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Upper limb motor rehabilitation impacts white matter microstructure in multiple sclerosis☆

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ABSTRACT

Upper limb impairments can occur in patients with multiple sclerosis, affecting daily living activities; however there is at present no definite agreement on the best rehabilitation treatment strategy to pursue. Moreover, motor training has been shown to induce changes in white matter architecture in healthy subjects.

This study aimed at evaluating the motor behavioral and white matter microstructural changes following a 2-month upper limb motor rehabilitation treatment based on task-oriented exercises in patients with multiple sclerosis.

Thirty patients (18 females and 12 males; age $= 43.3 \pm 8.7$ years) in a stable phase of the disease presenting with mild or moderate upper limb sensorimotor deficits were randomized into two groups of 15 patients each. Both groups underwent twenty 1-hour treatment sessions, three times a week. The “treatment group” received an active motor rehabilitation treatment, based on voluntary exercises including task-oriented exercises, while the “control group” underwent passive mobilization of the shoulder, elbow, wrist and fingers.

Before and after the rehabilitation protocols, motor performance was evaluated in all patients with standard tests. Additionally, finger motor performance accuracy was assessed by an engineered glove.

In the same sessions, every patient underwent diffusion tensor imaging to obtain parametric maps of fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. The mean value of each parameter was separately calculated within regions of interest including the fiber bundles connecting brain areas involved in voluntary movement control: the corpus callosum, the corticospinal tracts and the superior longitudinal fasciculi.

The two rehabilitation protocols induced similar effects on unimanual motor performance, but the bimanual coordination task revealed that the residual coordination abilities were maintained in the treated patients while they significantly worsened in the control group ($p = 0.002$). Further, in the treatment group white matter integrity in the corpus callosum and corticospinal tracts was preserved while a microstructural integrity worsening was found in the control group (fractional anisotropy of the corpus callosum and corticospinal tracts: $p = 0.033$ and $p = 0.022$; radial diffusivity of the corpus callosum and corticospinal tracts: $p = 0.004$ and $p = 0.008$). Conversely, a significant increase of radial diffusivity was observed in the superior longitudinal fasciculi in both groups ($p = 0.02$), indicating lack of treatment effects on this structure, showing damage progression likely due to a demyelination process.

All these findings indicate the importance of administering, when possible, a rehabilitation treatment consisting of voluntary movements. We also demonstrated that the beneficial effects of a rehabilitation treatment are task-dependent and selective in their target; this becomes crucial towards the implementation of tailored rehabilitative approaches.

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Introduction

Impaired sensorimotor function is frequent in multiple sclerosis (MS). Sensorimotor impairments of the lower limbs affecting mobility are reported in 75% of patients with MS (PwMS), whereas dysfunctions of the upper limbs occur in 66% of PwMS (Johansson et al., 2007; Spooren et al., 2012). The level of arm and hand functioning greatly defines the ability to perform daily living activities like eating, dressing, and grooming (Yozbatiran et al., 2006).

Neurorehabilitation is targeted at maintaining and possibly improving the residual capacities of neurological patients with the aim to preserve their personal and social activities, and it constitutes an important part of quality health care in PwMS. There is at present no definite agreement on which specific exercise therapy program can be considered the most successful in improving activities and participation. Different training programs have been employed for upper limb neurorehabilitation, ranging from more traditional strategies to newer techniques emphasizing the learning and practice of functional motor skills within a "task-specific" context (Solari et al., 1999; Spooren et al., 2012). In addition, it has been proposed that a training based on the performance of voluntary movements showed significant improvements in motor performance in healthy subjects with respect to passive training (Bayona et al., 2005; Lotze et al., 2003). Further, active training has been found to induce more prominent increases in fMRI activation of the contralateral primary motor cortex (M1), corticospinal excitability and intracortical facilitation than passive training (Lotze et al., 2003). All these findings suggest the important role for voluntary drive in motor learning and neurorehabilitation. In agreement with this notion, voluntary exercise has been convincingly shown to attenuate the clinical deficits and the underlying neuropathological process in animal models of neurodegenerative disorders (Ang and Gomez-Pinilla, 2007; Cotman and Berchtold, 2002; Cotman et al., 2007; Kramer and Erickson, 2007; Rossi et al., 2009).

Recently, changes in white matter (WM) architecture have been observed in healthy subjects after motor training (Draganski and May, 2008; Scholz et al., 2009; Taubert et al., 2010). WM fiber pathways form the brain communication network; thus, the physical condition of a given pathway can determine the efficiency of signal transmissions between brain regions and might thereby influence behaviors relying on that pathway (Fields, 2008; Johansen-Berg, 2010; Johansen-Berg et al., 2010; Scholz et al., 2009). In this framework, the increasing sensorimotor impairment observed in PwMS over the disease course could be mainly due to the progression of WM damage, that is present in these patients since the early stages (Evangelou et al., 2000; Ferguson et al., 1997; Ge et al., 2005; van Waesberghe et al., 1999). In particular, reductions in the microstructural integrity of the corpus callosum (CC) have been shown to be associated with decreased sensorimotor performance, impairment in visuomotor learning and deficit in bimanual coordination (Bonzano et al., 2008, 2011a,b; Larson et al., 2002; Pelletier et al., 1992).

The present study was designed to evaluate the motor behavioral and WM microstructural architecture changes, with a focus on the WM fiber bundles connecting brain areas involved in voluntary movement control, following a 2-month upper limb motor rehabilitation treatment including task-oriented exercises in PwMS.

Material and methods

Patients

Thirty right-handed PwMS in a stable phase of the disease presenting with mild or moderate sensorimotor deficit in one or both upper limbs were recruited for this study. The Medical Research Council (MRC) scale (0 to 5 grades) was adopted for testing muscle strength at the proximal (i.e., shoulder and elbow) and distal (i.e., wrist and fingers) segments (Compston, 2010). Inclusion criteria were the following MRC scores of patient's effort: grade 4 in all muscle groups or grade 3 in no more than two joints (mild deficit), or grade 3 in all muscle groups (moderate deficit). We excluded patients with relapses and steroid-use or a worsening of the Expanded Disability Status Scale (EDSS) score (Kurtzke, 1983) in the last three months, psychiatric disorders and severe cognitive impairment.

Among the included patients (18 females and 12 males; mean age = 43.3 ± 8.7 years) 22 were affected by a relapsing–remitting and 8 by a secondary progressive form of MS. Demographic and clinical characteristics of the patients are reported in Table 1.

The study was approved by the ethical committee of our institution and the patients' consent was obtained according to the Declaration of Helsinki.

Rehabilitative protocols

We were interested in investigating the effects of an active upper limb rehabilitation treatment based on volitional tasks on motor performance and white matter microstructure. To this aim, we defined a "control treatment", as strongly suggested in a recent critical review of studies assessing structural plasticity following training (Thomas and Baker, 2013). In fact, comparing two groups who have been trained on different tasks allows showing that potential changes are specific to a given task and not a general effect of any training. Therefore, the 30 recruited PwMS were randomly assigned to two groups, with the use of a computer-generated schedule: one receiving an active motor rehabilitation treatment ("treatment group"—15 patients) and one receiving a passive motor rehabilitation treatment ("control group"—15 patients) (Table 1).

The two rehabilitative protocols were designed with the intention that all the patients were similarly invested in the study by equating patients' overall experience thus limiting possible biases (Thomas and Baker, 2013); both groups of patients underwent twenty 1-hour treatment sessions, three times a week, at AISM Rehabilitation Centre, Italian Multiple Sclerosis Society, Genoa, Italy.

In details, the patients assigned to the treatment group were rehabilitated with an active protocol based on voluntary exercises for neuromuscular control to improve proprioceptive sensibility, muscle strength, stability and coordination of the upper limbs, mainly including task-oriented exercises with the goal to improve activities of daily living (Nelson, 1996). The first 5 sessions of the rehabilitative protocol were focused on voluntary exercises executed unilaterally with the right and left upper limbs (60% of treatment time). This part of the treatment dealt with both non task-oriented exercises, such as grasping wooden cubes of different sizes, pinching, reaching a target displayed in front of the patient, and task-oriented exercises such as ironing a shirt and putting a dish in a draining board. In the last 40% of the treatment, bimanual task-oriented exercises, such as sewing, doing patchwork and paper mandala, cooking, sweeping, and screwing a cap on a bottle, were administered to the patients. Gradually, from the 6th to the 12th sessions, the percentage of bimanual task-oriented exercises increased to reach 100% in the last 5 sessions. Thus, unimanual and bimanual voluntary exercises were differently weighted in each session along the rehabilitative program (sessions 1–5: 60%–40%, respectively; sessions 6–10: 40%–60%, respectively; sessions 11–15: 20%–80%, respectively; and sessions 16–20: 0%–100%, respectively).

The control group only performed tasks without detectable muscle activity, through passive mobilization of the shoulder, elbow, wrist and fingers delivered by a physical therapist. Analogously, in the passive rehabilitation protocol the percentage of unimanual and bimanual passive mobilizations delivered by the therapist followed the scheme used for the "treatment group" (i.e., sessions 1–5: 60%–40%, respectively; sessions 6–10: 40%–60%, respectively; sessions 11–15: 20%–80%, respectively; and sessions 16–20: 0%–100%, respectively).

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