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Neuroplasticity of the sensorimotor neural network associated with walking aid training in people with multiple sclerosis

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Abstract

The objective of this pilot study was to identify neural descriptors and correlates of participation in a multicomponent walking aid program, the Assistive Device Selection, Training and Education Program (ADSTEP), in people with multiple sclerosis, as reflected by resting state functional MRI. Fourteen people with multiple sclerosis who used a walking aid at baseline and reported falling at least once in the prior year were recruited from the multiple sclerosis clinic in a Veterans Affairs and the surrounding community to participate in a trial of ADSTEP, a multicomponent program of walking aid selection, fitting and six weekly progressive task-oriented walking aid training sessions and undergo resting state functional brain MRI. The functional MRI was performed at baseline and at program completion to assess for changes in neural connectivity of the sensorimotor neural network. Compared to baseline, following ADSTEP participation, functional connectivity between the supplementary motor areas and both the primary somatosensory cortices and the putamen was increased; whereas functional connectivity between the supplementary motor areas and the cerebellum was decreased. This study provides preliminary support for supraspinal sensorimotor neuroplasticity in response to rehabilitation interventions such as task-oriented walking aid training, suggests specific neural targets for future mobility interventions, and supports the need for full-scale randomized controlled trials in this area.

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Conflict of interest

No authors report any conflict of interest, either financial or non-financial.

Informed consent

This study was carried out at a Department of Veterans Affairs medical center in the Northwest USA with participants from the MS clinic and from the surrounding community. The institutional review board approved the investigation, all participants provided signed informed consent and this trial was registered on clinicaltrials.gov ().

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Keywords

Balance; Functional mobility; Multiple sclerosis; Physical therapy; Resting state functional MRI

1. Introduction

Impaired mobility is prevalent and disabling in people with multiple sclerosis (PwMS), limiting independence, resulting in falls, and reducing quality of life (Confavreux et al., 2000). While most PwMS use a walking aid within 18 years of diagnosis (Confavreux et al., 2000), using a walking aid is consistently associated with a significantly increased risk for falls in PwMS. Our recently reported pilot randomized controlled trial of ADSTEP, a multicomponent walking aid program in PwMS, found that program participation was associated with a reduction in the number of fallers compared with a wait list control condition (Martini et al., 2018). To better understand the neural mechanisms underlying hypothesized changes, resting state functional magnetic resonance imaging (fcMRI) of the locomotor neural network was performed directly before and after ADSTEP participation in 14 participants to evaluate the strength of functional connections within the supraspinal sensorimotor network responsible for locomotor control.

FcMRI quantifies low-frequency neural activity synchronization within neural networks when the individual is not performing any task within the scanner. FcMRI has a number of advantages over task-based functional MRI. It is not sensitive to subject compliance or differences in effort or performance during the scan. Further, it provides consistent results across subjects and scans (Shehzad et al., 2009). FcMRI is therefore a potentially powerful method for understanding mechanisms underlying dysfunction, and to monitor the effectiveness of and mechanisms underlying rehabilitation interventions, in people with neurological disorders (Prosperini et al., 2015). Our overarching hypothesis is that altered functional connectivity within the locomotor neural network is, in part, responsible for mobility deficits in PwMS and that task-oriented rehabilitation, such as in the ADSTEP program, can help reverse these changes. We hypothesized functional connectivity strength within the locomotor neural network would be greater after ADSTEP participation than before.

2. Methods

2.1. Study population

This study was carried out at a Department of Veterans Affairs medical center in the Northwest USA with participants from the MS clinic and from the surrounding community. The institutional review board approved the investigation, all participants provided signed informed consent and this trial was registered on clinicaltrials.gov ().

Inclusion criteria were: MS of any type; intermittent or constant use of unilateral or bilateral assistance for walking; self-reported history of one or more falls in the previous year; over age 18; able to walk at least 25 feet with or without a walking aid; clinically stable MS (no relapse in 30 days prior to enrollment); and right handed. Exclusion criteria were: more than

one hour of self-reported walking aid training within the previous three years; serious conditions precluding reliable participation; along with any MRI contraindications.

2.2. Intervention: ADSTEP

Forty subjects enrolled in the randomized controlled trial of ADSTEP. ADSTEP consists of six weekly 40-min one-on-one sessions with a physical therapist. ADSTEP content is guided by a manual, starting with walking aid selection and fitting followed by task-oriented walking aid training. Briefly, ADSTEP sessions were scheduled for the same day and time each week and took place in a small rehabilitation gym and nearby hallways and outdoor locations. The first session started with observation and assessment of walking with the current walking aid, including safety, comfort, acceptability, and functionality for expected tasks and environments. The participant then trialed other walking aids to help determine which device was ideal. The selected device was then fitted by the physical therapist. Progressive task-oriented training, focused on walking with the walking aid under varying conditions (e.g. even and uneven surfaces, stairs, corners, while performing another task) followed. Please see Martini et al. for a more detailed description of this program and the functional outcomes from program participation in a pilot trial (Martini et al., 2018).

2.3. Locomotor network connectivity strength assessed with fcMRI

The first 14 participants in the active intervention group completed fcMRI of the brain at baseline and directly following ADSTEP. FcMRI in this pilot evaluation was limited to before and after training in a subset of participants to maximize the richness of results within the constraints of the study budget. Repeated fcMRI over a short time frame, such as six weeks, without intervention, has shown stability in PwMS, limiting the value of scanning the control group (Shehzad et al., 2009). All scans were performed in the morning on a 3.0 Tesla Siemens Magnetom Tim Trio scanner with a 12-channel head coil. One high-resolution T1-weighted MP-RAGE sequence (echo time = 4 ms, repetition time = 9.7 ms, resolution $1.0 \times 1.0 \times 1.1$ mm) was acquired. One BOLD-weighted functional image was acquired with a T2*-weighted EPI (repetition time = 2000 ms, echo time = 30 ms, resolution = 3.8 mm^3 , total volumes = 300). Connectivity preprocessing followed previously described methods from our laboratory (Fling et al., 2015; Fling et al., 2014). No participants were excluded due to excessive movement.

2.3.1. fcMRI region of interest selection—Reduced functional activation and connectivity of the supplementary motor area (SMA) has repeatedly been implicated as underlying gait and balance deficits in people with neurodegenerative disorders (Hanakawa et al., 1999; Snijders et al., 2011). We therefore selected the right and left SMAs as our principal regions of interest. A 10-mm sphere was created at the peak coordinates of the SMA ($x = +/ - 5$, $y = -7$, $z = 55$) as identified by activation likelihood estimates identified in the three-dimensional locations and boundaries meta-analysis of motor regions (Mayka et al., 2006).

2.4. Statistical analyses

Whole brain group comparisons were performed to identify changes in functional connectivity strength for the right and left SMA following ADSTEP. The two fcMRI time

points were compared with a paired, two sample t-test, Monte-Carlo corrected for multiple comparisons and subsequently thresholded at $Z > 2.25$; $P < 0.05$.

3. Results

3.1. Participant demographics

Participants were an average of 54 years old, 64% were women, with a mix of MS subtypes, and had, by retrospective self-report, fallen an average of about 8 times in the year prior to study enrollment (Table 1). All participants completed all six ADSTEP sessions and both MRI data collections.

3.2. Locomotor network connectivity strength assessed with FcMRI

We found a well-defined functional locomotor network when seeded in the SMA(s) both before and after ADSTEP participation (Fig. 1). This network was defined by strong cortical intra- and inter-hemispheric communication between the SMAs, pre-motor areas, and the primary motor and somatosensory cortices. Functional connectivity between the motor cortices and the thalamus was also well-defined.

Compared to baseline, following ADSTEP, we found increased connectivity between the right SMA and the right primary somatosensory cortex (S1) and between the left SMA and the left S1 as well as the left putamen (Fig. 1) as well as reduced connectivity between the SMA and multiple regions in the cerebellum including the right Crus I and bilateral Crus II regions (Table 2).

4. Discussion

In this pilot study with fourteen PwMS, ADSTEP participation was associated with increased sensorimotor functional connectivity between the SMAs and the primary somatosensory cortices as well as the putamen, and decreased functional connectivity between the SMAs and the cerebellum, supporting neuroplasticity in specific neural regions following walking aid optimization and training in PwMS.

The presence of sensorimotor neural network abnormalities in PwMS has repeatedly been demonstrated (Fling et al., 2015; Janssen et al., 2013). The SMA is one of the primary targets of efferent projections from the basal ganglia-thalamo-cortical circuit and contributes to generating self-initiated, voluntary movement. Neurons in the SMA also have dense projections to the ponto-medullary reticular formation which are thought to contribute to postural preparation and anticipatory postural adjustments that precede gait initiation (Hanakawa et al., 1999; Snijders et al., 2011). Because the SMA is critical to planning and initiating movements, impaired communication along the striato-thalamo-cortical pathway secondary to demyelination is likely to contribute to mobility impairment in PwMS and increased communication along this pathway in response to an intervention such as ADSTEP suggests that the intervention influenced motor planning and initiation through neuroplasticity.

A substantial body of literature indicates that the cerebellum and the motor cortex are involved in the acquisition and adaptation of locomotor control (Morton and Bastian, 2006; Ilg et al., 2008). In particular, the fastigial nuclei output of the cerebellum is involved in the control of whole-body posture and locomotion (Chambers and Sprague, 1955) and receives inputs from the motor cortex (Coffman et al., 2011) through pathways that involve the thalamus (Middleton and Strick, 1994; Middleton and Strick, 1997). Pathological changes, including atrophy and functional activation differences within the cerebellar cortex of PwMS, are well characterized (Anderson et al., 2009; Gilmore et al., 2009; Kutzelnigg et al., 2007). Cerebellar atrophy is associated with greater physical disability including poorer scores on the nine-hole peg test (Anderson et al., 2009; Henry et al., 2008) and slower walking (Liptak et al., 2008; Damasceno et al., 2014). fcMRI studies have found decreased functional connectivity both within the cerebellum and externally with other neural hubs of the sensorimotor network during motor tasks in PwMS compared to age and sex-matched controls (Fling et al., 2015; Rocca et al., 2009). Bonzano and colleagues recently demonstrated that greater (motor) cortico-cerebellar connectivity (i.e. less inhibition) was correlated with learning on a finger-tapping task in PwMS (Bonzano et al., 2015). Conversely, recent work from our group found that while greater cortico-cerebellar connectivity strength was associated with better short-term postural adaptation in healthy young adults, this association was not observed in PwMS ($r = 0.03$) (Fling et al., 2015). In the current study, following ADSTEP training, functional connectivity between the SMA and cerebellum decreased significantly. Interestingly, Mawase and colleagues also recently reported decreased functional connectivity between the primary motor cortex and the cerebellum following multiple sessions of splitbelt treadmill locomotor training in healthy young participants (Mawase et al., 2017). Taken together, these recent findings suggest that there are differences in cerebellar contributions to upper extremity and lower extremity neural control and that specific locomotor adaption and assistive device training may reduce reliance on cortico-cerebellar connectivity for control of gait and balance.

Confidence in the intriguing findings from this study are limited by the small sample and the fact that neuroimaging data were not collected in a control group for comparison. However, numerous studies have demonstrated consistency and reliability in functional connectivity for participants with MS in other studies randomly allocated to a control group (Shehzad et al., 2009; Chapman et al., 2015; Magon et al., 2016; Diez-Cirarda et al., 2016; Shpaner et al., 2014). Further, changes in fcMRI following rehabilitation interventions in other populations also supported that we would have sufficient power to detect change in this study with 14 people (Parisi et al., 2014).

4.1. Implications and conclusions

While additional research is needed to fully assess neurorehabilitation-related changes in brain structure and function in PwMS, this study supports existing literature that locomotion control may depend on activating the SMA and communicating information throughout the supraspinal locomotor neural network and, furthermore, that motor cortico-cerebellar connectivity is reduced following mobility intervention. In sum, functional connectivity between the SMA, primary somatosensory cortices and the cerebellum are significantly influenced by locomotor rehabilitation in PwMS.

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References

- Anderson VM, Fisniku LK, Altmann DR, Thompson AJ, Miller DH, 2009 MRI measures show significant cerebellar gray matter volume loss in multiple sclerosis and are associated with cerebellar dysfunction. *Mult. Scler* 15, 811–817. 10.1177/1352458508101934. [PubMed: 19465449]
- Bonzano L, et al., 2015 An engineered glove for investigating the neural correlates of finger movements using functional magnetic resonance imaging. *Front. Hum. Neurosci* 9, 503 10.3389/fnhum.2015.00503. [PubMed: 26441600]
- Chambers WW, Sprague JM, 1955 Functional localization in the cerebellum. II. Somatotopic organization in cortex and nuclei. *AMA Arch. Neurol. Psychiatry* 74, 653–680. [PubMed: 13268132]
- Chapman SB, et al., 2015 Neural mechanisms of brain plasticity with complex cognitive training in healthy seniors. *Cereb. Cortex* 25, 396–405. 10.1093/cercor/bht234. [PubMed: 23985135]
- Coffman KA, Dum RP, Strick PL, 2011 Cerebellar vermis is a target of projections from the motor areas in the cerebral cortex. *Proc. Natl. Acad. Sci. USA* 108, 16068–16073. 10.1073/pnas.1107904108. [PubMed: 21911381]
- Confavreux C, Vukusic S, Moreau T, Adeleine P, 2000 Relapses and progression of disability in multiple sclerosis. *N. Engl. J. Med* 343, 1430–1438. 10.1056/NEJM200011163432001. [PubMed: 11078767]
- Damasceno A, Damasceno BP, Cendes F, 2014 The clinical impact of cerebellar grey matter pathology in multiple sclerosis. *PLoS One* 9, e96193 10.1371/journal.pone.0096193. [PubMed: 24789257]
- Diez-Cirarda M, et al., 2016 Increased brain connectivity and activation after cognitive rehabilitation in Parkinson's disease: a randomized controlled trial. *Brain Imaging Behav.* 10.1007/s11682-016-9639-x.
- Fling BW, et al., 2014 Functional reorganization of the locomotor network in Parkinson patients with freezing of gait. *PLoS One* 9, e100291 10.1371/journal.pone.0100291. [PubMed: 24937008]
- Fling BW, Gera Dutta G, Horak FB, 2015 Functional connectivity underlying postural motor adaptation in people with multiple sclerosis. *Neuroimage Clin.* 8, 281–289. 10.1016/j.nicl.2015.04.023. [PubMed: 26106552]
- Gilmore CP, et al., 2009 Regional variations in the extent and pattern of grey matter demyelination in multiple sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord. *J. Neurol. Neurosurg. Psychiatry* 80, 182–187. 10.1136/jnnp.2008.148767. [PubMed: 18829630]
- Hanakawa T, et al., 1999 Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. *Brain* 122 (Pt 7), 1271–1282. [PubMed: 10388793]
- Henry RG, et al., 2008 Regional grey matter atrophy in clinically isolated syndromes at presentation. *J. Neurol. Neurosurg. Psychiatry* 79, 1236–1244. 10.1136/jnnp.2007.134825. doi:jnnp.2007.134825 [pii]. [PubMed: 18469033]
- Ilg W, Giese MA, Gizewski ER, Schoch B, Timmann D, 2008 The influence of focal cerebellar lesions on the control and adaptation of gait. *Brain* 131, 2913–2927. 10.1093/brain/awn246. [PubMed: 18835866]
- Janssen AL, Boster A, Patterson BA, Abduljalil A, Prakash RS, 2013 Resting-state functional connectivity in multiple sclerosis: an examination of group differences and individual differences. *Neuropsychologia* 51, 2918–2929. 10.1016/j.neuropsychologia.2013.08.010. [PubMed: 23973635]
- Kutzelnigg A, et al., 2007 Widespread demyelination in the cerebellar cortex in multiple sclerosis. *Brain Pathol.* 17, 38–44. 10.1111/j.1750-3639.2006.00041.x. [PubMed: 17493036]

- Liptak Z, et al., 2008 Medulla oblongata volume: a biomarker of spinal cord damage and disability in multiple sclerosis. *AJNR Am. J. Neuroradiol* 29, 1465–1470. 10.3174/ajnr.A1162. [PubMed: 18556361]
- Magon S, et al., 2016 Striatal functional connectivity changes following specific balance training in elderly people: MRI results of a randomized controlled pilot study. *Gait Posture* 49, 334–339. 10.1016/j.gaitpost.2016.07.016. [PubMed: 27479219]
- Martini DN, et al., 2018 ADSTEP: preliminary investigation of a multicomponent walking aid program in people with multiple sclerosis. *Arch. Phys. Med. Rehabil* 99, 2050–2058. 10.1016/j.apmr.2018.05.023. [PubMed: 29958906]
- Mawase F, Bar-Haim S, Shmuelof L, 2017 Formation of long-term locomotor memories is associated with functional connectivity changes in the cerebellar-thalamic-cortical network. *J. Neurosci* 37, 349–361. 10.1523/JNEUROSCI.2733-16.2016. [PubMed: 28077714]
- Mayka MA, Corcos DM, Leurgans SE, Vaillancourt DE, 2006 Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage* 31, 1453–1474. [PubMed: 16571375]
- Middleton FA, Strick PL, 1994 Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science* 266, 458–461. [PubMed: 7939688]
- Middleton FA, Strick PL, 1997 Cerebellar output channels. *Int. Rev. Neurobiol* 41, 61–82. [PubMed: 9378611]
- Morton SM, Bastian AJ, 2006 Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. *J. Neurosci* 26, 9107–9116. 10.1523/JNEUROSCI.2622-06.2006. [PubMed: 16957067]
- Parisi L, et al., 2014 Changes of brain resting state functional connectivity predict the persistence of cognitive rehabilitation effects in patients with multiple sclerosis. *Mult. Scler* 20, 686–694. 10.1177/1352458513505692. [PubMed: 24072724]
- Prosperini L, Piattella MC, Gianni C, Pantano P, 2015 Functional and structural brain plasticity enhanced by motor and cognitive rehabilitation in multiple sclerosis. *Neural Plast.* 2015, 481574 10.1155/2015/481574. [PubMed: 26064692]
- Rocca MA, et al., 2009 Abnormal connectivity of the sensorimotor network in patients with MS: a multicenter fMRI study. *Hum. Brain Mapp* 30, 2412–2425. 10.1002/hbm.20679. [PubMed: 19034902]
- Shehzad Z, et al., 2009 The resting brain: unconstrained yet reliable. *Cereb. Cortex* 19, 2209–2229. 10.1093/cercor/bhn256. [PubMed: 19221144]
- Shpaner M, et al., 2014 Unlearning chronic pain: a randomized controlled trial to investigate changes in intrinsic brain connectivity following Cognitive Behavioral Therapy. *Neuroimage Clin.* 5, 365–376. 10.1016/j.nicl.2014.07.008. [PubMed: 26958466]
- Snijders AH, et al., 2011 Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. *Brain* 134, 59–72. 10.1093/brain/awq324. doi:awq324 [pii]. [PubMed: 21126990]

Fig. 1.

Motor connectivity maps identified from the seed regions placed within the right and left supplementary motor areas (SMAs). Group connectivity maps of all PwMS prior to (A) participating in the assistive device training intervention and following completion (B). Group maps are Monte Carlo corrected and thresholded at $Z > 2.25$. Data are overlaid on an averaged 1 mm Talairach anatomical template for display. ADSTEP, assistive device selection, training and education program.

Table 1

Participant demographics. Age was recorded at time of enrollment. Falls in previous year is the average number of falls over the year prior to enrollment. Data are reported as mean ($\pm$ standard deviation), with the exception of EDSS which is median ($\pm$ standard deviation). EDSS, Expanded Disability Status Scale.

Age (years)	53.9 (10.59)
Gender (Male/Female)	5/9
MS sub-type (RRMS, SPMS, PPMS)	6/4/4
EDSS	6.0 (0.22)
Falls in previous year	7.8 (17.10)

Table 2

Regions showing differences in supplementary motor area (SMA) functional connectivity strength after assistive device training compared to baseline. Coordinates are in Talairach space; *R* = right; Left = left.

		<i>x</i>	<i>y</i>	<i>z</i>	Z-score	P (2-tailed)
Right SMA	Baseline > After training					
	<i>R Cerebellum Crus II</i>	12	-78	-44	2.46	<0.05
	<i>R Cerebellum Crus I</i>	44	-55	-41	2.83	<0.01
	After training > Baseline					
	<i>R Primary somatosensory cortex</i>	7	-37	72	2.94	<0.01
Left SMA	Baseline > After training					
	<i>R Cerebellum Crus II</i>	10		-41	3.96	<0.0001
	<i>L Cerebellum Crus II</i>	-39	-81	-34	3.03	<0.01
	After training > Baseline					
	<i>L Primary somatosensory cortex</i>	-6	-35	71	2.95	<0.01
	<i>L Putamen</i>	-27	4	12	3.47	<0.001