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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Neural effects after motor rehabilitation in persons with Multiple Sclerosis

Jasmien Hooybergs
Laura Verwaest

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

PROMOTOR :
dr. Ilse LAMERS

COPROMOTOR :
Prof. dr. Peter FEYS

BEGELEIDER :
Mevrouw Joke RAATS

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NEURAL EFFECTS AFTER MOTOR REHABILITATION IN PERSONS WITH MULTIPLE SCLEROSIS

Outline

- In total, thirteen articles met the inclusion criteria and were included.
  In all studies, the experimental group existed of resistance training, endurance training, balance training or tasks of the hand, while the control group received no intervention, passive mobilization or were put on the waiting list. The healthy controls received either the same intervention as the experimental group or no intervention at all.
- In ten out of thirteen articles, the experimental group improved significantly better in clinical results than the control group or healthy controls after intervention. Some of these significant clinical effects were: VO_{2MAX}, sit-to-stand test, MS Walking Scale, Fatigue Scale for Motor and Cognitive Function, 2-min walking test, berg balance scale, dynamic gait index and postural sway.
- In twelve out of thirteen included studies significant neural changes in favour of the experimental group were observed. Some of these significant neural changes were: preserved microstructural integrity in the corpus callosum (CC) and corticospinal tract, an increase of radial diffusivity (RD) in the superior longitudinal fasciculi, an increase in the left pallidum volume, an increase of the fractional anisotropy (FA) and decrease of the mean diffusivity (MD) in the CC, and higher absolute cortical thickness in the anterior cingulate gyrus, temporale pole, orbital sulcus and the inferior temporal sulcus.
- In five studies, a significant moderate correlation between clinical and neural effects were found.
- The most frequently used imaging technique was the conventional magnetic resonance imaging (MRI), followed by diffusion tensor imaging (DTI) and functional MRI. Parameters most investigated were the T2 lesions, brain volume, microstructural integrity and the structural connectivity. The most common regions of interest (ROIs) were the supplementary (SMA) motor area and the CC.

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Context of the master thesis

This master thesis fits in the research domain of neurological rehabilitation. Persons with Multiple Sclerosis (MS) are often confronted with sensorimotor and cognitive disorders, leading to a lower quality of life. It is expected that rehabilitation may have beneficial clinical effects to achieve maximum independency. Because neuroplasticity can occur in the brain, it is important to investigate potential neural effects after rehabilitation as well. In this literature review, we focused on motor rehabilitation and its effect on clinical and neural outcome measurements in persons with MS. It is relevant to investigate if motor rehabilitation also achieves neural changes in the brain in a neurodegenerative disease as MS. If this is possible, it can be an important added value for further rehabilitation.

The literature study of this master thesis was based on the following research questions: (1) 'What are the neural effects after motor rehabilitation in persons with MS?' and (2) 'Which imaging techniques are used to evaluate the neural effects after motor rehabilitation in persons with MS?'

This master thesis 1 is a part of the first master year of the educational program 'Rehabilitation sciences and physiotherapy' at UHasselt in Diepenbeek. This master thesis was made under supervision of promotor Dr. I. Lamers, co-promotor Prof Dr. P. Feys and daily supervisor PhD student J. Raats. This review is part of an ongoing research project of Dr. I. Lamers.

The research questions for this literature review were formed in collaboration between the students and the promotors. The literature search was performed by the two students and by tips from the promotors, screening of the found articles was done by the two students independently. This master thesis has been made by the two students, following feedback from Dr. I. Lamers. The protocol for the master thesis 2 was based on a project application of Dr. I. Lamers, Prof. Dr. P. Feys and PhD student J. Raats. The central format was used for this thesis.

The primary aim of the second part of this master thesis is to investigate the clinical and neural effects after individualized high-dose function or task-specific upper limb rehabilitation program in persons with MS with different upper limb disability levels and (if found) the correlation between clinical and neural results. However, in this master thesis, only the baseline data of this intervention study will be used to investigate the correlation between the clinical measure and imaging parameters.

Participants will be recruited from the Rehabilitation and MS Centrum Overpelt (Prof. Dr. Bart Van Wijmeersch), MS Network Antwerp (Prof. Dr. Barbara Willekens) and The National MS center Melsbroek (Prof. Dr. Tom Meurrens). The individualized high-dose upper limb rehabilitation program will take place at these three centres. For the imaging acquisition and analysis there will be a collaboration with Ziekenhuis Oost-Limburg (ZOL), radiology department and Dr. Veronica Popescu (neurologist Rehabilitation and MS centre Overpelt, lecture REVAL- UHasselt, PhD on brain atrophy in Multiple Sclerosis). For data analysis, a collaboration is set up with the VUmc, department of Anatomy & Neuroscience, Amsterdam (The Netherlands), contact person: Prof. Dr. Hanneke Hulst & Prof. Dr. Jeroen Geurts. They will perform in collaboration with Dr. I. Lamers the analyses of the imaging data. We will perform the statistics to investigate the correlation between imaging outcome measurements and clinical outcome measurements.

Table content

Part one: literature review

Abstract

Background*:* Persons with Multiple Sclerosis (PwMS) may suffer sensorimotor and cognitive disorders, which may lead to a lower quality of life (QoL). Medication and rehabilitation helps PwMS to achieve maximum independency. Imaging is a well-established tool for diagnosis and medical management of this disease. However, imaging is recently also used as evaluation tool in rehabilitation studies.

Methods*:* This literature review aimed to give an overview of which techniques, regions of interest (ROIs) and parameters were used to evaluate the neural effects after a motor rehabilitation program and which were the components of the motor rehabilitation programs finding neural effects related to rehabilitation. Two databases were used for the literature search: PubMed and Web of Knowledge (WoK). Articles were selected if they included motor rehabilitation and imaging techniques as an outcome measurement.

Results*:* Thirteen studies met the inclusion criteria. Overall, the results showed that motor rehabilitation has a beneficial effect on clinical and neural outcome measurements. Two studies showed no clinical effects after motor rehabilitation, while they did show significant neural changes. All studies except one showed significant changes in neural outcomes after motor rehabilitation.

Discussion and conclusion*:* There was considerable heterogeneity in the designs of the included studies, the interventions and the outcomes. Due to the diversity of imaging techniques and ROIs of the brain, the best imaging technique cannot be described. Conventional MRI techniques were mostly used and the corpus callosum (CC) and supplementary motor area (SMA) were the most popular ROIs.

Purpose of the study*:* This review is part of planned research. The primary aim of the RCT is to investigate the clinical and neural effects after an individualized high-dose upper limb rehabilitation program in PwMS with different upper limb disability levels and (if found) the correlation between clinical and neural results. However, only the baseline data of this intervention study will be used to investigate the correlation between the clinical measure and imaging parameters.

Operationalization of research question*:* The clinical outcome measurements will be assessed in three centres, specialized in MS. For the imaging acquisition and analysis there will be a collaboration with Ziekenhuis Oost-Limburg (ZOL), radiology department and Dr. Veronica Popescu (neurologist Rehabilitation and MS centre Overpelt, lecture REVAL- UHasselt, PhD on brain atrophy in Multiple Sclerosis).

Keywords: Multiple Sclerosis; motor rehabilitation; imaging; (f)MRI; DTI

Introduction

Multiple Sclerosis (MS) is an inflammatory-mediated demyelinating chronic disease of the central nervous system (CNS). [1] These demyelinating processes induce focal lesions of the brain, therewith, neurodegenerative processes such as accelerated whole-brain atrophy and cortical thinning are present in persons with MS (PwMS). [2] Lesion development in PwMS is heterogeneous, both in terms of mechanisms and temporal differences. [3] Therefore, the clinical course of MS is not predictable. Depending on developments, MS can be subdivided into four types: relapsing remitting Multiple Sclerosis (RRMS), secondary progressive Multiple Sclerosis (SPMS), primary progressive Multiple Sclerosis (PPMS) and progressive relapsing Multiple Sclerosis (PRMS). The most common form of MS is RRMS, affecting 80 – 85 % of PwMS. SPMS occurs in 65% of persons with RRMS, they decline gradually between neurological relapses without remission periods. [42]

PwMS may suffer, depending on the number and place of the lesions, sensorimotor disorders and a larger dual task cost (DTC) in comparison with healthy people. [4] PwMS show impaired mobility that is associated with high-energy costs and effort, have poor endurance [5], muscle weakness in one or more groups, joint contractures, which can be present in the early stage of the disease, [6] and spasticity [7]. Somatosensory impairments [8] and optic neuritis, characterized by partially or totally loss of vision, most often unilateral [42], are symptoms common in PwMS.
PwMS may also suffer cognitive impairments which occur in 40 – 60 % of cases regardless of clinical type. Functions most affected are memory, attention and processing speed information. [42]
Bladder and bowel dysfunctions, pain syndromes, tremors, vertigo, depression and mood disorders are other impairments which can occur in PwMS. [9] Due to these aforementioned impairments, a lower quality of life (QoL) in PwMS in comparison with healthy people is measured. [9]

To date, no pharmacological treatment is available to cure MS. [10] Medication reduces the frequency and severity of relapses in RRMS, and also inhibits disease progression, [11] therefore, QoL can be improved by medication. [12] Nowadays, pharmacological treatment in combination with (multidisciplinary) rehabilitation is done in order to maintain the functional status of PwMS. [10] Rehabilitation helps PwMS to achieve maximum independency by managing and minimizing the above mentioned impairments. [13] Different types of rehabilitation strategies have proven to be effective. [10] Specific balance exercises, physical therapy, based on the individual, and resistance and aerobic training have a positive effect on balance [14] and walking ability [15] in ambulatory PwMS. Robot-based rehabilitation, strength and endurance training, and multidisciplinary rehabilitation can improve upper limb function in PwMS. [10] Exercise therapy has a positive effect on fatigue, [16] depressive symptoms [15] and does not increase spasticity in PwMS. [17] Physical activity is associated with benefits on ability outcomes, continuation is likely required to maintain benefits. [18]

Since several years, magnetic resonance imaging (MRI) is used for the diagnosis and management of PwMS. MRI shows sensitivity for detection of white matter lesions in the CNS and specificity for lesion spread in space and time. [19]*

Due to the recently developments and improvement of the MRI techniques such as voxel-based morphometry (VBM), proton density weighted images (PD weighted images), diffusion-weighted imaging (DTI), … MRI seems also a promising evaluation tool to measure neural changes after rehabilitation. The addition of imaging as an outcome measure in rehabilitation would help us to understand the underlying mechanisms of the clinical effects. Recently, more rehabilitation studies have included MRI techniques to evaluate the neural effect, but it is however unclear which techniques and which ROIs are important to use and to look at when evaluating the effects of a rehabilitation strategy. Therefore, this systematic review was conducted to investigate which techniques of imaging and which ROIs are used the most in recent publications in which clinical and neural effects are measured after motor rehabilitation.

With this paper we aimed to review the studies in which neural effects of motor rehabilitation are being investigated. An overview of techniques of used imaging techniques and ROIs to evaluate these neural effects was made. Finally, a resume of the neural and clinical effects of the different rehabilitation programs is given.

* Please consult the bookmark (appendix) if there are difficulties in relation with the imaging techniques.

Methods

Research question + PICO

The main research questions of this literature review were: (1) 'What are the neural effects after motor rehabilitation in persons with Multiple Sclerosis?' and (2) 'Which imaging techniques are used to evaluate the neural effects after motor rehabilitation in persons with Multiple Sclerosis?'.
These research questions could be represented as the following PICO:

- P: Patients with Multiple Sclerosis
- I: Motor interventions or a one-time exercise
- C: Other motor interventions or no control intervention
- O: Primary outcomes: neural outcome measurements – fMRI, MRI, DTI, …
  Secondary outcomes: clinical outcome measurements

The aim of this study was to give an overview of which techniques, ROIs and parameters were used to evaluate the neural effects after a motor rehabilitation program and which were the components of the motor rehabilitation programs finding neural effects related to treatment.

Literature search

Two databases were used for this literature search: PubMed and Web of Knowledge (WoK). These databases were using the following combination of Medical Subject Headings (MeSH) terms and keywords: Multiple Sclerosis AND (rehabilitation OR motor rehabilitation OR motor training OR training OR exercise) AND (imaging OR MRI OR fMRI OR DTI) NOT (cognitive OR drugs OR memory OR depression OR fatigue). The screening happened based on title and abstract. Inclusion and exclusion criteria were applied on the full texts. Afterwards, screening of references of the included studies took place.
In appendix there is an overview of the different search strategies (table 1).
The final update of this literature search was performed on January 23, 2018.

Selection criteria

Randomized Controlled Trials and Controlled interventional studies were included when investigating the neural effects of a motor intervention measured with imaging techniques in PwMS. The study needed to use neural outcome measurements (MRI, functional MRI (fMRI) or DTI) and the full text had to be available. Cross-sectional studies investigating the brain activity during the execution of a motor task were also included since they provide valuable information on the imaging techniques use in a rehabilitation context.

Quality assessment

To investigate the quality of the included studies, the Cochrane checklist for RCT's and Controlled interventional studies, and the STROBE checklist for cross-sectional studies were used.

Data extraction

The following data were extracted from the included articles: characteristics of the population, the aim of the study, the performed interventions and their description, the outcome measurements (clinical and neural outcomes, imaging techniques and brain regions) and the pre-and post-results.

Results

Literature search

Forty-four articles were found in Pubmed and sixty-six in WoK leading to a total of eighty articles (without doubles). After screening of on title and abstract nine articles were retrieved. After screenings of the references of the included articles, two studies were retrieved. Two other final studies were included that weren't retrieved from the literature search. These studies were not found during literature research because of the recent publication, see figure 1.
We excluded (1) reviews and (2) studies who only had a cognitive intervention. In total, thirteen articles were included in this literature review. [2, 20-31]
In table 2 (appendix) there is an overview of the included articles and excluded articles.

Quality assessment

RCT's
Seven studies [2, 20, 21, 23-25, 31] were screened on quality with the Cochrane checklist for RCT's (table 3). All studies scored high and were similar to each other. Blinded patients and trainers were not mentioned in any of the studies (table 3, items 3 and 4). The majority of the studies [2, 21, 22, 24, 25, 32] examined follow-up (table 3, item 7) and all but one study [23] had no difference between participants at baseline (table 3, item 9). Based on the previous questions of the checklist (table 3, items 1-9), the validity of all studies were questionable, except for one [2] where the validity was mentioned and assessed (nr10).

Controlled interventional studies
Four studies [22, 26-28] were screened on quality with the Cochrane checklist for Controlled before-and-after studies (table 4). Two out of four studies did not mention a randomization of the patients and blinded outcome measurements (table 4, items 1 and 5). [26, 27] The majority of the studies [27-29] had no blinded inclusion (table 4, item 2). All studies lacked information about blinded patients and trainers (table 4, items 3 and 4). Based on the previous questions of the checklist (table 4, items 1-9), the validity of all studies were questionable (table 4, item 10).

Cross-sectional studies
Two studies [29, 30] were screened on quality with the STROBE checklist for Cross-sectional studies (table 5). Both studies scored high and similar on the checklist. The study design was not mentioned in the studies (table 5, item 1a). Bonzano et al. (2011) lacked information on study size and descriptive data while Mancini et al. (2009) did not mention other analyses.

Data extraction

Characteristics of the participants (table 6)
The minimum number of participants included in the studies was twelve and the maximum 111. Some studies (n=7) included PwMS and healthy controls. The Expanded Disability Status scale (EDSS) of the PwMS included in the studies ranged from 0 to 7.7.

Type of intervention (table 7)
Seven studies [21, 23, 25, 26, 28-30] investigated the effects of the upper limb rehabilitation strategies such as neuromuscular control, strength and sensorimotor exercises. [21, 23, 25] The cross-sectional studies asked a task of the hand or tap movements. [29, 30] Eight studies [2, 20, 22-25, 27, 31] investigated the effects of the lower limb rehabilitation strategies. Two studies [24, 27] assessed balance, others [2, 20, 22, 23, 25, 31] included aerobic training, strength and sensorimotor exercises of the lower limb. The shortest intervention duration was in total twelve minutes, the longest twenty-four weeks. Frequencies ranged from one to seven times a week, with a duration of five to sixty minutes per session. The total of sessions varied from one session to sixty sessions.

Type of imaging and regions of interest (table 8)
The most frequently used imaging technique was the conventional MRI. This was used in ten out of the thirteen articles. [2, 20-22, 24, 26-30] Four of those articles performed DTI in combination with conventional MRI parameters. [21, 22, 24, 29] Two articles only used DTI as neural outcome measurements [20, 27], two articles [23, 31] used both DTI and fMRI and four articles [25, 26, 28, 30] only used fMRI.

The parameter that was most frequently evaluated were the T2 lesions, by eight articles. [2, 21, 22, 24, 26, 28-30] Other popular parameters were brain volume [2, 20, 24, 27, 28], the microstructural integrity [21-24, 27, 29, 31] and the structural connectivity. [20] T2 lesions and brain volume can be investigated using standard MRI techniques, structural connectivity can best be measured using fMRI techniques, and the microstructural integrity can be investigated using DTI parameters.

There was a great difference in ROIs between all the articles. The most common ROIs were the supplementary motor area (SMA) [23, 25-27] and the corpus callosum (CC) [21, 22, 24, 29], who were both assessed by four articles. The primary sensorimotor cortex was examined by three articles [25-27]. The putamen [20, 25], primary motor area [23, 27], inferior cerebellar peduncles [23, 24], middle cerebellar peduncles [23, 24] and superior cerebellar peduncles [23, 24] were investigated in two articles. All the other ROIs (thalamus, caudate, pallidum, hippocampus, amygdala, accumbens [20], cortical regions [2], corticospinal tract, superior longitudinal fasciculus [21], internal capsule and corona radiata, fronto-occipital fasciculi, inferior longitudinal fasciculi [24], parietal cortex [26], pre-supplementary motor area, primary somatosensory motor cortex [27], precentral and post-central gyrus [31]) were assessed in only one article.

Clinical outcomes (table 9)

In ten out of thirteen articles, the experimental group improved significantly better than the control group or healthy controls after intervention. [2, 20-23, 25, 28-31] The experimental group existed of resistance training, endurance training, balance training or specific tasks of the hand, while the control group received no intervention, passive mobilization or were put on a waiting list. The healthy controls received either the same intervention as the experimental group or no intervention at all.

The interventions that were focused on the upper limbs found a significantly improved and sustained bimanual coordination ($p = 0.002$) [21] and a significant improvement of motor performance that reduced the response time reacting to random stimuli during a pure motor reaction-time task ($p = 0.008$) [29].

Interventions based on the lower limbs found a significant improvement of VO_{2MAX} ($p < 0.05$), sit-to-stand test ($p < 0.001$), MS Walking Scale (MSWS-12) ($p < 0.05$), spatial recall test ($p < 0.05$), the physical part of the MS Impact Scale (MSIS-29) ($p < 0.01$) [20], Fatigue Scale for Motor and Cognitive Function (FSMC) [2, 20], 2-min walking test ($p = 0.03$), berg balance scale (BBS) ($p = 0.006$) and the dynamic gait index (DGI) ($p = 0.03$) [31]. In Prosperini et al. (2014), there was a significant difference of postural sway between the experimental group and the healthy controls at baseline ($p < 0.05$). [24] Changes of postural sway [24], the 2-min walking test, BBS and the DGI [31] did not persist beyond twelve weeks after training.

Interventions who included both upper and lower limbs found a significant improvement of fatigue, depression, impairment, disability, handicap and QoL. [25] The effects of the motor program activating therapy (MPAT) persisted one months after completing the program and the positive immediate and long-term effects were confirmed. [23]

Neural correlates (table 10)

All articles, but one [25], found significant differences on the neural outcomes.

The interventions of the upper limbs experienced a worsening of the microstructural integrity in the CC (FA: $p = 0.003$, RD: $p = 0.004$) and corticospinal tract (FA: $p = 0.022$, RD $p = 0.008$) in the control group, while this was preserved in the experimental group receiving task-oriented training. They also found a significant increase of radial diffusivity (RD) in the superior longitudinal fasciculi in both groups ($p = 0.02$), indicating a lack of treatment effects on this structure. [21] Another article found a higher variability in the transfer process of the CC, suggesting the presence of subtle impairments in interhemispheric communication. [29] A significant correlation (Pearson's $r = 0.74$, $p = 0.003$) was found in the subregion (CC), including posterior midbody, which seems to be essential for the interhemispheric transfer of information related to pure sensorimotor tasks. [29] Tomassini et al. (2011) found significant correlations between the nine hole peg test (NHPT) and both the T2 lesion volume ($r = 0.44$, $p < 0.05$) and the T1 lesion volume ($r = 0.45$, $p < 0.04$). A significant relationship was also found between 'mean tracking error across days of practice' and both the T2 lesion volume ($r = 0.66$, $p < 0.002$) and T1 lesion volume ($r = 0.66$, $p < 0.002$) [28].

Interventions of the lower limbs found a significant effect on the left pallidum volume ($p < 0.05$) [20], a significant increase of the fractional anisotropy (FA) ($p < 0.001$) and a significant decrease of the mean

diffusivity (MD) (p = 0.014) and RD (p = 0.002) in the CC in PwMS. [22] The percentage brain volume change (PBVC) tended to differ and higher absolute cortical thickness values were observed in four areas: anterior cingulate gyrus (p = 0.044), temporal pole (p = 0.021), orbital sulcus (p = 0.004) and the inferior temporal sulcus (p = 0.003) [2]. Tavazzi et al. (2018) found a significant reduction in the activation of the left precentral gyrus during the right foot motor task after intervention. This reduction did not maintain at follow-up. [31]

In an intervention based on balance, there was a significant interaction between time by group for FA and RD of the left and right superior cerebellar peduncles ($F_{2,23}$range, 5.555-3.450; p = 0.036-0.088). This was concluded to correlate with objective measures of balance improvement, detected at static posturography (r = -0.381 to 0.401, p < 0.05). These DTI changes did not persist beyond twelve weeks after training [24]. Another article based on balance found a significant correlation (p < 0.01) between improvement of the temporal performance and the genu (r = -0.468) and primary motor fibers (r = -0.558), and between the average temporal performance and the genu (r = -0.503). This correlated strongly in the improvements in postural control. [27]

The interventions on both the upper and lower limbs resulted in a significant increase of the FA (p = 0.006) and a decrease of the MD (p = 0.081) in the experimental group. There was also a decrease of the effective connectivity at the supplementary motor areas. Those changes persisted one month after completing the program. The positive immediate and long-term effects of MPAT on brain functions and brain microstructure were confirmed. [23]

The correlation between brain activity in the left and right hemisphere was greater in healthy controls at baseline. Rehabilitation resulted in a trend for increased correlation between left and right hemisphere in PwMS, but signal amplitudes in anatomical areas did not show any significant changes. [25]

Discussion

Reflection on the quality of the included studies

As shown in the result section (table 3 and 4), the quality of the included longitudinal studies was not excellent because of the lack of information on the blinding of patients and trainers (table 3 and 4, items 3 and 4). Due to the nature of the study design or the intervention, it is however sometimes difficult to blind the patient. In addition, the validity in the majority of the studies were questionable (based on the previous questions items 1-9).
As shown in the result section (table 5), the quality of the included cross-sectional studies was near to excellent. Based on these checklists, the studies could be read without any reservations.

Reflection on the findings in function of the research questions

This review demonstrated that only few studies investigated the clinical and neural effects after a motor intervention in PwMS. The neural and clinical changes were evaluated after different types of interventions, which makes it difficult to draw conclusions regarding the superiority of one type of intervention.

Investigating neural effects after rehabilitation is an uprising scientific field. However, the most optimal use of imaging technique(s) is still questionable. DTI was used in eight out of the thirteen studies oriented between 2011 and 2018. Earlier studies (2004-2011) used fMRI to investigate the neural effects. This shows a greater interest in DTI of the previous years and maybe the years to come. A reason could be that DTI appears to be indicated for diagnostic and prognostic information as well as for tracking recovery in the setting of ischemic, traumatic, inflammatory, infectious and degenerative disease, [32] such as MS.
The most frequently used parameter existed of T2 lesions, measured by conventional MRI. This could be the most popular parameter because T2 lesions are accepted MRI biomarkers of new inflammation. New MRI activity occurs more frequently than new clinical symptoms, such as relapses. [33]
The most common ROIs were investigated by four articles, the SMA and the CC. Cruz et al. (2013) assessed the neural correlates of fatigue in MS through gray and white matter concluding an association between high Fatigue Severity Scale (FSS) scores and reductions of white matter in the SMA. [34] Fatigue is one of the most common symptoms of MS, thus considering the SMA as a ROI could be beneficial. The CC is composed of compacted interhemispheric fibers traversing a large amount of subcortical white matter, thus the effects of myelin content loss, axonal damage and gliosis will be more severe. A study evaluating the FA values of the normal-appearing white matter of the CC in persons with RRMS found a significant decrease in the FA (comparing to healthy controls) in all

regions of the normal-appearing CC, the rostrum, body and splenium, suggesting there is a subtle and diffuse abnormality in the CC despite its normal appearance on conventional MRI. [35] It could be that some articles investigating neural effects by DTI took an interest of making the CC a ROI because of its structure and appearance.

Despite the great amount of significant differences on neural outcomes throughout the studies, the diversity of these results is large. This is due to the large amount of ROIs and different kind of interventions.

Because of the great difference in interventions and ROIs investigated, it is hard to compare the neural outcomes of these studies with each other. An explanation of the significant neural changes can be neuroplasticity. Neuroplasticity is the ability of the nervous system to change in favour of the conditions of the environment, encountered during development and learning. [36] Plasticity can be seen as changes in neuronal gray matter, white matter and in other tissue compartments. [37] Neuroplasticity can also occur in persons with a disease, for example PwMS. [38]

An intervention of the lower extremities was done in the studies of Tavazzi et al. (2018) and Feys et al. (2017). ROIs were different in these two studies: Tavazzi et al. (2018) investigated the pre-central gyrus and post-central gyrus as ROIs, Feys et al. (2017) investigated lots of different regions as ROIs like the left and right thalamus, caudate, putamen, pallidum, hippocampus, amygdala and accumbens. In both studies a significant reduction in activation of the left pre-central gyrus in both experimental groups was observed, however, there were no other significant neural changes. [31] In the study of Feys et al. (2017), besides the change in the pre-central gyrus, they also found a significant change in brain volume of the left pallidum in the experimental group, but no other significant changes of neural outcomes were observed. [20] In contrast to the small significant neural changes, large significant changes in the following clinical outcomes were observed: the two minute walk test (2MWT), BBS, DGI, [31] maximal oxygen intake (VO_{2MAX}), workload peak, maximum heart rate (HR max), five-repetition sit-to-stand (5-STS), Spatial Recall Test (SPART), MSIS-29 and FSMC (cognitive and physical domain). [20] There were no correlations between clinical and neural results.

Three studies included an upper extremity rehabilitation program. [21, 26, 28] Bonzano et al. (2013) included the brain areas involved in voluntary movement control as ROIs (CC, left and right corticospinal tract, left and right superior longitudinal fasciculus). These ROIs were chosen because of the voluntary exercises for neuromuscular control that were done during the intervention. Morgen et al. (2004) included two very specific areas, namely the left primary sensorimotor cortex and adjacent parietal association cortex as ROIs, these specific ROIs were chosen because of the specific task (flexion and extension of the right thumb) that was done during the intervention. No specific ROIs were chosen in the study of Tomassini et al. (2011), this is because there was only interest in T2 lesions of the brain and brain volume. Bonzano et al. (2013) found a significant interaction effect in two DTI parameters, RA and RD, in two ROIs, the CC and corticospinal tract after intervention. [21] In contrast

to the significant interaction effects of neural outcomes, the experimental group and control group induced similar significant effects of time on the Action Research Arm Test (ARAT), NHPT, grip strength and movement rate at maximum velocity (RATE-MV), only the inter hand interval (IHI) showed a significant interaction effect in favour of the experimental group. [21] Tomassini et al. (2011) observed in the second experiment correlations between the NHPT and T2 lesion volume (T2-LV) plus T1-lesion volume (T1-LV), tracking error across days of practice and T2-LV plus T1-LV. Moreover, a significant motor improvement was observed in both the experimental group and healthy control group after intervention. In the study of Morgen et al. (2004) no significant clinical changes were observed, this may be due to the short intervention period. Although, this way, a cross-sectional study, significant more activation of the contralateral dorsal premotor cortex was observed during thumb flexion and thumb extension in PwMS than in healthy controls.

Three studies included both the upper and lower limb in their intervention [2, 22, 25]. Ibrahim et al. (2011) had only one clinical outcome measurement, the Paced Auditory Serial Addition Test (PASAT 3). The PASAT 3 was also one of the many clinical outcome measurements of Rasova et al. (2005) and Kjølhede et al. (2017). Both Ibrahim et al. (2011) and Rasova et al. (2005) showed a significant change of the PASAT 3 after intervention for the experimental group but not for the control group [25] or healthy controls. [22] Kjølhede et al. (2017) found no significant changes. Both Rasova et al. (2005) and Kjølhede et al. (2017) had the NHPT and the timed 25-foot walk test (T25FW) as clinical outcome measurements. Both studies found a significant difference of the NHPT and T25FW after intervention for the experimental group but not for the control group. [2, 25] Although all studies found a significant change in the clinical effects, Rasova et al. (2005) found no neural changes while Ibrahim et al. (2011) found significant neural changes of FA, MD and RD in the CC and Kjølhede et al. (2017) found a significant absolute increase in cortical thickness in nineteen cortical areas. A reason can be the different choice of MRI technique. Both Kjølhede et al. (2017) and Ibrahim et al. (2011) used the conventional MRI to investigate T2 lesions, while Rasova et al. (2005) only used the functional MRI to investigate the amplitude size of the change of signal intensity between rest and activity of the primary sensorimotor cortex, supplementary motor cortex, nucleus dentatus and putamen. Ibrahim et al. (2011) also used DTI to investigate the microstructural integrity of the CC. No correlations were found between clinical and neural results.

Two studies investigated clinical and neural changes after an intervention based on balance. [24, 27] Both studies investigated brain volume with conventional MRI techniques and microstructural integrity with DTI. Although they both did the same imaging analysis and had the same type of intervention, the ROIs were very different in each study. Peterson et al. (2017) investigated the structural integrity of the CC by looking at the pre-supplementary motor area, SMA, primary motor cortex and primary somatosensory motor cortex. Prosperini et al. (2014) was more focused on the different peduncles of the cerebellum, the internal capsule and corona radiata, fronto-occipital fasciculus, the inferior longitudinal fasciculus and the CC itself. Peterson et al. (2017) showed worse structural connectivity of the CC and superior cortical white matter tract in PwMS than healthy controls, while Prosperini et al.

(2014) showed significant differences of the FA and RD of the left superior cerebellar peduncles and the FA of the right superior cerebellar peduncles in the experimental group. Both studies found no significant clinical changes after intervention, however, Prosperini et al. (2014) showed a significant difference of postural sway at baseline between the experimental group and the healthy controls. Finally, both studies investigated correlations between clinical and neural outcome measurements: Peterson et al. (2017) showed a significant moderate correlation between the improvements of postural control and the microstructural integrity of white matter tracts in the experimental group. The highest correlations between clinical and neural effects were found with the CC, the genu and midbody. [27] Prosperini et al. (2014) found low correlations between changes in postural sway and FA and RD of the superior cerebellar peduncles (left and right).

There were two cross-sectional studies included in this review. [29, 30] Both Bonzano et al. (2011) and Mancini et al. (2008) investigated a specific task of the hand. Both studies used conventional MRI techniques to investigate T2 lesions. Bonzano et al. (2011) used DTI to further investigate the microstructural integrity of the CC, while Mancini et al. (2008) used the functional MRI during the performance of the task of the hand. Mancini et al. (2008) did not mention any specific ROIs. Although both studies investigate the hand, the tasks performed are different. Bonzano et al. (2011) investigated the reaction time of the right (learning) and left (transfer) hand after a random stimulus, while Mancini et al. (2008) investigated adaptation after a repeated right-hand tapping task. Mancini et al. (2008) had no significant changes of clinical outcome measurements after one-year follow-up, but EDSS and T2 lesion load were both significant different after one-year follow-up in the experimental group. Correlations were found in both studies. Bonzano et al. (2011) showed a correlation between the amount of transfer as the difference in reaction time between block two of the right hand and block two of the left hand with the FA of the third subregion of the CC. Mancini et al. (2008) found an association between a significant greater fMRI activation and longer times to complete NHPT in PwMS compared to healthy controls.

One study did not found any significant changes on the neural outcomes after intervention. Rasova et al. (2005), found no significant changes of the amplitude of signal (brain activity) in the experimental group in comparison with the control group. This can probably be explained by the variability of MS, the selection and number of probands, method of evaluation or by the variable execution of the paradigm. [25]

In most studies, physical activity has beneficial clinical outcomes: walking distance, endurance, power, strength, manual dexterity and cognitive domains can be improved by motor therapy. [2, 20-23, 25, 28-31] This can be compared with the outcomes of the review, written by Charron et al., in which was shown that endurance and resistance training benefits in walking ability, balance, coordination, strength and mobility. [18]

Two studies, Peterson et al. (2017) and Morgen et al. (2004) showed no significant clinical changes after intervention. [26, 27] This can be due to the short intervention that has been done in these studies, respectively two days in which two sessions of five minutes were done and one session of forty-six minutes. Contradictory, in Bonzano et al. (2011), an intervention of twelve minutes has been done, and the response time of the learning hand changed significantly in favour in both the experimental group of PwMS and healthy controls. [29] In Tomassini et al. (2011), an intervention of 26 minutes has been done, and an effect of tracking error in this specific exercise was observed. [28] A plausible explanation can be a rapid learning effect of a very specific convenient task of the hand, although, this is not certain.

Tavazzi et al. (2018), Rasova et al. (2014) and Mancini et al. (2008) examined the long term clinical effects after a certain period in which no continuation of intervention was done. Tavazzi et al. (2018) and Mancini et al. (2008) showed no changes in clinical outcomes between baseline measurements and follow-up measurements, indicating no maintained significant changes after intervention. Contradictory, Rasova et al. (2014) shows that all significant improvements remained significant in the long term. This contradiction can be explained by the differences of clinical interventions that was done in these studies: the duration of program was two times longer in Rasova et al. (2014) in comparison with Tavazzi et al. (2018). The duration of program of Mancini et al. (2008) only lasted twelve minutes. Although, the frequency was most large in Tavazzi et al. (2018). The type of intervention can also have an influence on the whether or not maintenance of clinical effects after follow-up.

Reflection on the strengths and weaknesses of the literature study

Strengths

As mentioned before, investigating neural effects after rehabilitation is an uprising scientific field. The studies included are therefore quite recent.

The description of the inclusion and exclusion criteria of this literature review and in all of the studies separately were very clear.

This literature review also included more study designs to get a complete view of motor rehabilitation with neural effects and answer the research questions as good as possible. It took away the chance of excluding potentially good articles. This is also why references of included articles and recent studies not yet found on PubMed or WoK were included.

Limitations

Several limitations of this literature review can be discussed. First, cognitive interventions weren't included. There have been plenty of cognitive interventions investigating neural effects and much lesser motor interventions. Recently, a couple of reviews have been published investigating neural effects after cognitive rehabilitation in PwMS. [39-41] This is why the choice of excluding cognitive interventions was made. Nevertheless, results of these cognitive interventions have to be taken into account.

Also excluded were studies involving electrostimulation as intervention. This was not included under the taxonomy of 'motor rehabilitation'. The number of studies involving electrostimulation is rare. Thereafter, the description of the purpose and outcomes of the study of Mancini et al. [30] are not clearly explained. This caused for a lot of confusion.

Other limitations are (1) divergent studies in terms of rehabilitation program, (2) a small EDSS in all the studies, thus there is a lack of information about PwMS with greater dysfunctions, and (3) because of the diversity in interventions, the chosen ROIs are often different. The latter causes few results for a great number of ROIs, making it harder to find similar conclusions.

Recommendations for further research

Further research in this field is necessary. First, we recommend blinding of trainers and participants during the whole study. The studies included in this review, included particularly persons with RRMS. Studies are needed in which persons with PPMS, SPMS and PRMS are included, wherefore, generalization can be made. A rather small EDSS score was found in all the included studies. More investigation is needed for PwMS with a higher EDSS score, to investigate if these results have a similar effect as the results of the included studies of this review. When motor rehabilitation is done during the intervention, primary sensory motor cortex, supplementary motor cortex and CC must be used as ROIs. Investigating the structural connectivity of the left and right hemisphere must be done, using the CC. When balance is investigated as clinical outcome, the cerebellar structures must be used as ROIs for neural outcomes. Using the most optimal MRI technique is of great importance. To investigate T2 lesions, brain volume, brain atrophy and cortical thickness conventional MRI techniques are used. Structural connectivity and change of signal intensity between rest and activity can be measured using functional MRI techniques. DTI parameters are most useful investigating microstructural integrity and structural connectivity. Also important for future research is to add a follow-up period in the protocol that is made. This way possible long-lasting effects can be investigated. At last, a study with enough participants ($n \geq 92$) has to be done so that a sufficient can be achieved, in favour of the statistical analysis.

Conclusion

According to this literature review, overall, significant clinical and neural changes have been found after rehabilitation. In conclusion, motor rehabilitation has beneficial clinical effects and beneficial effects on brain plasticity in PwMS. Different motor interventions have been used to investigate different neural effects.

Conventional MRI, fMRI and DTI were used to investigate different ROIs and different parameters, like T2 lesions, brain volume, structural connectivity and microstructural integrity.

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Appendix

Progress form

Self-evaluation

Bookmark imaging

Table 1: *Overview of number of hits of different search strategies.*

Table 2: *Overview of search strategies 44 (PubMed), 66 (WoK) articles and 4 extra included articles.*

Figure 1: *Flow-chart included articles and excluded articles.*

Table 3: *Overview Cochrane checklist for RCT's.*

Table 4: *Overview Cochrane checklist for Controlled interventional studies.*

Table 5: *Overview checklist for cross-sectional studies (STROBE).*

Table 6: *Overview of the aim of the included studies and the characteristics of the participants included in these studies.*

Table 7: *Details clinical intervention(s) of the included studies.*

Table 8: *Details imaging intervention(s) of the included studies.*

Table 9: *Overview of the clinical outcomes of the included studies.*

Table 10: *Overview of the imaging outcomes of the included studies.*

Table 11: *Abbreviations.*

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VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
26/10/2017	Tekenen contract	Promotor: iov Copromotor: Student(e): Student(e):
09/11/2017	Uitleg/inleiding onderwerp thesis	Promotor: iov Copromotor: Student(e): Student(e):
23/11/2017	Overlopen gevonden artikels + bekijken goede zoekstrategie en de volgende stappen	Promotor: iov Copromotor: Student(e): Student(e):
15/01/2018	Overlopen zoekstrategie + uitleg en afspraken/deadlines volgende stappen	Promotor: Copromotor: Student(e): Student(e):
23/01/2018	Overlopen geïncludeerde artikels + strategie checklist en data-extractie	Promotor: Copromotor: Student(e): Student(e):
26/03/2018	Bespreking feedback inleiding, methodologie en data-extractie	Promotor: Copromotor: Student(e): Student(e):
23/04/2018	Bespreking feedback + protocol	Promotor: Copromotor: Student(e): Student(e):
06/06/2018	Bespreking feedback	Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):

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BEOORDELING VAN DE WETENSCHAPPELIJKE STAGE-DEEL 1

Wetenschappelijke stage deel 1 (Masterproef deel 1- MP1) van de Master of Science in de revalidatiewetenschappen en de kinesitherapie bestaat uit **twee delen**:

1) De literatuurstudie volgens een welomschreven methodiek.
2) Het opstellen van het onderzoeksprotocol ter voorbereiding van masterproef deel 2.

Omschrijving van de **evaluatie**:

1) 80% van het eindcijfer wordt door de promotor in samenspraak met de copromotor gegeven op grond het product en van het proces dat de student doorliep om de MP1 te realiseren, met name het zelfstandig uitvoeren van de literatuurstudie en het zelfstandig opstellen van het onderzoeksprotocol, alsook de kwaliteit van academisch schrijven.
2) 20% van het eindcijfer wordt door de interne jury gegeven op grond van het ingeleverde product en de mondelinge presentatie waarin de student zijn/haar proces toelicht.

In de beoordeling dient onderscheid gemaakt te worden tussen studenten die, in samenspraak met de promotor, een nieuw onderzoek uitwerkten en studenten die instapten in een lopend onderzoek of zich baseren op voorgaande masterproeven of onderzoeksprojecten. Van deze laatste worden bijkomende inspanningen verwacht zoals bv. het bijsturen van de eerder geformuleerde onderzoeksvraag, de kritische reflectie over het onderzoeksdesign, het uitvoeren van een pilotexperiment.

Beoordelingskader:

Beoordelingskader: criteria op 20	
18-20	Excellente modelmasterproef
16-17	Uitmuntende masterproef
14-15	Zeer goede masterproef die zich onderscheidt van de andere masterproeven
12-13	Goede masterproef
10-11	Voldoende masterproef die op een aantal vlakken zwak scoort
8-9	Onvoldoende masterproef die niet aan de minimumnormen voldoet
6-7	Ernstig onvoldoende masterproef of een masterproef die slechts één van beide bevat
≤ 5	Ernstig onvoldoende en onvolledige masterproef

ZELFEVALUATIERAPPORT

Onderstaand zelfevaluatierapport is een hulpmiddel om je wetenschappelijke stage -deel 1 zelfstandig te organiseren. Bepaal zelf je deadlines, evalueer en reflecteer over je werkwijze en over de diepgang van je werk. Check de deadlines regelmatig. Toets ze eventueel af bij je (co)promotor. Succes!

Prof. M. Vanvuchelen, coördinerende verantwoordelijke wetenschappelijke stages

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ZELFEVALUATIERAPPORT **WETENSCHAPPELIJKE STAGE - DEEL 1** **RWK**

Naam & Voornaam STUDENT: Hooybergs Jasmien & Verwaest Laura…..……

Naam & Voornaam (CO)PROMOTOR & PROMOTOR: Dr. Lamers Ilse, Prof. Dr. Feys Peter & PhD student Raats Joke……

TITEL masterproef (Nederlandstalig of Engels): Neural effects after motor rehabilitation in persons with Multiple Sclerosis……...

LITERATUURSTUDIE	Gestelde deadline	Behaald op	Reflectie
De belangrijkste concepten en conceptuele kaders van het onderzoekdomein uitdiepen en verwerken	15/11/2017	10/11/2017	
De belangrijkste informatie opzoeken als inleiding op de onderzoeksvraag van de literatuurstudie	30/11/2017	30/11/2017	
De opzoekbare onderzoeksvraag identificeren en helder formuleren in functie van de literatuurstudie	15/12/2017	10/12/2017	
De zoekstrategie op systematische wijze uitvoeren in relevante databanken	31/01/2018	23/01/2018	
De kwaliteitsbeoordeling van de artikels diepgaand uitvoeren	15/01/2018	15/01/2018	
De data-extractie grondig uitvoeren	31/03/2018	15/04/2018	Het verfijnen van de data-extractie vergde meer tijd dan verwacht.
De bevindingen integreren tot een synthese	15/05/2018	15/05/2018	

ONDERZOEKSPROTOCOL	Gestelde deadline	Behaald op	Reflectie
De onderzoeksvraag in functie van het onderzoeksprotocol identificeren	Begin juni 2018	21/05/2018	
Het onderzoeksdesign bepalen en/of kritisch reflecteren over bestaande onderzoeksdesign	Begin juni 2018	21/05/2018	
De methodesectie (participanten, interventie, uitkomstmaten, data-analyse) uitwerken	Begin juni 2018	03/06/2018	

ACADEMISCHE SCHRIJVEN	Gestelde deadline	Behaald op	Reflectie
Het abstract to the point schrijven	04/06/2018	04/06/2018	
De inleiding van de literatuurstudie logisch opbouwen	30/03/2018	09/04/2018	Resulterend uit de data-extractie die meer tijd in beslag nam dan verwacht.
De methodesectie van de literatuurstudie transparant weergegeven	01/02/2018	01/02/2018	
De resultatensectie afstemmen op de onderzoeksvragen	02/04/2018	15/04/2018	Omwille van een drukke periode werd dit even achteruit geschoven.
In de discussiesectie de bekomen resultaten in een wetenschappelijke tekst integreren en synthetiseren	02/05/2018	03/06/2018	Resulterend uit het verschuiven van de resultaten en een examenperiode.
Het onderzoeksprotocol deskundig technisch uitschrijven	Begin juni 2018	03/06/2018	
Referenties correct en volledig weergeven	Begin juni 2018	31/05/2018	

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ZELFSTUREND EN WETENSCHAPPELIJK DENLEN EN HANDELEN	**Aanvangsfase**	**Tussentijdse fase**	**Eindfase**
Een realistische planning opmaken, deadlines stellen en opvolgen	V	G	ZG
Initiatief en verantwoordelijkheid opnemen ten aanzien van de realisatie van de wetenschappelijke stage	ZG	ZG	ZG
Kritisch wetenschappelijk denken	G	G	ZG
De contacten met de promotor voorbereiden en efficiënt benutten	G	G	G
De richtlijnen van de wetenschappelijke stage autonoom opvolgen en toepassen	ZG	ZG	ZG
De communicatie met de medestudent helder en transparant voeren	G	ZG	ZG
De communicatie met de promotor/copromotor helder en transparant voeren	G	G	ZG
Andere verdiensten:	/	/	/

Magnetic Resonance Imaging (MRI)

MRI uses magnetic fields and radio waves to make images of the structures of the nervous system

Conventional MRI

Conventional MRI is used for detecting multiple sclerosis lesions and their changes over time

1. ***T1 weighted images***
   - CSF is dark
   - fat is bright
     → **visualizing normal anatomy like brain volume or cortical thickness**

2. ***T2 weighted images***
   - CSF is bright
   - fat is bright
     → **visualizing pathology (lesions)**

Structures that are bright on the T2 images, but dark on the T1 images are CSF.
Structures that are bright on both T1- and T2 images are fat.

3. ***PD weighted images***
   - CSF has a relatively high level of protons, making CSF appear bright
     → Proton Density is used to differentiate anatomical structures based on their proton density

4. ***Fluid-Attenuated Inversion Recovery (FLAIR) images***
   → evaluation of white matter plaques near the ventricles
   → identifying demyelination

Non Conventional MRI

Non Conventional MRI is used to localize changes as a consequence of disease-related or intervention-related effects in persons with multiple sclerosis

1. ***Voxel-Based Morphometry (VBM)***
   - Voxel-based morphometry provides an automated quantitative analysis of the distribution of gray and white matter

2. ***Magnetization Transfer Imaging (MTI)***
   → Low magnetization transfer ratio indicates a reduced capacity of the macromolecules in brain tissue to exchange magnetization with the surrounding water molecules, thus reflecting damage to myelin

3. ***Diffusion-Weighted Imaging (DWI/DTI)***
   DTI allows quantitative measurements of brain tissue microstructure, obtained by exploiting the properties of water diffusion

   - **Mean diffusivity (MD)** = shows overall extent of water diffusion + myelin loss
     → high MD values indicates high diffusivity, which indicates axonal and myelin loss
   - **Fractional anisotropy (FA)** = shows fibers directionality + axonal loss: sensitive to microstructural changes, less specific to the type of change (ranging from 0 to 1)
     → decrease of FA values indicates decreased alignment of cellular structures within fiber tracts and decreased microstructural integrity
   - **Axial diffusivity (AD)** = shows diffusivity parallel to the fibers + myelin and axonal content
     → decrease or increase of AD values indicates damage progression
     - decrease of AD = axonal loss
     - increase of AD = compensative mechanism to maintain functionality in the presence of white matter damage
   - **Radial diffusivity (RD)** = shows diffusivity perpendicular to the fibers + myelin content
     → increase of RD values indicates damage progression: loss of myelin

Table 1

Overview of number of hits of different search strategies.

Keyword(s)	# hits in PubMed	# hits in WoK
“Multiple Sclerosis”	51 670 hits	107 060 hits
“rehabilitation”	267 669 hits	171 127 hits
“Multiple Sclerosis” AND “rehabilitation”	1 098 hits	1 500 hits
“motor rehabilitation”	35 400 hits	818 hits
“rehabilitation” OR “motor rehabilitation”	268 006 hits	171 127 hits
“Multiple Sclerosis” AND “motor rehabilitation”	12 hits	15 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation”)	1 098 hits	1 500 hits
“motor training”	32 758 hits	849 hits
“rehabilitation” OR “motor training”	268 214 hits	171 696 hits
“motor rehabilitation” OR “motor training”	1 314 hits	1 634 hits
“rehabilitation” OR “motor rehabilitation” OR “motor training”	268 214 hits	171 696 hits
“Multiple Sclerosis” AND “motor training”	6 hits	8 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor training”)	1 841 hits	1 505 hits
“Multiple Sclerosis” AND (“motor rehabilitation” OR “motor training”)	759 hits	22 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training”)	2 396 hits	1 505 hits
“training”	1 464 412 hits	548 093 hits
“rehabilitation” OR “training”	547 467 hits	698 811 hits
“motor rehabilitation” OR “training”	333 523 hits	548 637 hits
“motor training” OR “training”	333 118 hits	548 093 hits
“rehabilitation” OR “motor rehabilitation” OR “training”	456 817 hits	698 811 hits
“rehabilitation” OR “motor training” OR “training”	456 817 hits	698 811 hits
“motor rehabilitation” OR “motor training” OR “training”	333 523 hits	548 637 hits
“rehabilitation OR “motor rehabilitation” OR “motor training” OR “training”	456 817 hits	698 811 hits
“Multiple Sclerosis” AND “training”	546 hits	736 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “training”)	1 467 hits	1 975 hits
“Multiple Sclerosis” AND (“motor rehabilitation” OR “training”)	557 hits	750 hits
“Multiple Sclerosis” AND (“motor training” OR “training”)	546 hits	736 hits
“Multiple Sclerosis” AND (“rehabilitation OR “motor rehabilitation” OR “training”)	1 467 hits	1 975 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor training” OR “training”)	1 467 hits	1 975 hits
“Multiple Sclerosis” AND (“motor rehabilitation” OR “motor training” OR “training”)	557 hits	750 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training”)	1 467 hits	1 975 hits
“exercise”	160 178 hits	336 730 hits
“rehabilitation” OR “exercise”	354 287 hits	488 278 hits
“motor rehabilitation” OR “exercise”	227 756 hits	337 449 hits
“motor training” OR “exercise”	227 882 hits	337 460 hits
“training” OR “exercise”	521 177 hits	832 522 hits
“rehabilitation” OR “motor rehabilitation” OR “exercise”	354 287 hits	488 278 hits
“rehabilitation” OR “motor training” OR “exercise”	354 774 hits	488 788 hits
“rehabilitation” OR “training” OR “exercise”	636 978 hits	970 512 hits
“motor rehabilitation” OR “motor training” OR “exercise”	228 405 hits	338 155 hits
“motor rehabilitation” OR “training” OR “exercise”	521 557 hits	833 012 hits

“motor training” OR “training” OR “exercise”	521 177 hits	832 522 hits
“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “exercise”	354 774 hits	488 788 hits
“rehabilitation” OR “motor rehabilitation” OR “training” OR “exercise”	636 978 hits	970 512 hits
“motor rehabilitation” OR “motor training” OR “training” OR “exercise”	521 557 hits	833 012 hits
“rehabilitation” OR “motor training” OR “training” OR “exercise”	636 978 hits	970 512 hits
“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”	636 978 hits	970 512 hits
“Multiple Sclerosis” AND “exercise”	572 hits	979 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “exercise”)	1 531 hits	2 187 hits
“Multiple Sclerosis” AND (“motor rehabilitation” OR “exercise”)	583 hits	991 hits
“Multiple Sclerosis” AND (“motor training” OR “exercise”)	577 hits	986 hits
“Multiple Sclerosis” AND (“training” OR “exercise”)	924 hits	1 420 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “exercise”)	1 531 hits	2 187 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor training” OR “exercise”)	1 532 hits	2 192 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “training” OR “exercise”)	1 773 hits	2 494 hits
“Multiple Sclerosis” AND (“motor rehabilitation” OR “motor training” OR “exercise”)	587 hits	998 hits
“Multiple Sclerosis” AND (“motor rehabilitation” OR “training” OR “exercise”)	934 hits	1 432 hits
“Multiple Sclerosis” AND (“motor training” OR “training” OR “exercise”)	924 hits	1 420 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “exercise”)	1 532 hits	2 192 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “training” OR “exercise”)	1 773 hits	2 494 hits
“Multiple Sclerosis” AND (“motor rehabilitation” OR “motor training” OR “training” OR “exercise”)	934 hits	1 432 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor training” OR “training” OR “exercise”)	1 773 hits	2 494 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”)	1 773 hits	2 494 hits
“imaging”	1 784 457 hits	1 967 946 hits
“Multiple Sclerosis” AND “imaging”	5 154 hits	5 997 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”) AND “imaging”	76 hits	96 hits
“MRI”	382 715 hits	264 177 hits
“imaging” OR “MRI”	848 854 hits	1 068 396 hits
“Multiple Sclerosis” AND (“imaging” OR “MRI”)	9 037 hits	8 844 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”) AND (“imaging” OR “MRI”)	112 hits	147 hits
“fMRI”	475 390 hits	60 559 hits
“imaging” OR “fMRI”	683 877 hits	991 519 hits
“MRI” OR “fMRI”	231 041 hits	306 809 hits
“imaging” OR “MRI” OR “fMRI”	759 929 hits	1 092 107 hits
“Multiple Sclerosis” AND “fMRI”	215 hits	337 hits
“Multiple Sclerosis” AND (“imaging” OR “fMRI”)	5 237 hits	5 588 hits
“Multiple Sclerosis” AND (“MRI” OR “fMRI”)	5 270 hits	6 676 hits
“Multiple Sclerosis” AND (“imaging” OR “MRI” OR “fMRI”)	7 729 hits	8 949 hits

“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”) AND (“imaging” OR “MRI” OR “fMRI”)	114 hits	154 hits
“DTI”	8 821 hits	10 303 hits
“imaging” OR “DTI”	669 057 hits	962 738 hits
“MRI” OR “DTI”	207 064 hits	269 217 hits
“fMRI” OR “DTI”	43 943 hits	69 877 hits
“imaging” OR “MRI” OR “DTI”	748 141 hits	1 070 182 hits
“imaging” OR “fMRI” OR “DTI”	684 865 hits	993 591 hits
“MRI” OR “fMRI” OR “DTI”	235 997 hits	311 432 hits
“imaging” OR “MRI” OR “fMRI” OR “DTI”	760 717 hits	1 093 801 hits
“Multiple Sclerosis” AND “DTI”	214 hits	231 hits
“Multiple Sclerosis” AND (“imaging” OR “DTI”)	5 168 hits	5 444 hits
“Multiple Sclerosis” AND (“MRI” OR “DTI”)	5 264 hits	6 578 hits
“Multiple Sclerosis” AND (“fMRI” OR “DTI”)	422 hits	557 hits
“Multiple Sclerosis” AND (“imaging” OR “MRI” OR “DTI”)	9 044 hits	8 858 hits
“Multiple Sclerosis” AND (“imaging” OR “fMRI” OR “DTI”)	5 251 hits	5 610 hits
“Multiple Sclerosis” AND (“MRI” OR “fMRI” OR “DTI”)	7 721 hits	6 746 hits
“Multiple Sclerosis” AND (“imaging” OR “MRI” OR “fMRI” OR “DTI”)	9 054 hits	8 963 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”) AND (“imaging” OR “MRI” OR “fMRI” OR “DTI”)	114 hits	154 hits
“cognitive”	327 473 hits	495 779 hits
“Multiple Sclerosis” NOT “cognitive”	49 093 hits	56 818 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”) AND (“imaging” OR “MRI” OR “fMRI” OR “DTI”) NOT “cognitive”	70 hits	87 hits
“drugs”	1 351 028 hits	1 497 504 hits
“Multiple Sclerosis” NOT “drugs”	50 162 hits	58 125 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”) AND (“imaging” OR “MRI” OR “fMRI” OR “DTI”) NOT (“cognitive” OR “drugs”)	68 hits	85 hits
“memory”	266 320 hits	604 871 hits
“Multiple Sclerosis” NOT “memory”	50 509 hits	59 350 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”) AND (“imaging” OR “MRI” OR “fMRI” OR “DTI”) NOT (“cognitive” OR “drugs” OR “memory”)	66 hits	83 hits
“depression”	98 854 hits	409 553 hits
“Multiple Sclerosis” NOT “depression”	50 833 hits	58 562 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”) AND (“imaging” OR “MRI” OR “fMRI” OR “DTI”) NOT (“cognitive” OR “drugs” OR “memory” OR depression”)	65 hits	74 hits
“fatigue”	25 937 hits	201 984 hits
“Multiple Sclerosis” NOT “fatigue”	50 598 hits	58 089 hits
“Multiple Sclerosis” AND (“rehabilitation” OR “motor rehabilitation” OR “motor training” OR “training” OR “exercise”) AND (“imaging” OR “MRI” OR “fMRI” OR “DTI”) NOT (“cognitive” OR “drugs” OR “memory” OR “depression” OR “fatigue”)	44 hits	66 hits

Table 2

Overview of search strategies 44 (PubMed), 66 (WoK) articles and 4 extra included articles.

Article	Source Included or excluded + reason
Ballario, C., et al. (2006). "Functional MRI and neuronal plasticity depending on the motor training in multiple sclerosis." Multiple Sclerosis 12: S42-S42.	Source: WoK Excluded No full text/abstract
Barkhof, F., et al. (1997). "Improving interobserver variation in reporting gadolinium-enhanced MRI lesions in multiple sclerosis." Neurology 49(6): 1682-1688.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Bejarano, B., et al. (2011). "Computational classifiers for predicting the short-term course of Multiple sclerosis." BMC Neurol 11: 67.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
(*) Bergsland, N., et al. (2015). "Effects of gait training on brain plasticity in multiple sclerosis: a functional MRI study." Multiple Sclerosis Journal 21: 60-60.	**Source: WoK Included**
(*) Bonzano, L., et al. (2014). "Upper limb motor rehabilitation impacts white matter microstructure in multiple sclerosis." Neuroimage 90: 107-116.	**Source: PubMed & WoK Included**
(*) Bonzano, L., et al. (2011). "Structural integrity of callosal midbody influences intermanual transfer in a motor reaction-time task." Hum Brain Mapp 32(2): 218-228.	**Source: PubMed Included**
Boutiere, C., et al. (2017). "Improvement of spasticity following intermittent theta burst stimulation in multiple sclerosis is associated with modulation of resting-state functional connectivity of the primary motor cortices." Mult Scler 23(6): 855-863.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Brand, J., et al. (2014). "Magnetic resonance imaging in multiple sclerosis--patients' experiences, information interests and responses to an education programme." PLoS One 9(11): e113252.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Braverman, D. L., et al. (1997). "Multiple sclerosis presenting as a spinal cord tumor." Arch Phys Med Rehabil 78(11): 1274-1276.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Brosch, T., et al. (2016). "Deep 3D Convolutional Encoder Networks With Shortcuts for Multiscale Feature Integration Applied to Multiple Sclerosis Lesion Segmentation." Ieee Transactions on Medical Imaging 35(5): 1229-1239.	Source: WoK Excluded No MI w/ PRE & POST
Brosch, T., et al. (2014). Modeling the Variability in Brain Morphology and Lesion Distribution in Multiple Sclerosis by Deep Learning. Medical Image Computing and Computer-Assisted Intervention - Miccai 2014, Pt Ii. P. Golland, N. Hata, C. Barillot, J. Hornegger and R. Howe. 8674: 462-469.	Source: WoK Excluded No MI w/ PRE & POST
Brosch, T., et al. (2015). Deep Convolutional Encoder Networks for Multiple Sclerosis Lesion Segmentation. Medical Image Computing and Computer-Assisted Intervention, Pt Iii. N. Navab, J. Hornegger, W. M. Wells and A. F. Frangi. 9351: 3-11.	Source: WoK Excluded No MI w/ PRE & POST
Calabrese, M., et al. (2013). "The changing clinical course of multiple sclerosis: a matter of gray matter." Ann Neurol 74(1): 76-83.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Carass, A., et al. (2017). "Longitudinal multiple sclerosis lesion segmentation: Resource and challenge." Neuroimage 148: 77-102.	Source: WoK Excluded No MI w/ PRE & POST

Carmosino, M. J., et al. (2005). "Initial evaluations for multiple sclerosis in a university multiple sclerosis center: outcomes and role of magnetic resonance imaging in referral." Arch Neurol 62(4): 585-590.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Corso, J. J., et al. (2007). "Detection and segmentation of pathological structures by the extended graph-shifts algorithm." Med Image Comput Comput Assist Interv 10(Pt 1): 985-993.	Source: PubMed Excluded No MI w/ PRE & POST
Dalgas, U. and E. Stenager (2012). "Exercise and disease progression in multiple sclerosis: can exercise slow down the progression of multiple sclerosis?" Therapeutic Advances in Neurological Disorders 5(2): 81-95.	Source: WoK Excluded Review
D'Hooghe M, B., et al. (2010). "Modifiable factors influencing relapses and disability in multiple sclerosis." Mult Scler 16(7): 773-785.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Enzinger, C., et al. (2016). "Longitudinal fMRI studies: Exploring brain plasticity and repair in MS." Mult Scler 22(3): 269-278.	Source: PubMed Excluded Review
Ferrari, R. J., et al. (2003). Segmentation of multiple sclerosis lesions using support vector machines. Medical Imaging 2003: Image Processing, Pts 1-3. M. Sonka and J. M. Fitzpatrick. 5032: 16-26.	Source: WoK Excluded No MI w/ PRE & POST & review
(*) Feys, P., et al. (2017). "Effects of an individual 12-week community-located "start-to-run" program on physical capacity, walking, fatigue, cognitive function, brain volumes, and structures in persons with multiple sclerosis." Mult Scler: 1352458517740211.	**Source: knowledge of article Included**
Fieschi, C., et al. (2005). "Medical education and MS: getting the training right." Int MS J 12(1): 21-31, 20.	Source: PubMed Excluded No MI w/ PRE & POST
Filippi, M., et al. (1998). "Effect of training and different measurement strategies on the reproducibility of brain MRI lesion load measurements in multiple sclerosis." Neurology 50(1): 238-244.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Filippi, M., et al. (2010). "Intracortical lesions Relevance for new MRI diagnostic criteria for multiple sclerosis." Neurology 75(22): 1988-1994.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Fling, B. W., et al. (2014). "Associations between proprioceptive neural pathway structural connectivity and balance in people with multiple sclerosis." Frontiers in Human Neuroscience 8.	Source: WoK Excluded No MI w/ PRE & POST
Freeman, J., et al. (2012). "Pilates based core stability training in ambulant individuals with multiple sclerosis: protocol for a multi-centre randomised controlled trial." BMC Neurol 12.	Source: PubMed & WoK Excluded No MI w/ PRE & POST & no neural outcome measurements
Fritz, N. E., et al. (2017). "Quantitative measures of walking and strength provide insight into brain corticospinal tract pathology in multiple sclerosis." Neuroimage Clin 14: 490-498.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Goldsmith, J., et al. (2011). "Penalized functional regression analysis of white-matter tract profiles in multiple sclerosis." Neuroimage 57(2): 431-439.	Source: PubMed & WoK Excluded No MI w/ PRE & POST

Gonzalez-Andrade, F. and J. L. Alcaraz-Alvarez (2010). "Disease-modifying therapies in relapsing-remitting multiple sclerosis." Neuropsychiatric Disease and Treatment 6: 365-373.	Source: WoK Excluded No MI w/ PRE & POST
Groppo, E., et al. (2017). "Intensive and multimodal upper limb rehabilitation can be effective in multiple sclerosis complicated by progressive multifocal leukoencephalopathy: a functional MRI study." Multiple Sclerosis Journal 23(6): 881-881.	Source: WoK Excluded No full text/abstract
Habek, M., et al. (2016). "Sympathetic cardiovascular and sudomotor functions are frequently affected in early multiple sclerosis." Clinical Autonomic Research 26(6): 385-393.	Source: WoK Excluded No MI w/ PRE & POST
Harmouche, R., et al. (2015). "Probabilistic Multiple Sclerosis Lesion Classification Based on Modeling Regional Intensity Variability and Local Neighborhood Information." Ieee Transactions on Biomedical Engineering 62(5): 1281-1292.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Harrison, L. C. V., et al. (2009). Manual Segmentation of Brain Tissue and Multiple Sclerosis Lesions for Texture Analysis. World Congress on Medical Physics and Biomedical Engineering, Vol 25, Pt 2 - Diagnostic Imaging. O. Dossel and W. C. Schlegel. 25: 300-303.	Source: WoK Excluded No MI w/ PRE & POST
Hobart, J., et al. (2004). "Outcome measures for multiple sclerosis clinical trials: relative measurement precision of the Expanded Disability Status Scale and Multiple Sclerosis Functional Composite." Multiple Sclerosis Journal 10(1): 41-46.	Source: WoK Excluded No MI w/ PRE & POST
Hubbard, E. A., et al. (2016). "Diffusion tensor imaging of the corticospinal tract and walking performance in multiple sclerosis." J Neurol Sci 363: 225-231.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
(*) Ibrahim, I., et al. (2011). "Fractional anisotropy and mean diffusivity in the corpus callosum of patients with multiple sclerosis: the effect of physiotherapy." Neuroradiology 53(11): 917-926.	**Source: reference article (Rasova, Prochazkova et al. 2015) Included**
Ion-Margineanu, A., et al. (2017). "Machine Learning Approach for Classifying Multiple Sclerosis Courses by Combining Clinical Data with Lesion Loads and Magnetic Resonance Metabolic Features." Frontiers in Neuroscience 11.	Source: WoK Excluded No MI w/ PRE & POST
Jain, S., et al. (2015). "Automatic segmentation and volumetry of multiple sclerosis brain lesions from MR images." Neuroimage Clin 8: 367-375.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Jog, A., et al. (2015). Multi-Output Decision Trees for Lesion Segmentation in Multiple Sclerosis. Medical Imaging 2015: Image Processing. S. Ourselin and M. A. Styner. 9413.	Source: WoK Excluded No MI w/ PRE & POST
Jonkman, L. E., et al. (2015). "Ultra-High-Field MRI Visualization of Cortical Multiple Sclerosis Lesions with T2 and T2*: A Postmortem MRI and Histopathology Study." AJNR Am J Neuroradiol 36(11): 2062-2067.	Source: PubMed Excluded No MI w/ PRE & POST
Jurynczyk, M., et al. (2017). "Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis." Brain 140(3): 617-627.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Khastavaneh, H. and H. Haron (2014). A Conceptual Model for Segmentation of Multiple Sclerosis Lesions in Magnetic Resonance Images Using Massive Training Artificial Neural Network. Proceedings Fifth International Conference on Intelligent Systems, Modelling and Simulation. D. AlDabass, Z. Sauli and Z. Zakaria: 273-278.	Source: WoK Excluded No MI w/ PRE & POST
Kindred, J. H., et al. (2015). "Glucose uptake heterogeneity of the leg muscles is similar between patients with multiple sclerosis and healthy controls during walking." Clin Biomech (Bristol, Avon) 30(2): 159-165.	Source: PubMed Excluded No neural outcome measurements

(*) Kjolhede, T., et al. (2017). "Can resistance training impact MRI outcomes in relapsing-remitting multiple sclerosis?" Mult Scler: 1352458517722645.	**Source: knowledge of article Included**
Korteweg, T., et al. (2007). "Interobserver agreement on the radiological criteria of the International Panel on the diagnosis of multiple sclerosis." Eur Radiol 17(1): 67-71.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Lipp, I., et al. (2016). "Brain imaging of short-term functional plasticity predicts performance improvement with longer-term motor sequence training in multiple sclerosis." Multiple Sclerosis Journal 22: 32-32.	Source: WoK Excluded Conference abstract
Lipp, I. and V. Tomassini (2015). "Neuroplasticity and motor rehabilitation in multiple sclerosis." Frontiers in Neurology 6.	Source: WoK Excluded Review
Lyksborg, M., et al. (2012). Segmenting Multiple Sclerosis Lesions Using a Spatially Constrained K-Nearest Neighbour Approach. Image Analysis and Recognition, Pt Ii. A. Campilho and M. Kamel. 7325: 156-163.	Source: WoK Excluded No MI w/ PRE & POST
(*) Mancini, L., et al. (2009). "Short-term adaptation to a simple motor task: A physiological process preserved in multiple sclerosis." Neuroimage 45(2): 500-511.	**Source: WoK Included**
Merwick, A. and B. J. Sweeney (2008). "Functional symptoms in clinically definite MS--pseudo-relapse syndrome." Int MS J 15(2): 47-51.	Source: PubMed Excluded No MI w/ PRE & POST
Molyneux, P. D., et al. (1999). "Visual analysis of serial T2-weighted MRI in multiple sclerosis: intra- and interobserver reproducibility." Neuroradiology 41(12): 882-888.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
(*) Morgen, K., et al. (2004). "Training-dependent plasticity in patients with multiple sclerosis." Brain 127: 2506-2517.	**Source: PubMed & WoK Included**
Onat, S. S., et al. (2015). "Demographic and Clinical Features of Hospitalized Multiple Sclerosis Patients Undergoing a Rehabilitation Program at our Clinic." Turkiye Fiziksel Tip Ve Rehabilitasyon Dergisi-Turkish Journal of Physical Medicine and Rehabilitation 61(1): 23-29.	Source: WoK Excluded No MI w/ PRE & POST
Pelletier, J., et al. (2009). "Plasticity in MS: from Functional Imaging to Rehabilitation." Int MS J 16(1): 26-31.	Source: PubMed Excluded No MI w/ PRE & POST
(*) Peterson, D. S., et al. (2017). "Corpus Callosum Structural Integrity Is Associated With Postural Control Improvement in Persons With Multiple Sclerosis Who Have Minimal Disability." Neurorehabil Neural Repair 31(4): 343-353.	**Source: PubMed & WoK Included**
Prochazkova, M., et al. (2015). "Changes of Effective Connectivity after Facilitation Physiotherapy in Multiple Sclerosis." Ceska a Slovenska Neurologie a Neurochirurgie 78(4): 423-429.	Source: WoK Excluded Full text in Czech
(*) Prosperini, L., et al. (2014). "Multiple sclerosis: changes in microarchitecture of white matter tracts after training with a video game balance board." Radiology 273(2): 529-538.	**Source: PubMed Included**
Prosperini, L., et al. (2011). "The relationship between infratentorial lesions, balance deficit and accidental falls in multiple sclerosis." J Neurol Sci 304(1-2): 55-60.	Source: PubMed & WoK Excluded No MI w/ PRE & POST
Raff, U., et al. (1997). Operator independent quantitation of total T2 lesion load in multiple sclerosis by MR imaging. Car '97 - Computer Assisted Radiology and Surgery. H. U. Lemke, M. W. Vannier and K. Inamura. 1134: 1024-1024.	Source: WoK Excluded No MI w/ PRE & POST
Raff, U., et al. (2000). "Quantitation of T2 lesion load in patients with multiple sclerosis: a novel semiautomated segmentation technique." Acad Radiol 7(4): 237-247.	Source: Pubmed & WoK Excluded No MI w/ PRE & POST

Rasova, K., et al. (2009). "Bimanual Tandem Motor Task with Multiple Sclerosis in Functional Magnetic Resonance Imaging: Effect of Physiotherapeutic Techniques - a Pilot Study." Ceska a Slovenska Neurologie a Neurochirurgie 72(4): 350-358.	Source: WoK Excluded Full text in Czech
(*) Rasova, K., et al. (2005). "Is it possible to actively and purposely make use of plasticity and adaptability in the neurorehabilitation treatment of multiple sclerosis patients? A pilot project." Clin Rehabil 19(2): 170-181.	**Source: reference article (Rasova, Prochazkova et al. 2015) Included**
(*) Rasova, K., et al. (2015). "Motor programme activating therapy influences adaptive brain functions in multiple sclerosis: clinical and MRI study." International Journal of Rehabilitation Research 38(1): 49-54.	**Source: WoK Included**
Reddy, H., et al. (2000). "Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis." Brain 123: 2314-2320.	Source: WoK Excluded No MI w/ PRE & POST
Rovaris, M., et al. (1999). "Reproducibility of brain MRI lesion volume measurements in multiple sclerosis using a local thresholding technique: effects of formal operator training." Eur Neurol 41(4): 226-230.	Source: Pubmed & WoK Excluded No MI w/ PRE & POST
Sa, M. J. (2012). "Physiopathology of symptoms and signs in multiple sclerosis." Arquivos De Neuro-Psiquiatria 70(9): 733-740.	Source: WoK Excluded No MI w/ PRE & POST
Schwartz, C. E., et al. (2016). "Reserve-related activities and MRI metrics in multiple sclerosis patients and healthy controls: an observational study." BMC Neurol 16: 108.	Source: PubMed Excluded No MI w/ PRE & POST
Sormani, M. P., et al. (2013). "Scoring treatment response in patients with relapsing multiple sclerosis." Mult Scler 19(5): 605-612.	Source: Pubmed & WoK Excluded No MI w/ PRE & POST
Storelli, L., et al. (2016). "A Semiautomatic Method for Multiple Sclerosis Lesion Segmentation on Dual-Echo MR Imaging: Application in a Multicenter Context." American Journal of Neuroradiology 37(11): 2043-2049.	Source: WoK Excluded No MI w/ PRE & POST
Sturm, B., et al. (2002). Automated approximation of lateral ventricular shape in magnetic resonance images of multiple sclerosis patients. Medical Image Computing and Computer-Assisted Intervention-Miccai 2002, Pt 1. T. Dohi and R. Kikinis. 2488: 483-491.	Source: WoK Excluded No MI w/ PRE & POST
Sweeney, E. M., et al. (2013). "Automatic lesion incidence estimation and detection in multiple sclerosis using multisequence longitudinal MRI." AJNR Am J Neuroradiol 34(1): 68-73.	Source: Pubmed & WoK Excluded No MI w/ PRE & POST
Tan, I. L., et al. (2002). "Image registration and subtraction to detect active T(2) lesions in MS: an interobserver study." J Neurol 249(6): 767-773.	Source: Pubmed Excluded No MI w/ PRE & POST
Tewarie, P., et al. (2012). "The OSCAR-IB consensus criteria for retinal OCT quality assessment." PLoS One 7(4): e34823.	Source: Pubmed Excluded No MI w/ PRE & POST
Thompson, A. J. (2017). "Challenge of progressive multiple sclerosis therapy." Curr Opin Neurol 30(3): 237-240.	Source: Pubmed & WoK Excluded Review
Tofts, P. S., et al. (1997). "An oblique cylinder contrast-adjusted (OCCA) phantom to measure the accuracy of MRI brain lesion volume estimation schemes in multiple sclerosis." Magn Reson Imaging 15(2): 183-192.	Source: Pubmed & WoK Excluded No MI w/ PRE & POST
(*) Tomassini, V., et al. (2011). "Preservation of motor skill learning in patients with multiple sclerosis." Multiple Sclerosis Journal 17(1): 103-115.	**Source: WoK Included**

Vollmer, T. L., et al. (2002). "Disability and treatment patterns of multiple sclerosis patients in United States: A comparison of veterans and nonveterans." Journal of Rehabilitation Research and Development 39(2): 163-174.	Source: WoK Excluded No MI w/ PRE & POST
Wang, W., et al. (2017). "Neuroradiologists Compared with Non-Neuroradiologists in the Detection of New Multiple Sclerosis Plaques." American Journal of Neuroradiology 38(7): 1323-1327.	Source: WoK Excluded No MI w/ PRE & POST
WeinstockGuttman, B. and R. A. Rudick (1997). "Prescribing recommendations for interferon-beta in multiple sclerosis." Cns Drugs 8(2): 102-112.	Source: WoK Excluded No MI w/ PRE & POST
Willis, M. A. and R. J. Fox (2016). "Progressive Multiple Sclerosis." Continuum (Minneap Minn) 22(3): 785-798.	Source: PubMed Excluded Review
Yoo, Y., et al. (2014). Deep Learning of Image Features from Unlabeled Data for Multiple Sclerosis Lesion Segmentation. Machine Learning in Medical Imaging. G. Wu, D. Zhang and L. Zhou. 8679: 117-124.	Source: WoK Excluded No MI w/ PRE & POST
Yoo, Y., et al. (2016). Deep Learning of Brain Lesion Patterns for Predicting Future Disease Activity in Patients with Early Symptoms of Multiple Sclerosis. Deep Learning and Data Labeling for Medical Applications. G. Carneiro, D. Mateus, L. Peter et al. 10008: 86-94.	Source: WoK Excluded No MI w/ PRE & POST
Zaaraoui, W., et al. (2010). "Unfolding the long-term pathophysiological processes following an acute inflammatory demyelinating lesion of multiple sclerosis." Magn Reson Imaging 28(4): 477-486.	Source: Pubmed & WoK Excluded No MI w/ PRE & POST
Zamboni, P., et al. (2011). "Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound--recommendations for a protocol." Int Angiol 30(6): 571-597.	Source: PubMed Excluded No MI w/ PRE & POST

MI = motor intervention; w/ = with

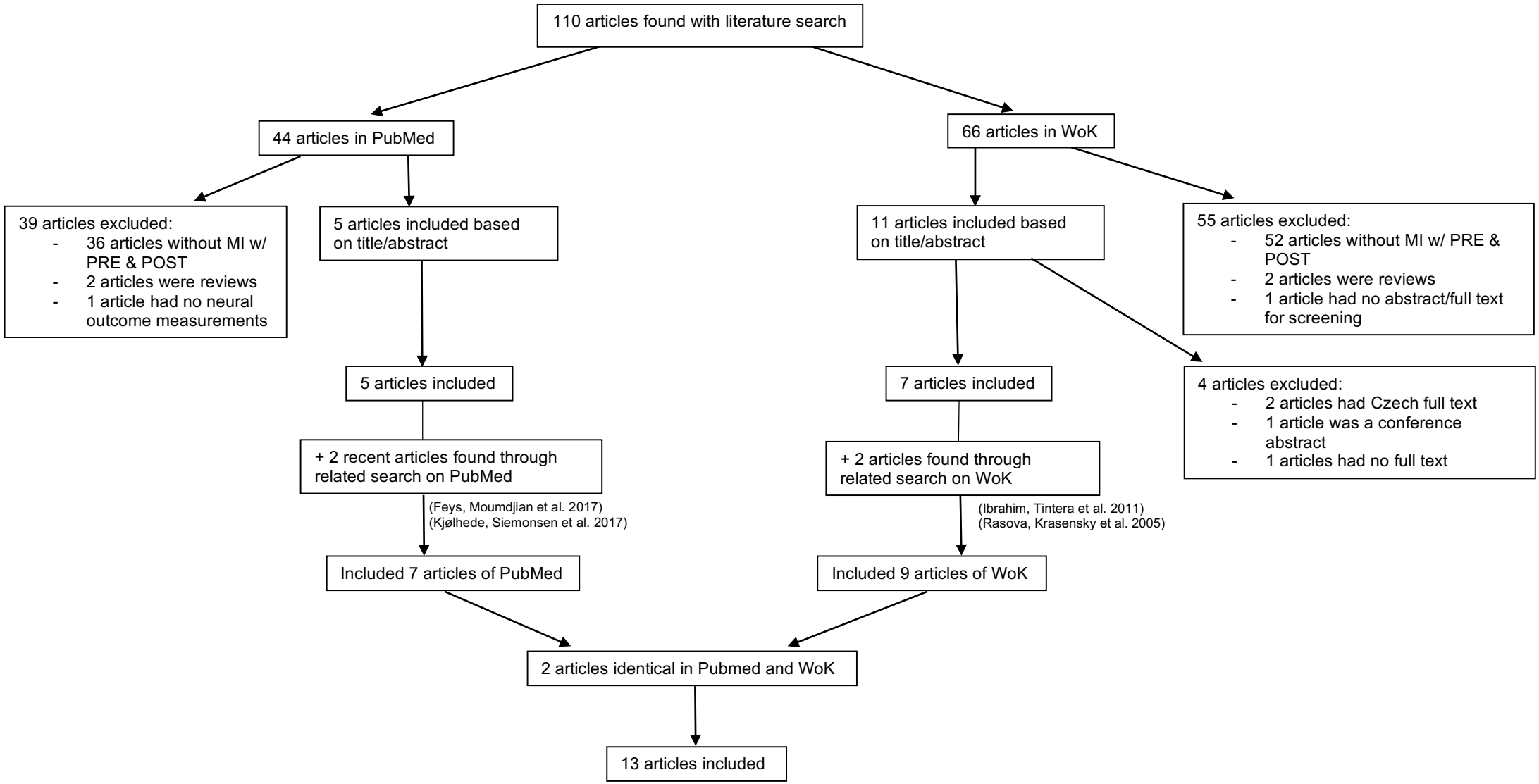

Fig.1: Flow-chart included articles and excluded articles

Table 3

Overview Cochrane checklist for RCT's.

Cochrane checklist for RCT's	Bonzano et al., 2013	Feys et al., 2017	Kjølhede et al., 2017	Prosperini et al., 2014	Rasova et al., 2005	Rasova et al., 2014	Tavazzi et al., 2018
1. Patients randomised?	Y	Y	Y	Y	Y	Y	Y
2. Blinded inclusion?	Y	Y	Y	Y	Y	Y	Y
3. Blinded patients?	na	na	na	na	na	na	na
4. Blinded trainers?	na	na	na	na	na	na	na
5. Blinded outcome measurement?	Y	Y	Y	Y	Y	Y	Y
6. Comparable groups at baseline?	Y	Y	Y	Y	Y	Y	Y
7. Follow up for sufficient numbers?	Y	Y	Y	Y	na	Y	Y
8. Analysed in randomized group?	Y	Y	Y	Y	Y	Y	Y
9. Groups treated equally?	Y	Y	Y	Y	Y	na	Y
10. Valid results?	Y?	Y?	Y	Y?	Y?	Y?	Y?
11. Not Applicable*	/	/	/	/	/	/	/
12. Applicable to population?	Y	Y	Y	Y	Y	Y	Y
13. Which echelon?	2e	2e	2e	2e	2e	2e	2e

* Item 11: results of probability calculations

Y= yes; na= not applicable

Table 4

Overview Cochrane checklist for Controlled interventional studies.

Cochrane checklist for Controlled interventional studies	Ibrahim et al., 2011	Morgen et al., 2004	Peterson et al., 2017	Tomassini et al., 2013
1. Patients randomised?	Y	na	na	Y
2. Blinded inclusion?	Y	na	na	na
3. Blinded patients?	na	na	na	na
4. Blinded trainers?	na	na	na	na
5. Blinded outcome measurement?	Y	na	na	Y
6. Comparable groups at baseline?	Y	Y	Y	Y
7. Follow up for sufficient numbers?	Y	Y	Y	Y
8. Analysed in randomized group?	Y	Y	Y	Y
9. Groups treated equally?	Y	Y	Y	Y
10. Valid results?	Y?	Y?	Y?	Y?
11. Not Applicable*	/	/	/	/
12. Applicable to population?	Y	Y	Y	Y
13. Which echelon?	2e	2e	2e	2e

* Item 11: results of probability calculations

Y= yes; na= not applicable

Table 5

Overview checklist for cross-sectional studies (STROBE).

Checklist for cross-sectional studies ***Are these items included in the study?***	**Bonzano et al., 2011**	**Mancini et al., 2009**
1. Title and abstract		
(a) Study's design?	N	N
(b) Informative and balanced summary	Y	Y
2. Introduction		
(a) Background/rationale	Y	Y
(b) Specific objectives?	Y	Y
3. Methods		
(a) Study design	Y	Y
(b) Setting	Y	Y
(c) Participants	Y	Y
(d) Variables	Y	Y
(e) Data sources/measurement	Y	Y
(f) Bias	Y	Y
(g) Study size	N	Y
(h) Quantitative variables	Y	Y
(i) Statistical methods	Y	Y
4. Results		
(a) Participants	Y	Y
(b) Descriptive data	N	Y
(c) Outcome data	Y	Y
(d) Main results	Y	Y
(e) Other analyses	Y	N?
5. Discussion		
(a) Key results	Y	Y
(b) Limitations	Y	Y
(c) Interpretation	Y	Y
(d) Generalisability	Y	Y
6. Other information		
(a) Funding	Y	Y

Y= yes; N= no

Table 6

Overview of the aim of the included studies and the characteristics of the participants included in these studies.

Article	Aim of the study	Group	Number of participants	Type of MS (RRMS/PPMS/SPMS/PRMS)	Sex (M/F)	Duration of disease (years)	EDSS at baseline	Number of drop-outs
Tavazzi et al. (2018)	To study functional and structural brain changes induced by gait rehabilitation. Assessments were performed at baseline (T0), after the end of the rehabilitation period (T1) and three months later (T2).	*EXP RT*	14	12/3/14/0	10/19	17.2 ± 6.7	6.0 (4.5 - 6.5)	analysed at T1: n=13 analysed at T2: n=9
		EXP ET	15					
Feys et al. (2017)	To investigate the effects of a remotely supervised community-located 'start-to-run' program on physical and cognitive function, fatigue, quality of live, brain volume, and connectivity in PwMS.	*EXP*	21	U	1/20	8.1 ± 6.1	U	6
		CON	21		3/18	9.2 ± 5.3		7
Kjølhede et al. (2017)	To evaluate the effects of PRT by MRI and clinical measures of disease progression in PwMS.	*EXP*	18	18/0/0/0	U	7 ± 7	mean: 2.9 (2 - 4)	6
		CON	17	17/0/0/0				
Peterson et al. (2017)	To understand the neural underpinnings of postural motor learning in PwMS.	*EXP*	24	19/2/2/1	3/21	12.9 ± 7.8	3.5 (2-4)	5
		HC	14		3/11			1
Prosperini et al. (2014)	To determine if high-intensity, task-oriented, visual feedback training with a video game balance board induces significant changes in DTI parameters and if these changes are related to clinical improvement(s) in PwMS.	*EXP + CON*	30	27/3/0/0	12/18	10.5 ± 5.2	3.0 (1.5 - 5)	3
		HC	15		6/9			
Rasova et al. (2014)	To evaluate the immediate and long-term effects of MPAT on clinical and brain functions, and on brain microstructure in PwMS.	*EXP*	12	11/1/0/0	5/7	7 ± 6.02	3.5 ± 0.89	6
Bonzano et al. (2013)	To evaluate the motor behavioural and white matter microstructural changes following upper limb motor rehabilitation treatment based on task-oriented exercises in PwMS.	*EXP*	15	11/0/4/0	5/10	9.1 ± 4.6	4.4 ± 1.2	
		CON	15	11/0/4/0	7/8	8.9 ± 7.1	4.3 ± 1.1	
Bonzano et al. (2011)	To investigate the role of the corpus callosum in nonspecific transfer during a pure motor reaction-time task.	*EXP*	22	22/0/0/0	8/14	8.9 ± 4.5	1.1 ± 0.5	
		HC	10		U			
Ibrahim et al. (2011)	To investigate changes in the brain's microstructure in PwMS after facilitation physiotherapy.	*EXP = CON*	11	11/0/0/0	4/7	6.10 ± 2.34	3.50 ± 0.80	
		HC	11		3/8			

Table 6 – sequel

Article	Aim of the study	Group	Number of participants	Type of MS (RRMS/PPMS/SPMS/PRMS)	Sex (M/F)	Duration of disease (years)	EDSS at baseline	Number of drop-outs
Tomassini et al. (2011) (EXP1)	To test whether the dynamics of skill learning, rehabilitation and motor learning share similar mechanisms of brain plasticity in PwMS relative to healthy controls (short-term motor skill learning).	*EXP*	43	23/0/20/0	17/26	12.5 ± 1.3	4 (1.0 - 7.5)	
		HC	18		10/8			
Tomassini et al. (2011) (EXP2)	To test whether the dynamics of skill learning, rehabilitation and motor learning share similar mechanisms of brain plasticity in PwMS relative to controls (long-term motor skill learning).	*EXP*	23	U/U/4/U	5/18	12.0 ± 1.5	4.0 (0 - 7.0)	4
		HC	12		3/9			
Mancini et al. (2008) (EXP1)	To take adaptation into account in the design and interpretation of a study using a repetitive simple motor task in PwMS.	*EXP*	56	49/0/7/0	20/36	6.25 (1 - 28)	2.25 (0 - 7.5)	
		HC	55		32/23			
Mancini et al. (2008) (one-year follow-up)	To take adaptation into account in the design and interpretation of a study using a repetitive simple motor task in PwMS.	*EXP*	26	20/0/6/0	9/17	8.5 (2.0 - 22.0)	2.5 (1.0 - 7.5)	2
		HC	33		19/14			2
Rasova et al. (2005)	To investigate whether neurorehabilitation is able to influence clinical parameters and brain function, measured radiologically (fMRI).	*EXP*	17	U	U	U	EDSS ≤ 6.5	
		CON	11	U	U	U	EDSS ≤ 6.5	
		HC	13		U			
Morgen et al. (2004)	To examine fMRI activation patterns associated with performance of a motor task, before and after motor training in a group of PwMS with mild motor impairment of the right upper limb.	*EXP*	9	8/1/0/0	4/5	9.6 ± 9.0	2.2 ± 1.6 (1.0 - 6.0)	
		HC	9		4/5			

Abbreviations: U = unknown; PwMS = persons with Multiple Sclerosis; RRMS = relapsing remitting Multiple Sclerosis; PPMS = primary progressive Multiple Sclerosis; SPMS = secondary progressive Multiple Sclerosis; PRMS = progressive relapsing Multiple Sclerosis; HC = healthy control group; EXP = experimental group with PwMS; CON = control group with PwMS; RT = resistance training; ET = endurance training; M = male; F = female; EXP1 = experiment one; EXP2 = experiment two; EDSS = Expanded Disability Status scale; PRT = progressive resistance training; MPAT = motor program activating therapy; MRI = magnetic resonance imaging; fMRI = functional magnetic resonance imaging; DTI = diffusion tensor imaging
Data are presented as 'mean ± standard deviation' or 'median (range)' or 'mean ± standard deviation (range)'.

Table 7

Details clinical intervention(s) of the included studies.

Article	Group	Intervention	Duration of program (weeks)	Frequency (X times/week)	Duration of session (minutes)	Total number of sessions
Tavazzi et al. (2018)	*EXP RT*	First session: global physical functioning, second session: resistance training	4	5 times/week 2 sessions/day	30-45	40
	EXP ET	First session: global physical functioning, second session: endurance training	4	5 times/week 2 sessions/day	30-45	40
Feys et al. (2017)	*EXP* *CON*	'Start-to-run' program for 5km Waiting list control group	12	3	U	36
Kjølhede et al. (2017)	*EXP*	A supervised PRT program: each session consisted of four lower and two upper body exercises	24	2	U	48
	CON	Waiting list control group				
Peterson et al. (2017)	*EXP*	One day of balance training and one day of balance testing for retention (on a hydraulically controlled platform that oscillated at a fixed, sinusoidal frequency (0.5Hz) in the forward and backward directions)	2 days	2	± 5	2
	HC	No intervention				
Prosperini et al. (2014)	*EXP*	A balance home-based training using a video game balance board system (WBBS) (repetitions of several games)	12	5	30	60
	CON	Waiting list control group				
	HC	No intervention				
Rasova et al. (2014)	*EXP*	MPAT: different kind of afferent somatosensory stimuli combined in different functionally centred initial postural positions; patients' schedule of investigation: E1 = two weeks before, no therapy; E2 = start of therapy; E3 = end of two months of therapy; E4 = one month without any therapy	8	2	60	16
Bonzano et al. (2013)	*EXP*	Active protocol based on voluntary exercises for neuromuscular control to improve proprioceptive sensibility, muscle strength, stability and coordination of the upper limbs	7	3	60	20
	CON	Passive mobilization of the shoulder, elbow, wrist and fingers	7	3	60	20
Bonzano et al. (2011)	*EXP + HC*	Respond (reaction time) to random stimuli with appropriate finger opposition movements with the right (learning) and then the left (transfer) hand	12 minutes	1 day	12	1

Table 7 – sequel

Article	Group	Intervention	Duration of program (weeks)	Frequency (X times/week)	Duration of session (minutes)	Total number of sessions
Ibrahim et al. (2011)	*EXP = CON*	One month without intervention, after one month: facilitation therapy, sensorimotor stimuli are applied repetitively in standard postural positions and motor functions	9	2h/week	U	U
	HC	No intervention				
Tomassini et al. (2011) (EXP1)	*EXP + HC*	Track vertical movements of a computer-controlled bar (target bar) displayed on a screen by altering the amount of pressure applied to a hand-held plastic rod, matching the height of the pressure sensitive bar to that of the target bar – sequence block = two repeats of smoothly varying sequence; random block = pseudo-random sequence (1 block = 38 seconds)	26 minutes	1 day	± 13	1
Tomassini et al. (2011) (EXP2)	*EXP + HC*	Same intervention as *Tomassini et al. (2011) (EXP1)*	2	7	± 13	14
Mancini et al. (2008) (EXP1)	*EXP + HC*	Repeated right-hand tapping task, visually cued (1 Hz), hand tapping movement was limited to three cm amplitude	24 minutes	1	6 periods of 30 seconds of rest with 30 seconds of tapping, this sequence is repeated 4 times in each scanning session	1
Mancini et al. (2008) (one-year follow-up)	*EXP + HC*	Same intervention as *Mancini et al. (2008) (EXP1)*	24 minutes	1	Same duration of session as *Mancini et al. (2008) (EXP1)*	1
Rasova et al. (2005)	*EXP*	Physiotherapeutic programme, based on sensorimotor learning and adaptation	8	2	60	16
	CON + HC	No intervention				
Morgen et al. (2004)	*EXP + HC*	Flexion and extension movements of the right thumb visually cued at 1 Hz, passively return to the start position	46 minutes	1 day	8 min. pre-training run 30 min. training period 8 min. post-training run	1

Abbreviations: U = unknown; HC = healthy control group; EXP = experimental group with PwMS; CON = control group with PwMS; RT = resistance training; ET = endurance training; M = male; F = female; EXP1 = experiment one; EXP2 = experiment two; EDSS = Expanded Disability Status scale; PRT = progressive resistance training; MPAT = motor program activating therapy; WBBS = Wii balance board system; MRI = magnetic resonance imaging; fMRI = functional magnetic resonance imaging; DTI = diffusion tensor imaging; min. = minutes
Data are presented as ‘mean ± standard deviation’ or ‘median (range)’ or ‘mean ± standard deviation (range)’.

Table 8

Details imaging intervention(s) of the included studies.

Article	Type of scanner	Technique	Analysis	Parameters (ROIs)
Tavazzi et al. (2018)	1.5-Tesla scanner	fMRI DTI	T1 weighted images Motor-task fMRI and Resting state fMRI Microstructural integrity (FA - RD - AD - MD)	Pre-central gyrus (primary motor cortex) Post-central gyrus (primary somatosensory cortex)
Feys et al. (2017)	3-Tesla scanner	Conventional MRI DTI	Brain volume Gray matter- and white matter-volumes Structural connectivity (FA)	Left and right thalamus Caudate Putamen Pallidum Hippocampus Amygdala Accumbens
Kjølhede et al. (2017)	1.5-Tesla scanner	Conventional MRI	T2 lesions Cortical thickness Brain volume Percentage brain volume change	74 cortical regions were investigated
Peterson et al. (2017)	3-Tesla scanner	Conventional MRI Voxelwise analysis DTI	Brain volume Gray matter-, white matter- and CSF-volumes Microstructural integrity (FA - RD - AD - MD) → Interhemispheric connections between homologous left and right sensorimotor cortical regions	Pre-supplementary motor area Supplementary motor area Primary motor cortex Primary somatosensory motor cortex
Prosperini et al. (2014)	3-Tesla scanner	Conventional MRI DTI	T2 lesions Brain volume Brain atrophy Microstructural integrity (FA - RD - AD - MD)	Corpus callosum Left and right inferior cerebellar peduncles Middle cerebellar peduncles Superior cerebellar peduncles Internal capsule and corona radiata Fronto-occipital fasciculi Inferior longitudinal fasciculi
Rasova et al. (2014)	3-Tesla MR scanner	fMRI DTI	Effective connectivity Changes in 'self-coupling' Microstructural integrity (FA - MD)	Corpus callosum Supplementary motor area Primary motor area on the right for left-side motion control Primary motor area on the left for right-side motion control
Bonzano et al. (2013)	PD/T2 weighted scan 1.5-Tesla scanner	Conventional MRI DTI	T2 lesions White matter fiber bundles Microstructural integrity (FA - RD - AD - MD)	Brain areas involved in voluntary movement control: - Corpus callosum - Left and right corticospinal tract - Left and right superior longitudinal fasciculus
Bonzano et al. (2011)	1.5-Tesla scanner	Conventional MRI DTI	T2 lesions Microstructural integrity (FA)	Corpus callosum (CC1; CC2; CC3; CC4; CC5)
Ibrahim et al. (2011)	3-Tesla MR scanner	Conventional MRI DTI	T2 lesions Microstructural integrity (FA - RD - AD - MD)	Corpus callosum
Tomassini et al. (2011) (EXP1)	No imaging outcomes			
Tomassini et al. (2011) (EXP2)	1.5-Tesla scanner	Conventional MRI	T2 lesions Brain volume	No specific ROIs

Table 8 – sequel

Article	Type of scanner	Technique	Analysis	Parameters (ROIs)
Mancini et al. (2008) (EXP1)	1.5-Tesla scanner	Conventional MRI fMRI	T2 lesions T1 weighted images	No specific ROIs
Mancini et al. (2008) (one-year follow-up)	1.5-Tesla scanner No imaging outcomes in HC	Conventional MRI	T2 lesions	No specific ROIs
Rasova et al. (2005)	1.5-Tesla scanner	fMRI	Amplitude size of the change of signal intensity between rest and activity	Primary sensorimotor cortex Supplementary motor cortex Cerebellum (nucleus dentatus) Basal ganglia (putamen)
Morgen et al. (2004)	1.5-Tesla Signa unit 1.5-Tesla MR scanner	Conventional MRI fMRI	- *Structural image analysis:* T2 lesions Lesion load Brain atrophy - *Functional image analysis:* Task-specific effects in different regions of the brain Activation patterns of different ROIs	Left primary sensorimotor cortex and adjacent parietal association cortex (Brodmann area 40)

Abbreviations: HC = healthy control group; EXP1 = experiment one; EXP2 = experiment two; MRI = magnetic resonance imaging; fMRI = functional magnetic resonance imaging; DTI = diffusion tensor imaging; FA = fractional anisotropy; RD = radial diffusivity; AD = axial diffusivity; MD = mean diffusivity; ROI(s) = region(s) of interest; PD = proton density; CSF = cerebrospinal fluid; CC = corpus callosum

Table 9

Overview of the clinical outcomes of the included studies.

Article	Parameter	Group	PRE (raw scores)	POST (raw scores)	P-value (time)	P-value (group)	P-value (interaction)
Tavazzi et al. (2018)	*T0 - T1 (n=26)*						
	2MWT (m)	*EXP RT + EXP ET*	75.6 ± 37.3	91.5 ± 48.0	p=0.03		
	BBS	*EXP RT + EXP ET*	38.5 ± 12.1	42.6 ± 10.9	p=0.006		
	DGI	*EXP RT + EXP ET*	14.6 ± 4.5	16.7 ± 4.1	p=0.03		
	No significant changes after intervention were observed for T25FW; MFIS; MSWS12.						
	T0 - T2 (n=16)						
	No significant changes after intervention and period of no intervention were observed for 2MWT; T25FW; BBS; DGI; MFIS; MSWS12, indicating no maintained changes.						
Feys et al. (2017)	VO_{2MAX} (mL/kg/min)	*EXP*	23.9 ± 5.9	25.4 ± 5.0	ns	p<0.05	p<0.05
		CON	21.8 ± 4.0	20.1 ± 4.8			
	Workload peak (W)	*EXP*	127.1 ± 31.5	145.8 ± 30.5	p<0.001	ns	p<0.001
		CON	133.6 ± 25.1	133.5 ± 27.1			
	Heart rate, HR max	*EXP*	173.1 ± 12.8	173.2 ± 11.0	ns	p<0.05	ns
	(bpm)	*CON*	166.5 ± 17.4	160.9 ± 20.6			
	5-STS	*EXP*	10.4 ± 2.4	8.7 ± 1.9	p<0.001	ns	p<0.05
		CON	9.8 ± 2.3	9.5 ± 2.2			
	SPART	*EXP*	43.1 ± 6.8	48.0 ± 5.8	ns	ns	p<0.05
		CON	44.7 ± 5.0	44.4 ± 6.4			
	MSWS12	*EXP*	19.1 ± 16.4	15.0 ± 12.8	ns	ns	p<0.05
		CON	16.3 ± 18.9	21.1 ± 26.1			
	MSIS-29 Physical	*EXP*	23.5 ± 14.4	16.3 ± 12.6	ns	ns	p<0.01
		CON	16.4 ± 13.3	22.3 ± 18.9			
	MSIS-29	*EXP*	30.0 ± 24.3	23.0 ± 17.2	ns	ns	p=0.06
	Psychological	*CON*	21.3 ± 20.8	23.7 ± 18.0			
	FSMC cognitive	*EXP*	33.4 ± 10.0	28.0 ± 12.6	p<0.05	ns	p<0.05
	domain	*CON*	28.9 ± 10.0	28.9 ± 10.1			
	FSMC physical	*EXP*	32.3 ± 8.8	26.2 ± 10.2	p<0.001	ns	p<0.05
	domain	*CON*	29.3 ± 9.4	29.6 ± 8.2			
	No significant changes in group, time or interaction in both groups were observed for T25FW; 6MWT; DSST; Word List Generation; Selective reminding test_LST; Selective reminding test_CLTR; PASAT.						
Kjølhede et al. (2017)	$MSFC_{TOTAL}$ (a.u.)	*EXP*	0.02 ± 0.18	0.43 ± 0.18			p=0.05
		CON	-0.02 ± 0.18	0.14 ± 0.19			
	$MSFC_{NHPT}$ (a.u.)	*EXP*	-0.03 ± 0.23	0.46 ± 0.24			p<0.05
		CON	0.03 ± 0.24	0.03 ± 0.25			
	$MSFC_{T25FW}$ (a.u.)	*EXP*	-0.09 ± 0.24	0.36 ± 0.24			p<0.01
		CON	0.09 ± 0.24	0.05 ± 0.25			
	MVC_{COM} (Nm)	*EXP*	216.0 ± 20.3	259.6 ± 20.5			p<0.01
		CON	217.5 ± 20.9	226.8 ± 21.2			
	No significant changes in group, time or interaction in both groups were observed for EDSS; $MSFC_{PASAT}$; T2 lesion count; T2 lesion load; $MSIS_{PHYSICAL}$; $MSIS_{PSYCHOLOGICAL}$.						

Table 9 – sequel

Article	Parameter	Group	PRE (raw scores)	POST (raw scores)	P-value (time)	P-value (group)	P-value (interaction)
Peterson et al. (2017)	No significant changes after training were observed, similar improvement in both groups.						
Prosperini et al. (2014)	Postural sway at baseline	*EXP* *HC*				p<0.05	
Rasova et al. (2014)			Median value				
	MAS	*EXP*	23.25		p=0.013		
	T	*EXP*	8.5		p=0.027		
	DD	*EXP*	5.75		p=0.034		
	DM	*EXP*	4		p=0.034		
	REP	*EXP*	28.5		p=0.025		
	NHPT	*EXP*	23.4		p=0.041		
	T25FW	*EXP*	5.22		p=0.012		
	No significant changes were observed between E1 and E2.						
	All significant improvements remained significant in the long term (E3 - E4).						
	There was a trend toward improvement in the MI; no significant improvement was observed in L-CLA; BBS; PASAT 3.						
Bonzano et al. (2013)	ARAT	*Total group*			p=0.022		
	NHPT	*Total group*			p<0.000001		
	GRIP strength	*Total group*			p=0.0013		
	RATE-MV	*Total group*			p=0.0018		
	IHI	*EXP*			p=0.001		p=0.007
	EXP and CON induced similar effects on unimanual motor performance (effect of time). No changes were observed in RATE-SV.						
	The similar trend between the groups was seen by the lack of interaction.						
	No patient showed any change in EDSS score after treatment.						
Bonzano et al. (2011)	Mean Response Time Right, learning hand (ms)	*EXP* *HC* *EXP + HC* *EXP* *HC*	375.48 ± 53.19 325.10 ± 58.24 389.07 ± 65.11	347.57 ± 53.40	p<0.001 p<0.001 p=0.006	p=0.008	
	No significant time*group interaction was observed in the Mean Response Time Right, learning hand.						
	A significant nonspecific transfer-hand performance improvement was observed in both groups (EXP: p=0.002 and HC: p=0.004).						
	EXP showed a nonspecific improvement of the skill to the transfer hand, similarly to HC.						
Ibrahim et al. (2011)	EDSS	*CON* *EXP* *HC*	3.59 ± 0.85	3.59 ± 0.85 3.41 ± 0.93	p=0.087		
	PASAT 3	*CON* *EXP* *HC*	43.00 ± 13.65 45.73 ± 12.62 51.40 ± 9.22	45.73 ± 12.62 49.46 ± 9.64 51.60 ± 8.11	 p=0.037 p=0.842		

Table 9 – sequel

Article	Parameter	Group	PRE (raw scores)	POST (raw scores)	P-value (time)	P-value (group)	P-value (interaction)
Tomassini et al. (2011) (EXP1)	Significant effect of block	*EXP + HC*			p<0.0001		
	Significant effect of block*condition interaction	*EXP + HC*			p<0.008		
	No significant effect of condition, block*group interaction and condition*group interaction during 10 blocks of learning was observed.						
	Tracking error in sequence condition	*EXP*	191.8 ± 14.8	129.0 ± 7.3	p<0.0001		
		HC	154.9 ± 14.5	87.4 ± 8.3	p<0.0001		
	Tracking error in random condition	*EXP*	180.9 ± 15.2	139.7 ± 7.3	p<0.003		
		HC	126.7 ± 11.7	105.6 ± 15.8	p=0.098		
Tomassini et al. (2011) (EXP2)	Effect of days of practice	*EXP + HC*			p<0.0001		
	Motor improvement	*EXP*	70.5 ± 4.4	50.2 ± 3.7	p<0.0001		
		HC	61.2 ± 4.6	41.3 ± 4.0	p<0.002		
	No significant days*group interaction and no significant difference in the slope of long-term learning between HC and EXP were observed.						
Mancini et al. (2008) (EXP1)	<u>*Effect of task*</u> Greater task-related activation in PwMS than HC during hand movement in a large network of cortical and subcortical motor-related areas. In PwMS, significant greater fMRI activation was associated with longer times to complete the NHPT in comparison with HC. No significant independent effect of EDSS measures of disability or disease duration between fMRI activation was seen in any brain region.						
Mancini et al. (2008) (one-year follow-up)	EDSS	*EXP*			p=0.05		
	No significant changes in baseline vs one-year follow-up of right hand NHPT; left hand NHPT; right hand tapping during 30 seconds; left hand tapping during 30 seconds were observed.						

Table 9 – sequel

Article	Parameter	Group	PRE (raw scores)	POST (raw scores)	P-value (time)	P-value (group)	P-value (interaction)
Rasova et al. (2005)	NHPT right (s)	*EXP*	43.60 ± 36.61	-5.81 ± 7.18	p=0.001		p<0.001
		CON	45.13 ± 41.44	1.26 ± 3.41	p=0.050		
	NHPT left (s)	*EXP*	39.18 ± 25.48	-5.26 ± 7.84	p<0.001		p<0.001
		CON	35.90 ± 17.78	1.80 ± 5.39	p=0.201		
	T25FW (s)	*EXP*	12.26 ± 20.73	-2.66 ± 7.64	p=0.002		p=0.001
		CON	8.03 ± 5.16	0.05 ± 0.16	p=0.329		
	PASAT 3	*EXP*	39.12 ± 15.81	6.41 ± 5.41	p=0.001		p<0.001
		CON	41.45 ± 16.82	-0.27 ± 1.19	p=0.492		
	PR-seat	*EXP*	0.53 ± 0.80	0.94 ± 0.24	p<0.001		p<0.001
		CON	0.91 ± 1.14	0.00 ± 0.00	p=0.999		
	PR-stand	*EXP*	0.53 ± 0.80	0.88 ± 0.49	p<0.001		p<0.001
		CON	0.91 ± 1.14	0.00 ± 0.00	p=0.999		
	MSQOL physical	*EXP*	48.25 ± 13.31	9.41 ± 7.86	p=0.001		p<0.001
		CON	52.75 ± 17.23	-2.96 ± 4.28	p=0.010		
	MSQOL psychological	*EXP*	58.26 ± 18.51	10.18 ± 11.57	p=0.002		p<0.001
		CON	58.22 ± 20	-7.73 ± 13.43	p=0.010		
	MFIS	*EXP*	43.71 ± 13.86	-6.03 ± 4.69	p<0.001		p<0.001
		CON	41.64 ± 14.48	1.73 ± 2.41	p=0.035		
	BDIS	*EXP*	10.26 ± 8.67	-3.50 ± 3.66	p=0.001		p=0.001
		CON	7.18 ± 7.05	-0.50 ± 1.50	p=0.371		
	No significant changes after intervention in both EXP and CON for BI and EDSS were observed.						
Morgen et al. (2004)	No significant changes after training in both groups were observed (performance was consistent throughout the experiment in both groups).						

Abbreviations: n = number; m = meter; s = second; ms = millisecond; ns = not significant; PwMS = persons with Multiple Sclerosis; HC = healthy control group; EXP = experimental group with PwMS; CON = control group with PwMS; RT = resistance training; ET = endurance training; EXP1 = experiment one; EXP2 = experiment two; EDSS = Expanded Disability Status scale; 2MWT = two meter walk test; BBS = Berg Balance scale; DGI = Dynamic Gate Index; T25FW = Timed 25-Foot Walk; MFIS = Modified Fatigue Impact Scale; MSWS12 = Twelve Item MS Walking Scale; VO_{2MAX} = maximal oxygen intake; W = Watt; HR = heart rate; bpm = beats per minute; 5-STS = five-repetition sit-to-stand; SPART = Spatial Recall Test; MSIS-29 = Multiple Sclerosis Impact Scale; FSMC = Fatigue Scale for Motor and Cognitive Functions; 6MWT = Six Minute Walk Test; DSST = Digit Symbol Substitution Test; LST = long-term storage; CLTR = consistent long-term retrieval; PASAT = Paced Auditory Serial Addition Test; MAS = Modified Ashworth Scale; T = tremor; DD = dysdiadochokinesis; DM = dysmetry; REP = righting, equilibrium and protective reactions; MSFC = Multiple Sclerosis Functional Composite; NHPT = nine hole peg test; MVC_{COM} = Maximal Voluntary Contraction combined for knee extensors and flexors ; L-CLA = low-contrast letter acuity testing; ARAT = Action Research Arm Test; RATE-MV = movement rate at maximum velocity; RATE-SV = movement rate at spontaneous velocity; IHI = inter hand interval; MI = Motricity Index; PR-seat = postural reaction sitting; PR-stand = postural reaction standing; MSQOL = Multiple Sclerosis Quality of Life; BDIS = Beck Depression Inventory Score; BI = Barthel Index; fMRI = functional magnetic resonance imaging
Data are presented as ‘mean ± standard deviation’.

Table 10

Overview of the imaging outcomes of the included studies.

Article	Parameter	Group	PRE (raw scores)	POST (raw scores)	P-value (time)	P-value (group)	P-value (interaction)
Tavazzi et al. (2018)	The direct comparison between subjects who completed the right foot motor task at T0 and T1 showed a significant reduction in the activation of the left precentral gyrus. No other significant changes were observed, a trend towards an increase in FA was found in the left (p=0.061) and right (p=0.067) cingulum at T1.						
Feys et al. (2017)	L-pallidum	*EXP*	2255.7 ± 201.7	2306.6 ± 194.6	ns	ns	p<0.05
		CON	2364.1 ± 184.2	2323.8 ± 218.2			
	After twelve weeks (intervention), in both groups, no significant change in volume of other brain areas was observed and there was no significant change in any group in sturctural connectivity.						
Kjølhede et al. (2017)	Cortical thickness (G_and_S_cingul.Ant)	*EXP*					p=0.044
		CON					
	Cortical thickness (Pole_temporal)	*EXP*					p=0.021
		CON					
	Cortical thickness (S_orbital.H_Shaped)	*EXP*					p=0.004
		CON					
	Cortical thickness (S_temporal_inf)	*EXP*					p=0.003
		CON					
	19 out of 74 cortical areas showed a significant absolute increase in cortical thickness. There was no significant absolute increase neither in global white or gray matter volume nor volumes of subcortical gray matter structures.						
	4 areas showed significant change after comparing relative changes following PRT with control intervention (validation of findings).						
Peterson et al. (2017)	*Improvement in temporal performance*						
	Genu	*EXP*		-0.468	p<0.01		
	Primary motor fibers	*EXP*		-0.558	p<0.01		
	Average temporal performance						
	Genu	*EXP*		-0.503			
	PwMS showed worse structural connectivity in the CC and superior cortical white matter tracts compared with HC.						
	Temporal, but not spatial improvements on day 1 were correlated to structural connectivity in PwMS.						
	Temporal postural performance was correlated to the CC and brainstem structural connectivity.						
	Retention of improvements tested on day 2 was correlated to MD, but not FA or RD imaging outcomes.						

Table 10 – sequel

Article	Parameter	Group	PRE (raw scores)	POST (raw scores)	P-value (time)	P-value (group)	P-value (interaction)
Prosperini et al. (2014)	FA of the left superior cerebellar peduncles	*EXP*					p=0.036
	FA of the right superior cerebellar peduncles	*EXP*					p=0.047
	RD of the left superior cerebellar peduncles	*EXP*					p=0.042
	Correlations between changes in postural sway and in FA of superior cerebellar peduncles (left)	*EXP*					p=0.038
	Correlations between changes in postural sway and in FA of superior cerebellar peduncles (right)	*EXP*					p=0.042
	Correlations between changes in postural sway and in RD of superior cerebellar peduncles (left)	*EXP*					p=0.047
	Correlations between changes in postural sway and in RD of superior cerebellar peduncles (right)	*EXP*					p=0.049
	No significant effect of time, group, and time*group interaction was observed on FA, MD, AD and RD of the corpus callosum; corona radiata; fronto-occipital fasciculi; inferior longituinal fasciculi.						
	The observed improvements in clinical balance and microstructural changes did not persist after stop of the training protocol.						
Rasova et al. (2014)	FA	*EXP*	0.53		p=0.006		
	MD	*EXP*	1.15		p=0.081		
	No significant changes were observed between E1 and E2.						
	All significant improvements remained significant in the long term (E3 - E4).						
Bonzano et al. (2013)	*DTI-FA*						
	CC	*EXP*					p=0.03
		CON					
	CST (left and right)	*EXP*					p=0.0019
		CON					
	DTI-RD						
	CC	*EXP*					p=0.01
		CON				p=0.004	
	CST (left and right)	*EXP*					p=0.01
		CON				p=0.008	
	No significant change in DTI-AD was observed in the investigated ROIs after intervention period in both EXP and CON.						
	No significant change in DTI-MD was observed in the investigated ROIs after intervention period in both EXP and CON.						

Table 10 – sequel

Article	Parameter	Group	PRE (raw scores)	POST (raw scores)	P-value (time)	P-value (group)	P-value (interaction)
Bonzano et al. (2011)	Correlation between Delta_Transfer and FA in CC3	*EXP*					p=0.003
	No significant correlation between Delta_Transfer and FA in the other CC ROIs and in the whole CC was observed.						
	No significant correlation between lesion load and the amount of transfer was observed.						
Ibrahim et al. (2011)						*CON vs. HC*	*EXP vs. HC*
	FA	*CON*	0.52 ± 0.06	0.51 ± 0.07		p<0.001	
		EXP	0.51 ± 0.07	0.55 ± 0.07	p<0.001		p<0.001
		HC	0.68 ± 0.02	0.67 ± 0.02	p=0.937		
	RD	*CON*	0.86 ± 0.21	0.84 ± 0.20		p<0.001	
		EXP	0.84 ± 0.20	0.77 ± 0.21	p=0.002		p=0.002
		HC	0.46 ± 0.04	0.47 ± 0.04	p=0.336		
	AD	*CON*	1.89 ± 0.20	1.86 ± 0.17		p=0.001	
		EXP	1.86 ± 0.17	1.86 ± 0.19	p=0.543		p=0.910
		HC	1.64 ± 0.07	1.64 ± 0.07	p=0.966		
	MD	*CON*	1.20 ± 0.20	1.18 ± 0.19		p<0.001	
		EXP	1.18 ± 0.19	1.13 ± 0.20	p=0.014		p=0.024
		HC	0.86 ± 0.05	0.85 ± 0.04	p=0.693		
	Two months after initiating facilitation physiotherapy, differences were observed in FA, RD and MD, they were significantly higher in EXP than in HC (EXP approached the values of HC).						
	No significant change in AD was observed in the CC in EXP.						
Tomassini et al. (2011) (EXP1)	EXP1 has no imaging outcomes.						
Tomassini et al. (2011) (EXP2)	NHPT in correlation with T2-LV	EXP + HC				p<0.05	
	Tracking error across days of practice in correlation with T2-LV	EXP + HC				p<0.002	
	NHPT in correlation with T1-LV	EXP + HC				p<0.04	
	Tracking error across days of practice in correlation with T1-LV	EXP + HC				p<0.002	
	No significant correlation was observed between the rate of long-term learning and T2-LV or T1-LV.						
Mancini et al. (2008) (EXP1)	*Effect of task* Greater task-related activation in PwMS than HC during hand movement in a large network of cortical and subcortical motor-related areas. In PwMS, significant greater fMRI activation was associated with longer times to complete the NHPT in comparison with HC. No significant independent effect of EDSS measures of disability or disease duration between fMRI activation was seen in any brain region.						
Mancini et al. (2008) (one-year follow-up)	T2 lesion load	*EXP*			p=0.004		

Table 10 – sequel

Article	Parameter	Group	PRE (raw scores)	POST (raw scores)	P-value (time)	P-value (group)	P-value (interaction)
Rasova et al. (2005)	No significant changes of the amplitude of signal were observed in EXP in comparison with CON. No significant correlation was observed between brain activity changes and clinical parameter changes.						
Morgen et al. (2004)	Thumb flexion versus rest before training: more activation of the contralateral dorsal premotor cortex (PMd, Brodmann area 6) in MS patients than in HC in the left dorsal premotor cortex (PMd) - p=0.07 Thumb extension versus rest before training: more activation of the contralateral dorsal premotor cortex (PMd, Brodmann area 6) in MS patients than in HC in the left dorsal premotor cortex (PMd) - p=0.01 More pronounced reductions in activation of the left postcentral gyrus (S1) and left inferior parietal gyrus (IPL) in HC than in PwMS during the trained task.						

Abbreviations: PwMS = persons with Multiple Sclerosis; HC = healthy control group; EXP = experimental group with PwMS; CON = control group with PwMS; EXP1 = experiment one; EXP2 = experiment two; ns = not significant; L = left; G_and_S_cingul.Ant = anterior cingular sulcus and gyrus; Pole_temporal = temporal pole; S_orbital.H_Shaped = orbital H-shaped sulcus; S_temporal_inf = temporal inferior sulcus; PRT = progressive resistance training; CC = Corpus Callosum; CST = Corticospinal Tract; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; AD = axial diffusivity; DTI = Diffusion Tensor Imaging; ROI(s) = Region(s) of Interest; Delta_Transfer = the amount of transfer as the difference in reaction time between the second block of the right hand and the second block of the left hand; NHPT = nine-hole peg test; T2-LV = T2-lesion volume; T1-LV = T1-lesion volume; fMRI = functional Magnetic Resonance Imaging; EDSS = Expanded Disability Status scale.
Data are presented as ‘mean ± standard deviation’.

Table 11

Abbreviations.

Term	Abbreviation
Action Research Arm Test	ARAT
berg balance scale	BBS
central nervous system	CNS
corpus callosum	CC
density weighted images	PD weighted images
diffusion-weighted imaging	DTI
dual task cost	DTC
dynamic gait index	DGI
Expanded Disability Status scale	EDSS
Fatigue Scale for Motor and Cognitive Function	FSMC
Fatigue Severity Scale	FSS
five-repetition sit-to-stand	5-STS
fractional anisotropy	FA
functional magnetic resonance imaging	fMRI
inter hand interval	IHI
magnetic resonance imaging	MRI
maximal oxygen intake	VO_{2MAX}
maximum heart rate	HR max
mean diffusivity	MD
motor program activating therapy	MPAT
movement rate at maximum velocity	RATE-MV
Multiple Sclerosis	MS
Multiple Sclerosis Impact Scale	MSIS-29
Multiple Sclerosis Walking Scale	MSWS-12
nine hole peg test	NHPT
Paced Auditory Serial Addition Test	PASAT 3
percentage brain volume change	PBVC
persons with Multiple Sclerosis	PwMS
primary progressive Multiple Sclerosis	PPMS
primary relapsing Multiple Sclerosis	PRMS
quality of life	QoL
radial diffusivity	RD
region(s) of interest	ROIs
relapsing remitting Multiple Sclerosis	RRMS
secondary progressive Multiple Sclerosis	SPMS
Spatial Recall Test	SPART
supplementary motor area	SMA
T1 lesion volume	T1-LV
T2 lesion volume	T2-LV
timed 25-foot walk test	T25FW
two minute walk test	2MWT
voxel-based morphometry	VBM
Web of Knowledge	WoK

Table content

Part two: protocol

Introduction

Multiple sclerosis (MS) is an inflammatory-mediated demyelinating chronic disease of the central nervous system (CNS). [1] These demyelinating processes induce focal lesions of the brain, therewith, neurodegenerative processes such as accelerated whole-brain atrophy and cortical thinning are present in persons with MS (PwMS). [2] Lesion development in PwMS is heterogeneous, both in terms of mechanisms and temporal differences. [3] Therefore, the clinical course of MS is not predictable.

Upper limb dysfunction in MS is highly prevalent (>60%), increasing with overall disability level. The detrimental impact on Activities of Daily Living (ADL) is high, because symptoms often occur bilaterally. [4]

Nowadays, pharmacological treatment in combination with (multidisciplinary) rehabilitation is done in order to maintain the functional status of PwMS. [5] To date, only a small number of rehabilitation studies targeted the upper limb in PwMS, however indicating clear potential for substantial upper limb improvements after rehabilitation. [5, 6] More research is warranted since it is unclear whether upper limb improvements in MS result from neuroplasticity induced by rehabilitation or by improvement on the peripheral level (joint mobility, muscle strength and endurance).

Since several years, magnetic resonance imaging (MRI) is used for the diagnosis and management of PwMS. MRI shows sensitivity for detection of white matter lesions in the CNS and specificity for lesion spread in space and time. [7]

Due to the recent developments and improvement of the MRI techniques such as fMRI, DTI,…, MRI seems also a promising evaluation tool to measure neural changes after rehabilitation. The addition of imaging as an outcome measure in rehabilitation would help us to understand the underlying mechanisms of the clinical effects.

To date, a few rehabilitation studies of the upper limb have included MRI techniques to evaluate the neural effect. For example, Bonzano et al. (2013), who investigated motor training of the upper limb, found preserved white matter integrity in the corpus callosum and corticospinal tracts in the treatment group (active motor rehabilitation treatment) while a microstructural integrity worsening was found in the control group (passive mobilization of the upper limb). [8]

In summary, including imaging as an outcome measure in rehabilitation of the upper limb can be beneficial to understand the underlying mechanisms of the clinical effects. In this cross-sectional study, correlations between clinical measures and imaging parameters at baseline will be investigating. The RCT following this cross-sectional study will investigate clinical and neural results after intervention of the upper limb.

Aim of the study

The primary aim of this RCT in which this master thesis is embedded, is to investigate the clinical and neural effects after individualized high-dose upper limb rehabilitation program in PwMS with different upper limb disability levels and (if found) the correlation between the clinical and neural results. However, in this master thesis, we will only use the baseline data of this intervention study to investigate the correlation between the clinical measure and imaging parameters. The investigated association between clinical measures and imaging parameters may help us to understand the underlying neural correlates of clinical impairments and disabilities.

Research questions

The following research questions regarding our master thesis are formulated: (1) “What are the correlations between the clinical measures and imaging parameters at baseline?”, (2) “Are these correlations different in PwMS with different upper limb disability level of PwMS with different phenotypes of MS?”

Hypothesis

There are two null hypothesis that can be translated from the aim of the study and the research questions:
$H_{0,a}$ = there are no correlations between clinical measures and imaging parameters at baseline.
$H_{0,b}$ = the correlations in PwMS with different upper limb disability level and PwMS with different phenotypes of MS are the same.

The alternative hypothesis:
$H_{1,a}$ = there are correlations between clinical measures and imaging parameters at baseline.
$H_{1,b}$ = the correlations in PwMS with different upper limb disability level and PwMS with different phenotypes of MS are different.

Method

Study design

A large Randomized Controlled Trial is set up to investigate the research questions and hypothesis. All participants will be stratified in 2 groups based on their baseline upper limb disability (mild or moderate upper limb disability) and will be randomly (blinded) assigned to either the 'Impairment-Oriented Training group' (IOT) or the 'Task-Oriented Training group' (TOT), see figure 1.

The intervention of the upper limb will consist of one hour training sessions, five days a week, for eight weeks, during their occupational therapy hours provided in the conventional multidisciplinary rehabilitation program. During the other training sessions (physiotherapy, speech therapy, cognitive therapy) planned in their conventional multidisciplinary rehabilitation, the upper limb function is not trained.

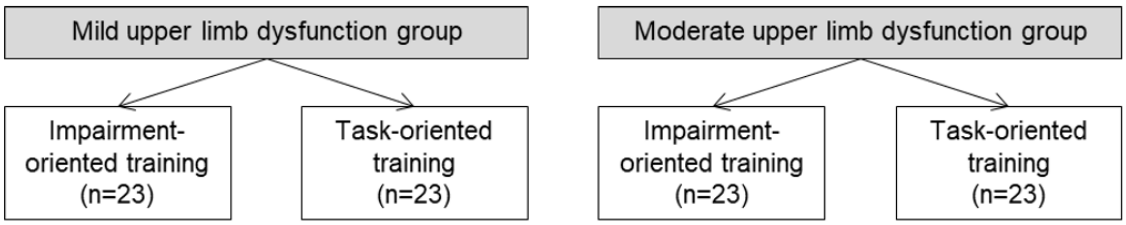

Figure 1. Randomisation of participants

Participants

The study focuses on persons with Multiple Sclerosis (PwMS; n=92). Because the extra intervention involves the upper limb, PwMS should show some kind of difficulty with activities of daily life including one or both upper limbs. The sample size of each group (n=23) is calculated using a power analyse (power 0.80, α: 0.05, effect size: 0.80,drop-out: 10%) based on the results of an previous pilot study and is an exceeding sample size compared with most previous upper limb research in MS. [9]

PwMS with all phenotypes of MS (relapsing remitting – RRMS, primary and secondary progressive MS – PPMS & SPMS) are included.

Inclusion

Patients participating in this study should meet the following criteria: PwMS referred for upper limb rehabilitation, diagnosed according to the MCDonald criteria, aged > 18y and had a minimal-to-severe self-reported upper limb dysfunction (six-point Likert scale).

Exclusion

Patients will be excluded if they meet the following criteria: patients who had a relapse or relapse-related treatment within the last three months prior to the study, a complete paralysis of both upper limbs, a severe cognitive or visual deficits interfering with testing and training or other medical conditions interfering with upper limb function (orthopaedic or rheumatoid impairment).

Recruitment

Participants (n=92) will be recruited in three Flemish rehabilitation centres specialized in MS: Rehabilitation and MS centrum Overpelt (http://www.msreva.be); Prof. dr. Bart Van Wijmeersch), MS Network Antwerp (http://www.ms-antwerpen.be; Dr. Barbara Willekens) and The National MS center Melsbroek (https://www.mscenter.be; Dr. Tom Meurrens). These centres have the capacity to accommodate 240 in-patients and more than 1200 out-patients.

Medical ethics

Ethical approval will be requested at the ethical committee of Hasselt University and the local committee of each participating centre. The application will be submitted in September 2018.

Intervention

Participants will be stratified into two blocks of upper limb disability (mild or moderate) depending on the capability of raising the arms to 90° anteflexion for 20s and a cut-off score on the NHPT (33.3s [10]). After this, they will be block randomized into two intervention groups by an independent blinded investigator. In addition, the participants will be blinded.

These training sessions will be one hour each, five days/week, during eight weeks. Within a training session, blocked practice order and massed practice will be used. Participants from both groups will be training under constant supervision.

Rehabilitation program 1: Task-oriented training (TOT)

This intervention involves practicing of functional daily tasks, with the intention to acquire or reacquire a skill. Most functional tasks require reaching, moving, positioning, transporting, lifting the upper limb and/or an object and grasping, releasing, stabilizing and/or manipulating an object. [11] Participants will be asked to choose three tasks from a list of 46 activities of daily living, based on the items of two questionnaires (ABILHAND and Manual Ability Measure-36 (MAM-36), table 1) before starting the interventions. One unilateral task and two bilateral tasks. After this, the individual maximum number of repetitions will be decided for each chosen task during a single session of 60 minutes. The difficulty of the task will be adapted to the capabilities of the participants and the task will be repeated until the individual maximum number of repetitions is reached. Task difficulty will be progressed throughout the training period and new tasks can be introduced following pre-defined criteria.

Table 1. List of training tasks based on the ABILHAND and Manual Ability Measure-36 questionnaires.

#	Training task	#	Training task
1	Eating a slice of bread	24	Opening a carton (milk, cereals) **(1)**
2	Drinking a glass of water **(1)**	25	Pouring liquid from a bottle in a glass **(4)**
3	Picking-up a half-full can **(2)**	26	Opening a bottle with a child-proof top **(1)**
4	Using a spoon or fork **(3)**	27	Opening an envelope **(1)**
5	Spreading butter/jam on a slice of bread **(2)**	28	Peeling fruits or vegetables
6	Cutting meat with a fork and a knife **(8)**	29	Handling money **(4)**
7	Squeezing toothpaste on a toothbrush **(1)**	30	Taking things out of a wallet
8	Brushing teeth	31	Writing sentences **(9)**
9	Brushing, combing or drying your hair	32	Turning pages **(3)**
10	Washing your hands	33	Shuffling cards **(4)**
11	Wringing a towel	34	Using a screwdriver
12	Zipping pants	35	Hammering a nail
13	Zipping a jacket	36	Folding clothes
14	Buttoning clothes **(10)**	37	Opening a CD/DVD
15	Fastening a snap (jacket, bag)	38	Peeling onions
16	Cutting nails **(5)**	39	Sharpening a pencil
17	Tying shoes **(1)**	40	Taking the cap off a bottle **(3)**
18	Using a remote control **(1)**	41	Filing one's nails
19	Dialing a telephone number	42	Tearing open a pack of chips **(1)**
20	Turning a door knob	43	Unwrapping a chocolate bar
21	Turning a key in a keyhole	44	Threading a needle **(2)**
22	Loading and carrying a shopping bag **(3)**	45	Wrapping up gifts **(1)**
23	Opening a jar (jam, mayonnaise) **(7)**	46	Shelling hazel nuts

Values in parentheses: number of participants training the task.

Rehabilitation program 2: Impairment-oriented training (IOT)

This intervention aims to improve upper limb muscle strength, muscle endurance and active range of motion in proximal and distal part of the upper limbs. Participants will be asked to perform an interval training on the MOTOmed Viva2 at a target heart rate corresponding to 65%-75% of VO_{2peak}. [12] To determine the individual maximal number of repetitions for the E-link training, the participants will be asked to perform as many repetitions as they can. Train difficulty will be progressed throughout the training period and can be introduced following pre-defined criteria.

Outcome measurements

Clinical

Clinical outcome measurements will be taken at baseline (week 0), after the intervention (week 8) and after 8 weeks follow-up (week 16). All assessments will be performed by an assessor blinded for group allocation and the sequence of the assessments will be randomized to avoid order effects. Unilateral tests will be completed with both upper limbs and hand dominance will be established with the Edinburgh Handedness Inventory. [13]

<u>TOT clinical outcome measures</u>

The NHPT, Box and Block Test (BBT), Action Research Arm Test (ARAT) and the Test d'évaluation des Membres Supérieurs des Personne Âgées (TEMPA) will be used as capacity measures, and the Manual Ability Measure (MAM-36) as perceived performance measure on the ICF activity level.

The NHPT is a unilateral assessment of manual dexterity measuring the time needed to insert and remove nine pegs as fast as possible. [14] The mean time will be calculated based on two trials performed with each hand.

For the BBT, participants will be asked to move as many blocks as possible from one side of a box to the other side within 60 seconds and the score reflects the total number of blocks transported by each hand. [15]
The ARAT addresses unilateral arm-hand function with four subscales (grasp, grip, pinch, gross arm movements). Nineteen items are given a score (0,1,2,3) with a maximum score of 57. [15]
The TEMPA measures the execution time and the amount of difficulty (score 0, -1, -2, -3) on nine standardized daily life tasks. [16] Only the amount of difficulty score will be used for statistical analysis.
The MAM-36 questionnaire measures the perceived arm-hand performance in daily life by scoring 36 unilateral and bilateral tasks using a four-point scale. [17] The sum score of each subject is subsequently Rasch-calibrated and converted into a 'manual ability measure'.

IOT clinical outcome measures

Maximal isometric hand strength tests and the Motricity Index will be used to evaluate strength. A Static Fatigue Index (SFI) during a maximal sustained handgrip strength test will be calculated to assess motor fatigability.
Maximal isometric strength of handgrip, key grip, 3-jaw grip and thumb-index grip will be measured as the average force produced during three trials of three seconds maximum voluntary contraction using the E-link. [26] A 30-second sustained maximal handgrip strength test will be used to assess motor fatigability by calculating the SFI. [18] A higher SFI value indicates a greater decline in grip strength over time, and thus more motor fatigability.
The Motricity Index is a six-point ordinal scale assessing general muscle strength during shoulder abduction, elbow flexion and pinch grip, with a total score 0-100. [19]

Neural

Neural outcome measurements will be taken at baseline (week 0), after the intervention (week 8) and after 8 weeks follow-up (week 16). All assessments will be performed by an assessor blinded for group allocation and the sequence of the assessments will be randomized to avoid order effects. MR imaging of the brain and spinal cord is sensitive for detecting white matter lesions typical of MS. [20]
The MRI protocol will include:
1) 3D T1-weighted MPRAGE (voxel size 1 mm^3);
2) 3D FLAIR;
3) axial T2-weighted TSE;
4) gradient-echo field mapping;
5) T2-weighted echo-planar imaging (EPI) for resting state-fMRI;
6) DTI single-shot EPI (voxel size 2 mm^3).
Participants will undergo brain MRI at 3.0T (Siemens)-scanner in Ziekenhuis Oost-Limburg (ZOL), radiology department.

Brain analysis

The entire imaging protocol will take ~50 minutes. Participants are repositioned following published guidelines. [21] Following measures are calculated for each subject at each time point:

1) 3D T1-weighted, 3D FLAIR and axial T2-weighted: white matter (WM) T2 and T1 lesion load;

2) 3D T1-weighted: normalized brain, gray and white matter volumes [22];

3)DTI single-shot EPI: MD, FA, directional diffusivity (RD and AD), FA in several regions of interest (ROIs) the corpus callosum (CC), cortico-spinal tract (CST) and cerebellar peduncles bilaterally and the superior longitudinal fasciculi after masking out WM lesions using the FMRIB's Diffusion Toolbox, FDT 230 [23].

4) T2-weighted EPI: Resting-state fMRI processing are performed using SMP8 [24]. For more subtle gray matter comparisons FSL-VBM will be used. [25] In FSL-VBM, the GM images will be registered to the MNI 152 standard space and averaged to create a left-right symmetric, study-specific gray matter template.

Data-analysis

Statistical analyses will be performed with SAS JMP PRO 13.2. The significance level will be set at 5%. The dominant and non-dominant test scores of unilateral tests will be analysed together in order to obtain a larger data set. Baseline characteristics of the two groups will be compared using the Kruskal-Wallis test for continuous variables and the Fisher Exact test for categorical variables. Correlations at baseline will be analysed by either Pearson or Spearman, depending on the normality of the residuals that will be checked by visual inspection of the normal quantile plots.

Time planning

Year	2018				2019					
	sept	oct	nov	dec	jan	feb	mar	apr	may	jun
Preparing ethics approval										
Preparing data management protocol										
Training of staff who will perform the training										
Recruitment of participants										
Baseline data collection										
Data analyses of the baseline data										
Scientific output and valorisation										

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