	6.0 (2.0–6.5)
T25FW, ft/s	3.3 (1.9)

Note. All values are reported as mean (SD), unless otherwise noted. MS = multiple sclerosis; RRMS = relapsing-remitting MS; EDSS = Expanded Disability Status Scale; T25FW = Timed 25-foot Walk.

3. Results

3.1. Sample characteristics and walking performance

The sample was composed of all women (n = 29) who had a mean age of 51.6 (SD=9.4) years. Most participants had relapsing-remitting MS (75%), with 25% reporting progressive MS. The average disease duration was 17.6 (SD=9.3) years and the majority of participants used an assistive device (58.3%). The median Expanded Disability Status Scale (EDSS) score was 6.0 (min – max: 2.0 – 6.5), representing moderate-to-severe disability (i.e., unilateral support is required for walking) (Kurtzke, 1983). Participants completed the T25FW at an average speed of 3.3 (1.9) ft/s.

3.2. Correlations between cortical connections of brain regions and T25FW

The partial Pearson product-moment correlations (*r*), controlling for age, between cortical connections of brain regions and T25FW are presented in Table 2. There were eight brain regions that demonstrated statistically significant ($p < 0.05$, FDR-corrected) correlations with the T25FW, including the left (L) parahippocampal gyrus, L transverse temporal gyrus, right (R) fusiform gyrus, R inferior temporal gyrus, R lingual gyrus, R pericalcarine cortex, R superior temporal gyrus, and R transverse temporal gyrus. Importantly, all of these correlations were strong in magnitude ($r = 0.54–0.66$).

Table 2. Statistically significant partial Pearson product-moment correlations (r), controlling for age, between cortical connections of brain regions and walking performance (T25FW) in persons with MS (n = 29).

Brain region	T25FW, ft/s	
	r-value	*p*-value, FDR-corrected
L Parahippocampal Gyrus	0.66	0.02
L Transverse Temporal Gyrus	0.54	0.03
R Fusiform Gyrus	0.65	0.02
R Inferior Temporal Gyrus	0.54	0.03
R Lingual Gyrus	0.54	0.03
R Pericalcarine Cortex	0.61	0.02
R Superior Temporal Gyrus	0.56	0.03
R Transverse Temporal Gyrus	0.58	0.02

Note. Statistical significance of $p < 0.05$ with Benjamani Hochberg false discovery rate (FDR) correction for multiple comparisons; MS = multiple sclerosis; T25FW = Timed 25-foot Walk; L = left hemisphere; R = right hemisphere.

4. Discussion

Although walking dysfunction is common and problematic for persons with MS (Motl, 2013), there is little literature on the CNS representation of these deficits, especially from a network perspective, in motor and non-motor, higher level networks. Herein, we examined the correlations of RSFC in 68 cortical gray matter regions involved in motor and non-motor networks with walking performance (i.e., T25FW) in persons with MS. On average, participants completed the T25FW at speed of 3.3 (1.9) ft/s, or over a duration of 7.6 s; a previous study demonstrated a T25FW of 6–7.99 s to be associated with a change in occupation due to MS, occupational disability, and needing help with activities of daily living (Goldman et al., 2013). After controlling for age, cortical connections of eight brain regions demonstrated significant ($p < 0.05$; FDR-corrected) and strong correlations with the T25FW, including the L parahippocampal gyrus, L transverse temporal gyrus, R fusiform gyrus, R inferior temporal gyrus, R lingual gyrus, R pericalcarine cortex, R superior temporal gyrus, and R transverse temporal gyrus.

Importantly, our results provide novel evidence of greater RSFC in specific brain regions to be significantly correlated with better walking performance. Several of these brain regions, including the R fusiform gyrus, R inferior temporal gyrus, R lingual gyrus, R pericalcarine cortex, and R superior temporal gyrus, play important roles in the visual network. For example, the fusiform gyrus is considered a key brain structure involved in high-level, specialized visual processing (Weiner and Zilles, 2016) and the superior temporal gyrus is a brain area that is part of the mirror neuron system, assumed to support action recognition and interpretation of human movement (Herrington et al., 2011). The function of inferior temporal gyrus is visual perception and is associated with the prefrontal cortex, a brain region that has consistently been associated with walking performance (Koenraadt et al., 2014). The paraphippocampal gyrus is a brain region that is part of the DMN that is important for spatial orientation and navigation (Buckner et al., 2008) and reduced RSFC in the DMN was previously associated with higher disability in persons with MS (Rocca et al., 2017).

Importantly, the associations of greater RSFC of specific brain regions and walking performance identified in this study are consistent with previous research examining associations between brain activation and locomotion (Hamacher et al., 2015). For example, one study in healthy adults examined brain activation patterns during imagined walking using fMRI and demonstrated walking imagery to be associated with activation in the parahippocampal and fusiform gyri and in occipital visual areas (Jahn et al., 2004). Another study demonstrated the parahippocampal and fusiform gyri to be important for visually guided locomotion and landmark recognition during navigation in healthy, blind, and vestibular-loss participants (Jahn et al., 2009). In the current study, our results demonstrated increased RSFC of the parahippocampal ($r = 0.66$) and fusiform ($r = 0.65$) gyri were strongly correlated faster T25FW speed. Another more recent study examined prefrontal

cortex activation in stroke survivors and healthy controls using near-infrared spectroscopy (NIRS) during treadmill walking and fMRI during simulated walking under single-task and dual-task conditions (Al-Yahya et al., 2016). The results demonstrated increased prefrontal cortex activation during dual task (DT)-walking compared with single task (ST)-walking and increased activity during DT-walking in the inferior temporal gyri, superior frontal gyri, cingulate gyri, and precentral gyrus (Al-Yahya et al., 2016). Similarly, the results of the current study demonstrated increased RSFC was associated with better walking performance in the inferior temporal gyrus (r = 0.54). However, our results did not demonstrate statistically significant associations between RSFC and walking performance in brain regions that have previously been identified including the premotor cortex, primary motor cortex, and supplementary motor areas (Hamacher et al., 2015).

Previous research has demonstrated significant deficits of RSFC in persons with MS in five cognitive networks, including attention, DMN, verbal memory, memory, and visuospatial memory, suggesting widespread functional abnormalities associated with cognitive impairment (Nejad-Davarani et al., 2016). Another recent study demonstrated that lower RSFC, especially in the DMN, predicted clinical worsening and progression to a more severe clinical phenotype, based on EDSS scores, in persons with MS (Pirro et al., 2017). In the current study, a region of the DMN, the parahippocampal gyrus, demonstrated a significant and positive association between RSFC and walking performance. Importantly, our results suggest that, in addition to cognitive- and disability-related measures, reduced RSFC may predict motor-related measures, such as walking performance outcomes, in persons with MS. The eight brain regions identified in this study as being significantly correlated with the T25FW should be further examined to determine if these nodes correlate with performance in other motor and cognitive tasks in MS and if they are sensitive to longitudinal changes in performance within persons with MS.

The strengths of this study include a valid and objective measure of walking performance; control for age during correlation analyses; and a robust statistical correction for multiple comparisons. However, this study is not without limitations. The correlational nature of our analyses does not allow for causal interpretation between cortical RSFC and walking performance outcomes. The cross-sectional design further does not allow us to assess temporal changes of RSFC and walking performance outcomes. We further only included one measure of walking performance (i.e., T25FW); future research should include other specific measures of spatial (e.g., step width and length) and temporal (e.g., stance time, and step time) gait parameters as well as DT paradigms to investigate how the associations between RSFC and walking performance might differ while performing a secondary cognitive interference task. Our sample was only female and most participants with MS were of the relapsing-remitting phenotype, and therefore our results may not be generalized to men or to persons with primary or secondary progressive MS. Participants further were instructed to keep eyes open in the MRI scanner which might influence visual network activation and introduce another element of variability.

5. Conclusion

We provide novel evidence that RSFC is associated with walking performance in persons with MS, including brain regions involved in non-motor networks such as the DMN. RSFC is a valuable tool to monitor the networks that are impacted in MS that relate to declines in both motor and cognitive impairment. Further, RSFC can identify critical nodes that play a role in a range of motor and cognitive tasks that may be more sensitive to disruption by MS.

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Appendix A. Supplementary material

Appendix. Regions of interest using a cortical parcellation technique

Region of Interest	Lobe
Lateral Orbital Frontal	Frontal
Pars Orbitalis	
Frontal Pole	
Medial Orbital Frontal	
Pars Triangularis	
Pars Opercularis	
Rostral Middle Frontal	
Superior Frontal	
Caudal Middle Frontal	
Precentral	
Paracentral	
Rostral Anterior Cingulate	Cingulate
Caudal Anterior Cingulate	
Posterior Cingulate	
Isthmus Cingulate	
Postcentral	Parietal
Supramarginal	
Superior Parietal	
Inferior Parietal	
Precuneus	
Cuneus	Occipital
Pericalcarine	

Lateral Occipital	
Lingual	
Insula	
Fusiform	Temporal
Parahippocampal	
Entorhinal	
Temporal Pole	
Inferior Temporal	
Middle Temporal	
Banks of Superior Temporal Sulcus	
Superior Temporal	
Transverse Temporal	

Note. 34 regions are located in both right and left hemispheres, resulting in 68 regions of interest.