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How changes in brain activity and connectivity are associated with motor performance in people with MS

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ABSTRACT

People with multiple sclerosis (MS) exhibit pronounced changes in brain structure, activity, and connectivity. While considerable work has begun to elucidate how these neural changes contribute to behavior, the heterogeneity of symptoms and diagnoses makes interpretation of findings and application to clinical practice challenging. In particular, whether MS related changes in brain activity or brain connectivity protect against or contribute to worsening motor symptoms is unclear. With the recent emergence of neuromodulatory techniques that can alter neural activity in specific brain regions, it is critical to establish whether localized brain activation patterns are contributing to (i.e. maladaptive) or protecting against (i.e. adaptive) progression of motor symptoms. In this manuscript, we consolidate recent findings regarding changes in supraspinal structure and activity in people with MS and how these changes may contribute to motor performance. Furthermore, we discuss a hypothesis suggesting that increased neural activity during movement may be either adaptive or maladaptive depending on where in the brain this increase is observed. Specifically, we outline preliminary evidence suggesting sensorimotor cortex activity in the ipsilateral cortices may be maladaptive in people with MS. We also discuss future work that could supply data to support or refute this hypothesis, thus improving our understanding of this important topic.

1. Introduction

Multiple sclerosis (MS) is an autoimmune pathology that leads to numerous neurological (Nylander and Hafler, 2012) and behavioral (Johansson et al., 2007) changes. In particular, people with MS (PwMS) exhibit multifocal demyelinating lesions or 'plaques', that can occur in both grey and white matter (Matthews et al., 2016). These changes are accompanied by grey (Jacobsen and Farbu, 2014) and white (Sbardella et al., 2013) matter atrophy and, perhaps unsurprisingly, numerous changes in brain activity (Tomassini et al., 2012b) and connectivity (Sbardella et al., 2015b). Neuroimaging techniques have furthered our understanding of 1) how structure, activity, and connectivity of the brain change with multiple sclerosis, and 2) how these changes may relate to motor performance. However, Our understanding of which neural changes protect against worsening of symptoms, and which are the result of or contribute to worsening of symptoms remains limited. For the purposes of this review, we operationally define these changes in brain activity and connectivity as: 1) adaptive – a change in brain activity or connectivity that results in fewer symptoms and/or better motor performance or 2) maladaptive – a change in brain activity or connectivity that results in worse symptoms and/or poorer motor performance. There has been considerable interest in this topic, including several reviews and commentaries debating whether neural changes in PwMS are adaptive or maladaptive. However, these reports focus primarily on changes to resting state functional connectivity and its relationship to cognition (Penner and Aktas, 2017; Rocca and Filippi, 2017; Schoonheim, 2017). Whether MS-related changes in brain activity are adaptive vs. maladaptive for *motor performance* has received less attention.

During motor tasks, the amplitude of brain activity in PwMS is often increased, and this increase is typically interpreted as adaptive, counteracting changes in functional or structural connectivity (Lipp and Tomassini, 2015). However, others (Lenzi et al., 2007; Manson et al., 2006; Tomassini et al., 2012b) suggest an alternative interpretation-that increased activity in some brain regions may be maladaptive; related to reduced transcallosal inhibition (TCI) and callosal degradation. However, a current and comprehensive assessment of the data surrounding this hypothesis is lacking. Neuromodulatory techniques such as repetitive transcranial magnetic stimulation (Hulst et al., 2017), transcranial direct current stimulation (Kasschau et al., 2015; Palm

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et al., 2014), and deep brain stimulation (Roy and Aziz, 2014) provide the means to facilitate or depress activity in specific brain regions. Understanding whether MS-related changes in brain activity are adaptive or maladaptive is crucial to inform the location and direction of neural manipulation via these methods.

To provide clarity on this issue, we first review the effects of MS on brain structure, activity, and connectivity, including how these neural changes relate to motor performance. Then, we discuss our current understanding of whether changes in neural activity are adaptive or maladaptive for motor performance. In particular, we focus on recent evidence suggesting that increased activity of specific motor regions (e.g. ipsilateral motor areas), may be maladaptive, rather than adaptive, thus contributing to worsening motor symptoms. Finally, we discuss future directions regarding how the described brain changes may contribute to motor performance, including the need for longitudinal studies to clarify these relationships.

2. Structural changes in PwMS

2.1. Grey matter atrophy

PwMS exhibit grey matter atrophy in virtually all brain regions, including the basal ganglia, cortex (frontal, parietal, temporal lobes), cerebellum, and brainstem (for reviews, see: Horakova et al., 2012; Jacobsen and Farbu, 2014; Messina and Patti, 2014; Pirko et al., 2007). This atrophy typically progresses slowly (approximately 0.5–1% per year globally (Filippi, 2015)), and varies by diagnosis, such that progressive forms of MS exhibit faster degradation of brain volume (particularly grey matter) than relapsing forms (Roosendaal et al., 2011). However, atrophy is evident in numerous cortical and subcortical regions even early in the disease (Battaglini et al., 2009). The location of atrophy can also differ across disease types, with RMSS exhibiting predominantly ventricular enlargement, and secondary forms of MS exhibiting more cortical atrophy (Pagani et al., 2005).

Regional grey matter atrophy is related to worse motor performance (see Table 1). For example, brainstem volume was specifically correlated to clinical gait outcomes including the 25 foot walk (Edwards et al., 1999; Jasperse et al., 2007; Shiee et al., 2012), and the ambulation index (Liptak et al., 2008; Liu et al., 1999). Perhaps unsurprisingly, general clinical assessments, such as the EDSS, are related to atrophy of many cortical and subcortical regions (see Table 1). Cerebellar grey matter is also affected in PwMS (Kutzelnigg et al., 2007), with cerebellar atrophy and pathology relating to poorer scores on the EDSS (Damasceno et al., 2014; Tjoa et al., 2005), upper extremity assessments (e.g. nine-hole peg test (Anderson et al., 2009; Henry et al., 2008), and gait (Damasceno et al., 2014; Tjoa et al., 2005). Together, these findings suggest that grey matter volume plays an important role in disability in PwMS, and brainstem and cerebellar atrophy may be specifically related to declines in lower limb performance and locomotion.

2.2. White matter integrity

In addition to alterations in grey matter, white matter dysfunction remains a hallmark of MS. Diffusion tensor and diffusion weighted imaging (DTI and DWI, respectively) measure the diffusion or movement of water molecules within the brain to characterize the structural integrity of white matter and degree of myelination. Investigations measuring DTI and DWI have demonstrated widespread changes in myelination and white matter microstructural integrity in PwMS compared to people without MS.

White matter lesions (Werring et al., 1999) and changes to “normally appearing white matter” (for review, see Sbardella et al., 2013) in PwMS can be found throughout the brain of PwMS, and damage becomes more pronounced as pathology progresses (Braley et al., 2012; Castriota Scanderbeg et al., 2000; Horsfield et al., 1996). Although there is considerable variability across patients, damage is commonly observed in corticospinal, superior longitudinal fasciculus, periventricular, and corpus callosum tracts (Sbardella et al., 2013). Of these structures, damage is often most pronounced in the corpus callosum, the largest white matter fiber tract in the brain (Bonzano et al., 2008; Warlop et al., 2008).

Although results are somewhat mixed (Fink et al., 2010; Griffin et al., 2001), clinical disability in PwMS (e.g. EDSS) is generally related to lower structural connectivity (i.e. DTI), with corticospinal and proprioceptive tracts being particularly well correlated to EDSS (for review, see: Sbardella et al., 2013). Balance has specifically been related to changes in the corticospinal (Hubbard et al., 2016; Tovar-Moll et al., 2015), brainstem (Peterson et al., 2016) and cerebellar (Anderson et al., 2011; Prosperini et al., 2014) white matter tracts. Finally, integrity of white matter within the corpus callosum has been associated with motor performance and motor learning of the upper extremities (Bonzano et al., 2008; Bonzano et al., 2011; Kern et al., 2011; Peterson et al., 2017; Rimkus et al., 2013). Taken together, these results underscore the widespread and heterogeneous structural dysfunction in the brain directly relating to poorer motor performance in PwMS.

3. Brain activity and connectivity in PwMS

3.1. Brain activity during motor tasks

Task-based functional magnetic resonance imaging (fMRI) is a technique that characterizes brain activity during behavioral tasks. Numerous task-based fMRI analyses have been carried out on PwMS, demonstrating considerable alterations in supraspinal activity during simple and complex motor tasks (for reviews, see: Filippi, 2015; Filippi and Agosta, 2009; Sacco et al., 2013; Sbardella et al., 2013; Tomassini et al., 2012b).

Most imaging studies have investigated brain activity during unilateral upper extremity motor tasks. These studies show that, compared to healthy controls, PwMS exhibit increased activity in typically recruited regions (e.g. contralateral motor areas) as well as brain regions not typically active during unilateral motor tasks in healthy adults (e.g. non-motor cortical and subcortical structures, ipsilateral motor areas, etc.) (Pantano et al., 2005). For example, patients with mild MS (EDSS $\leq$ 1.5; Colorado et al., 2012), and benign MS (EDSS $\leq$ 3 at least 15 years after diagnosis) (Giorgio et al., 2010; Rocca et al., 2010b) exhibited increased brain activity in motor and non-motor regions compared to healthy controls. Increases in sensorimotor brain activity during movement were also observed in people with RMSS compared to healthy controls (Rocca et al., 2002). Later in the course of disease (e.g. in people with SPMS) the elevated neural activity spreads to other regions not typically active during simple motor tasks, including secondary sensorimotor regions, and subcortical structures (Rocca et al., 2005). Importantly, the spread of activation is directly related to lesion load in the brain and spinal cord (De Stefano et al., 2006; Lee et al., 2000; Lenzi et al., 2007; Reddy et al., 2000a; Rocca et al., 2006).

Taken together, this work suggests that PwMS exhibit elevated brain activity during motor tasks with respect to people without MS. These results prompted the hypothesis that increased activity in asymptomatic patients may be adaptive or protective, warding off symptoms (Rocca et al., 2005). However, as will be described in detail in Section 4, recent work provides preliminary evidence that region specific increases in brain activity may be, in part, maladaptive. In particular, increased activity in motor regions ipsilateral to the side of the body completing the motor task may be maladaptive, mediated by poorer corpus callosum integrity and reduced TCI.

3.2. Functional connectivity

Functional connectivity MRI (fcMRI) analyses assess the degree to which activity of different parts of the brain oscillate together. This low-