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Brain activity changes following neuroproprioceptive “facilitation, inhibition” physiotherapy in multiple sclerosis: a parallel group randomized comparison of two approaches

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Abstract

Background

Imaging methods bring new possibilities for describing the brain plasticity processes that underly the improvement of clinical function after physiotherapy in people with multiple sclerosis (pwMS). Although these processes have been described mainly in connection with task oriented physiotherapy and aerobic training, they haven't been properly verified in neuroproprioceptive "facilitation, inhibition" (facilitation) approaches.

Aim

The study determined whether facilitation physiotherapy could enhance brain plasticity, compared two facilitation methods, and looked for any relation to clinical improvement in pwMS.

Design

The study was designed as parallel group (38 outpatients) randomized comparison of two kinds of physiotherapeutic interventions referred to healthy controls.

Population

The study had 80 participants (38 pwMS and 42 healthy controls).

Methods

PwMS were divided into two groups and underwent a two-month physiotherapy program - Vojta reflex locomotion (VRL) or Motor Program Activating Therapy (MPAT), (1 hour, twice a week). Functional Magnetic Resonance Imaging (fMRI) and clinical examination was performed before and after therapy. Healthy controls underwent one fMRI examination.

Results

Physiotherapy in pwMS leads to extension of brain activity in specific brain areas (cerebellum, suplementary motor areas and premotor areas) in connection with the improvement of the clinical status of individual patients after therapy (p=0.05). Greater changes (p=0.001) were registered after MPAT than after VRL. The extension of activation was a shift to the examined activation of healthy controls, whose activation was higher in the cerebellum and secondary visual area (p=0.01).

Conclusions

Neuroproprioceptive "facilitation, inhibition" physiotherapy may enhance brain activity and could involve processes connected with the processing of motion activation.

Clinical Rehabilitation Impact

The study showed that facilitation approach can modulate brain activity. This could be useful for developing of effective physiotherapeutic treatment in MS.

Key Words

multiple sclerosis, functional magnetic resonance imaging, neuronal plasticity, physical rehabilitation

Introduction

The incidence of multiple sclerosis (MS) is still rising and therefore the management of this disease is highly relevant in ensuring sufficient treatment[1]. MS is characterized by extensive demyelination in white matter followed by diffuse inflammation and diffuse axonal damage. This is manifested by clinical disability of varying severity. Although pharmacotherapy for this disease is increasingly effective, it has little effect on already existing motor and cognitive deficits[2]. It has been proven that regular physiotherapy (PT) positively influences impaired clinical functions such as fatigue, motor, mental and cognitive functions and quality of life in general[3-7]. Even if MS – related clinical deficit could be reversible due to several spontaneous mechanisms, PT has the potential to improve motor and cognitive functions in pwMS [7, 8]. It is apparent that PT can induce these changes by utilizing brain plasticity.

Brain plasticity promotes the recovery of clinical functions by inducing adaptive changes[9] or by helping to create a predisposition of the functional system to plasticity[10]. It encompasses a wide range of changes such as the formation of novel synapses or the induction of neurogenesis, the altered strength of synaptic transmission, changes in the equilibrium of excitation and inhibition and also systematic changes including cortical reorganization and changes of brain activation[11]. Specifically, in people with MS, the damage to the CNS is compensated for by adaptation processes (at the axonal, neuronal and synaptic level and also by systemic reorganization), but mainly by remyelinization and functional reorganization[10]. It turns out that influencing MS at this level (enhancing brain plasticity with appropriate therapy, and its physiological justification and meaningful monitoring of functional and structural reorganization of the brain) is an important task of management of MS[12]. Monitoring of the reorganization is possible due to imaging methods – primarily by functional Magnetic Resonance Imaging (fMRI) for monitoring brain activity and connectivity (task related and resting state fMRI) and Diffusion Tensor Imaging (DTI) for evidence of structural changes[13, 14].

If we focus on the possibilities of PT in influencing brain plasticity, all kinds of PT categories[15] have potential/useable mechanisms for it: physical activity (fitness/endurance/resistance) training through non-specific activity induces new angiogenesis and an increase in cerebral blood flow; it also influences brain connectivity[16, 17], motor/skill acquisitions (individualized therapy led intervention) and technology based interventions through a re-training process[18, 19] induce changes in the cortical topography closely related to the trained movement. Moreover, neuroproprioceptive "facilitation and inhibition" interventions through interference with the neuronal tactility threshold[15, 20] directly influence the nervous system. To do a summary, PT can involve brain structure, brain activation and connectivity of brain areas[8].

Neuroproprioceptive "facilitation and inhibition" intervention, also used in this study, has a big potential to directly affect the function and structure of the CNS[21-23], the site that is primarily affected by the disease. This group of approaches includes, among others, e.g. Proprioceptive Neuromuscular Facilitation, Vojta reflex locomotion or Motor Program Activating Therapy. Neurofacilitation PT uses different kind of afferent somatosensory stimuli to address nervous system[21]. By this facilitation we are able to activate automatic motor programmes in the brain. These programmes were described as genetically determined factors of motor behaviors and mature during the course of postural ontogenesis [21, 24].

Neurofacilitation PT has a big potential to enhance adaptive plasticity, which can promote the recovery of clinical functions[10].

While enhancing brain plasticity by motor/skill acquisitions, physical activity and technology based interventions have been documented in many studies[8], doing so by neuroproprioceptive "facilitation and inhibition" PT has been documented only in a few pilot projects[21, 22, 25, 26]. While the most known/frequently used method from this intervention category, Proprioceptive Neuromuscular Facilitation, is used on an empirical basis without proven effectiveness on brain plasticity, two locally used[15] methods developed in the Czech Republic, Motor Program Activating Therapy and Vojta reflex locomotion, bring promising results [21-23]. Understanding how these therapies enhance brain plasticity could help to extend their use worldwide.

The aim of this study is to extend knowledge of how neuroproprioceptive "facilitation and inhibition" interventions influence brain activity. In this study, changes in brain activity triggered by watching a video and monitored by fMRI are evaluated after Motor Program Activating Therapy and Vojta reflex locomotion. The results from fMRI were correlated with clinical functions and referred to healthy controls. Main hypotheses of this study are:

1. There will be differences in brain activity between people with MS (pwMS) and healthy controls.
2. Facilitation physiotherapy (irrespective the type) will lead to change of brain activity in pwMS.
3. There will be differences between MPAT and VRL physiotherapy group in brain activity.
4. The change of clinical status of pwMS will correspond to change of brain activity.

This study was conducting following CONSORT guidelines.

Materials and Methods

Design of the study, ethical approval

The study (NCT04448444) was designed as parallel group randomized comparison of two kinds of physiotherapeutic interventions referred to healthy controls.

MS patients were examined by fMRI (primary outcomes) and clinical tests (secondary outcomes) at the beginning of study. Then, they were randomly divided into two groups (by drawing lots in a 1:1 ratio). The first group underwent Vojta reflex locomotion (VRL), and the second Motor Program Activating Physiotherapy (MPAT). The length and intensity of treatment was the same in both groups (two months, one hour twice a week). After the treatment, a clinical and fMRI examination was performed. Healthy volunteers underwent an fMRI examination that was considered to be a control.

This study was approved by the the Ethics Committee of Kralovske Vinohrady University Hospital in Prague. The chairperson of this Committee is Marek Vácha, Ph.D. Trial protocol approved also by the Ethics Committee of Kralovske Vinohrady University Hospital in Prague has number EK-VP/22/0/2014 and was approved on 12.11.2012. All participants signed an informed consent form approved by the Ethics Committee of Kralovske Vinohrady University Hospital in Prague.

Participants

People with MS (pwMS) were chosen from the MS center database according to inclusion criteria and initially examined by neurologists. The inclusion criteria for MS participants were: definite MS[27], stable clinical status in the preceding 3 months, imuno-modulatory treatment for at least two years (including glatiramer acetate, interferon beta-1a, 1b, mitoxantrone, fingolimod, natulizumab), Expanded Disability Status Scale (EDSS)≤6, predominant motor impartment, six months or more without any physiotherapy, ability to undergo ambulatory physiotherapy. The healthy controls were sex and age paired with MS patients. Sample size was determined based on our previous research[23], which indicates that 13 subjects were sufficient to document clinical and brain activity changes.

FMRI examination (primary outcomes)

This examination was performed at the MR Unit, Department of Diagnostic and Interventional Radiology, Institute for clinical and experimental medicine (IKEM, Prague). All participants underwent fMRI examinations on a 3T magnetic resonance scanner (Siemens Trio Tim, Erlangen, Germany) using a 12-channel head coil. The examination was performed in the 3 days before and after therapy using a BOLD technique.

During the fMRI measurement, a video with alternating dynamic and static scenes (10 scenes, each 30 seconds of duration) with first person view was played during the examination. The kinetic scenes were focused on stimulation of equilibrium and balancing responses (prediction of activation in the cerebellum), e.g. the view from a balance cycle, swaying swing, rotating carousel, etc. The static scenes included slight motion (view of a river, treetop breeze, steam escaping from a pot); these scenes should induce a calming effect. The measurement time of this stimulated fMRI examination was 5 minutes.

Protocol of fMRI acquisition

For the measurement of stimulated fMRI, a gradient echo sequence with rapid data acquisition using echo-planar-imaging (GE-EPI) was used. The spatial resolution chosen (voxel size) was 3 × 3 × 3 mm with 45-slice brain coverage. The other sequence parameters used for fMRI were: TE (time to echo) = 30 ms, flip angle of the excitation RF pulse = 90 °, BW (bandwidth) = 1594 Hz / pixel, TR (repetition time) = 3000 ms. During this measurement, a total of 100 brain volumes were collected (in blocks of 10 volumes for each type of video scene), so the duration of the whole measurement was 5 minutes.

Clinical examination (secondary outcomes)

At the beginning of the study the neurologist verified the exact type and duration of MS and evaluated actual motor deficit and the degree of EDSS for each patient. The examination of clinical function was performed by a skilled physiotherapist (in the 3 days before and after therapy). Both examiners where the same throughout the study and were blinded to assignment of patients to interventions. The examination was executed at the Department of Neurology, Kralovske Vinohrady University Hospital in Prague.

The complex of clinical functions examined includes walking abilities, stability, fine motor skills and mental functions. These were evaluated according to the set of routinely used functional clinical outcome scales (Timed 25 Foot Walk – T25FW, Timed Up and Go – TUG, Berg Balance Scale – BBS, Nine Hole Peg Test – NHPT, Paced Auditory Serial Addition Test – PASAT)[28].

Physiotherapy

Two kinds of neuroproprioceptive "facilitation, inhibition" interventions (Vojta reflex locomotion and Motor Program Activating Therapy) were used in this study. Both methods have in common that initial postural positions are based on ontogenesis and activate global motor patterns, but differ in stimuli application (VRL uses stimulation of "initiation zones"[24] while MPAT combines proprioceptive, tactile, visual and auditory stimuli[21]), and in activated motor functions (reflex turning and reflex creeping in VRL and sitting, standing up, standing, stepping and walking in MPAT).

1) The MPAT was chosen for our clinical experience - it was developed and verified by our team. In this therapy, patients are corrected into a postural position where the joints are functionally centred. Then somatosensory (manual and verbal) stimuli were applied to activate motor programs in the brain, which then lead to the co-contraction of the patient's whole body when the patient is lying, sitting, standing up or moving forward. Manual stimuli

were applied: a) in sitting: on the feet upright against the support of the legs, on the external side of the knees against internal rotation and adduction of the coxae, on the sternum against the flexion of the trunk, on the shoulders against the flexion of the trunk, against the extension of the trunk and against the rotation of the trunk, b) in standing up: on the feet upright against the support of the legs, under the knees, on the spina iliaca anterior superior against the anteversion of the „pelvis and against the rotation, on the spina iliaca posterior superior forward and against rotation, on sternum against the flexion of the trunk, on shoulders against the flexion of the trunk, against the extension of the trunk and against the rotation of the trunk. The duration and intensity of treatment is immediately modified according to the response to the stimuli. A set of stimuli is applied to change the posture with anatomical centration of the joint while sitting with attitude to stand up, and while standing with attitude to step forward. Each stimulus lasts about 1 to 10 seconds when applied in one place, e.g. the external part of the knee (places where manual stimuli were applied are described lower). After right reaction to the stimulus, the stimulation continued in another place after 1 to 10 seconds, e.g. the sternum and the external part of the right knee. The places of stimulation are continuously changing 7-10 times in each position. The complete stimulation usually takes 10-20 minutes.

Activated programs are repeated under various conditions and in different situations and environments to teach the patients to use the acquired motor skills automatically in daily life[20]. Therapy was undertaken at the ambulatory section of the Department of Neurology, Kralovske Vinohrady University Hospital in Prague.

2) VRL was developed by prof. Vojta and is standardly used in the Czech Republic. Patients should be set up into the precisely given initial position with defined angular setting of extremities. There were used three global coordination complexes in this therapy - reflex creeping (prone position), reflex turning (supine or side-lying position) and process of verticalization (kneeling position). Most of activation zones (trunk zone, acromion, scapula,

epicond. med. humeri, proc. styl. radii, spina iliaca sup. ant., mus. gluteus, epicond. med. femoris), calcaneum) and their combination were used during the therapy. Activation points (zones) ~~are~~ were stimulated with precise localization and pressure direction. The pressure was applied manually by a therapist using her thumb placed on one of predefined zone. For example: The pressure was applied on the lateral heel zone (processus lateralis tuberis calcanei) according to Vojta[30]. Throughout the session, the stimulated limb was semi-flexed in the knee joint and supported above the table by the therapist who maintained constant tactile contact until the quality motor response was observed. This sustained manual pressure stimulation of specific points on the skin surface ("stimulus points" or "stimulation/reflex/trigger zones") gradually evokes a widespread motor response (asymmetrical muscle contraction in both sides of the neck, trunk, and limbs). In addition to motor involuntarily reaction, also sensory and autonomic response is activated[29].

Therapy was undertaken at the Department of Rehabilitation and Sport Medicine, Motol University Hospital.

Patients in both groups underwent 16 sessions (1 hour, twice a week for two months). Therapy was led face to face by a well-educated (MSc.) therapist, who was also experienced (minimally two years' practice with pwMS), and specially trained in each method. The intensity of load during therapy corresponded to moderate activities[30]. The therapist was maximally helpful and adopted the schedule for each patient to reach all 16 sessions.

DATA ANALYSIS

FMRI analysis

FMRI activation stimulation from watching a video was rated in 3 respects:

1) The difference in activation between the patients and the healthy subjects was assessed (p=0.01).

2) Changes in general activation after physiotherapy in pwMS were monitored, first for all pwMS ($p=0.001$ FWE) and then for each treatment group separately ($p=0.001$).

3) On the basis of the established hypotheses, activation relating to improvement of the clinical condition was assessed in the following areas: cerebellum, premotor area (PMA) and supplementary motor area (SMA) and basal ganglia, ($p=0.05$).

FMRI data processing

SPM (Statistical Parametric Mapping, version 8), one of the most commonly used brain imaging softwares, was used for data processing [31]. After conversion of the DICOM format data, a realignment and slice timing correction was performed. In the next step, the images were normalized to the standard size MNI 152 so that they could be used for group statistics. The final step of data preparation was spatial smoothing with a 6x6x6 mm Gaussian filter. This analysis resulted in the display of activation sites. Activated areas were identified by *XYZ* coordinates and the correct localization verified with MARINA software [32].

The statistical evaluation at the individual level (for each subject) was done using a general linear model for a simple block diagram, alternating between two types of video scenes: a video containing a dynamic action and a static video. The resulting activity was a consequence of the difference in activation between kinetic and static video activation. Individual-level statistical maps were used for group analysis, which was performed by a t-test on individual statistical maps, separately for the control group and two examinations of patients. The effect of therapy with respect to change of clinical index was studied by a paired t-test.

Analyses of clinical data

A clinical index was determined as the mean of the normalized values of the five clinical trials (NHPT, PASAT, BBS, T25FW, TUG). This value represents the clinical status of each individual and ranges from 0 to 1 where 0 is the most serious clinical condition and 1 means no clinical deficit.

The data are presented as average ± standard deviation (SD) or as median ± interquartile range (IQR) or as the absolute and relative frequencies in the case of categorical data.

Results

Characteristic of participants

From 45 allocated patients, 38 finished the therapeutic program (10 men, 28 women, average age of 46.9±12.7). Twenty-five of the participants have a relaps-remitting form of MS, 13 have the secondary progressive form and 1 the primary progressive form. Their stage of the Expanded Disability Status Scale (EDSS) was in the average 4.2±1.7 and the average of the disease duration was 12.3±7.2 years.

FMRI data were analyzed with respect to the fMRI quality, so in 42 healthy controls (16 men, 26 women, average age of 43.7±14.8) from 45 allocated and 35 pwMS from 38 allocated.

Baseline demographic and clinical characteristics are shown in Table 1. VRL and MPAT groups were compared before the therapy. There were significant differences in age and disease duration, but no differences between the groups in EDSS and clinical index, or in brain activity (we can say that the groups were coherent in this respect and the effect of the therapy can be compared). An overview of the flow of participants can be found in Figure 1.

FMRI analysis

The difference in brain activation between pwMS and the healthy subjects

In healthy subjects, there is a statistically more pronounced activation in the area of the visual cortex (especially in the secondary visual area - V4 and V5) and activation in the cerebellum (absent in patients), (Figure 2). These differences are statistically unchanged over time. For this analysis, the p-value of the uncorrected threshold was 0.01.

An effect of neuroproprioceptive “facilitation, inhibition” intervention on brain activity (irrespective type of therapy)

Before the therapy the brain activation is mainly visible in the extrastriate cortex (V2, V3, V4, V5) that correspond to the dorsal and ventral connection of the striate region. Activation is further extended to the parietal area. The pattern of activation does not statistically significantly change after therapy. The p value for detecting activity at this analysis was 0.001 with FWE correction (FWE – Family Wise Error). However, by the simple observation we can see a slight increase of activation in the area V3 and slight decrease of activation in the frontal lobe after therapy (Figure 3).

The difference of brain activity between VRL and MPAT

After therapy, MPAT showed slightly higher cerebellar activation and, in addition, little activation in the right frontal lobe. Figure 4 shows how much higher the activation was in the MPAT group than in the VRL group.

Correlation between brain activity changes and clinical improvement

Increased activation in conjunction with a positive change in clinical index was demonstrated in the cerebellum and SMA and PMA after therapy. In the basal ganglia, the increase has not been demonstrated (Figure 5). The uncorrected threshold for p value of 0.05 was used for this analysis.

Analyses of clinical data

An increment of clinical index (median 0.015, IQR 0.049) after the therapy was not statistically significant (Wilcoxon test, $p = 0.2675$). There was no difference between the MPAT and VRL in the change of clinical index (Wilcoxon test, $p = 0.3495$).

Discussion

Current research, study advantages

The effectiveness of physiotherapy in MS has mainly been demonstrated by improvement of clinical functions [33]; using imaging methods could be beneficial for deeper understanding of these positive changes. Imaging methods are still more frequently used in current research[8], yet investigation of brain microstructure and brain activity and connectivity changes after motor rehabilitation brings discrepancies in results[8]. If we focus on brain activity, previous studies documented a decrease[34, 35] as well as increase[36-38] of brain activation after therapy. Previous studies also have differing type and length (from 2 to 14 week) of therapy, and various number of participants (from 12 to 41). Some studies do not have an MS control group [34, 35], and/or do not contain a healthy control group [34, 35, 38]. Our study included a healthy control group and the 38 participants with MS represent the second largest sample size compared to previous research. In this study an innovative type of “event” as the stimulation during fMRI measurement is used. Instead of the motor paradigm a visual stimulus (video) is performed, which could bring better replicability without the necessity of exact movement repetition [21, 37] (avoiding artefacts and change of activation area due to another type of movement). The use of kinetic video allows us to see similar brain activity in similar brain areas as is seen during movement[39, 40], and this could be helpful for examination of people with motor dysfunction.

Comparison of brain activation between healthy and pwMS

Healthy controls had more extensive activation (Figure 2) than pwMS at the baseline - especially in the secondary visual cortex (V4, V5), the area where the visual signal is processed. This result can be interpreted as a greater readiness of healthy people to respond to these visuomotor stimuli; they meet more often and respond to situations requiring balance and faster processing of the visual stimulus. Patients maybe do not have such a strong functional response to the kinetic stimulus in the visual cortex. Activation in the cerebellum, which might correspond to readiness to respond to such situations, is largely absent in people with MS in our study. A study comparing functional activation in MS patients with healthy controls at a similar stimulus has not yet been published. We can only notice that healthy participants had activations in similar areas (V1, V2, V3, V5, SMA, PMA) by similar visuomotor stimulus (projection of moving black and white lines or moving sinusoid) in the following publications[39, 40]. From other studies using the motor paradigm (used during fMRI scanning) the pattern of activation is more extensive in pwMS [41, 42,43] than in healthy people, so we assume that the visual paradigm brings opposite results – extensive activation in healthy subjects (should be verified in future research).

In summary, in this study, which compares healthy subjects and pwMS, a clear difference in brain activation is evident (more extensive in healthy people), while there were specific activity changes after physiotherapy (shift of activation pattern of pwMS to activation pattern of healthy people).

An effect of neuroproprioceptive "facilitation, inhibition" intervention on brain activity (irrespective of the type of therapy)

Taking a look at the overall results of our study (independent of categorization by type of therapy), we can say that the pattern of activation did not change significantly after the therapy (Figure 3). We can assume that possible changes were so small that at this strict threshold ($p = 0.001$ FWE) they were not noticeable.

Although there was only a trend for improvement in clinical status (contrary to our previous research where significant changes were documented [4, 25]), the clinical condition improvement (by those pwMS whose clinical status has improved) is followed by an increase in cerebellar and supplementary motor and premotor area activation after physiotherapy (Figure 5). We are aware that other factors than physiotherapy could influence brain activity.

Comparison of two neuroproprioceptive facilitation and inhibitions methods

Although both chosen therapies, MPAT and VRL, address the nervous system and activation of a global motor pattern, in MPAT, unlike VRL, we use more active co-operation of the patient, higher postural positions during therapy and we teach patients to activate motor programs in normal daily motion. We have indeed shown (Figure 4) that in the MPAT group after the therapeutic program there was a higher functional activation in the cerebellum compared to VRL, an area where the difference in MS patients and healthy controls had already been hypothesized. Another higher activation in the frontal lobe is located in the premotoric region. Therefore, MPAT seems to have greater potential to target areas involved in motor planning and control. The difference in therapies was not reflected in the assessment of clinical functions in this study.

Correlation between brain activity changes and clinical improvement in pwMS

In the context of findings of previous research [25, 34, 35, 44] we focus on changes of the brain activity in connection to the change of clinical index (improvement of clinical status) in these brain areas: PMA, SMA, basal ganglia and cerebellum. After therapy (irrespective of the group), we can see higher activity in the supplementary motor area and premotor area as well as in the cerebellum in all pwMS (Figure 5). In comparison with the mentioned research, instead of decreasing activation (in left cuneus and precuneus and supracalcarine cortex[34], in the contralaterar motor area[35], primary motor area, supplementary motor area, primary sensory cortex, sensory-motor cortex and cerebellum[44]), in our study there is an increase of activation after therapy in connection with better clinical status. This can be explained by another kind of stimulus for brain activation (watching a video instead of a motor paradigm). The conclusions corresponding to our results have been reached by authors in similar research focused on cognitive functions (increased activation often in cerebellum after cognitive training, stimulation by visual stimulus during fMRI examination)[45-47]. Such conclusions were also reached by Tomassini et al[10, 34]. They demonstrated, in patients after prolonged motor training, an association between improvement in exercise performance with changes in the cognitive system that were not present in improvement in healthy controls. Increase of activation in PMA was also documented by Leonard et al.[36], these authors use cognitive training together with physical rehabilitation in the study. Also Rocca et al. refer to higher activity after action observation training (in frontal gyrus and superior frontal gyrus and insula – similar areas as in our research). Maybe the VRL and MPAT therapies are more focused on cognition processes during the movement (no automatically performed movements).

Thus, the therapy undertaken by participants in our study was likely to have a positive effect on the processing of motion information and increase activation in areas, that are responsible for planning of motion, and complicated and complex motion and coordination.

Limitations of the study and future recommendation

It can be stated that analyses of resting state fMRI bring more consistent conclusions than task related fMRI (used in this study). All studies[35, 37, 48-50] refer to an increase of connectivity of motor control areas after physiotherapy (irrespective of the type of therapy). The analyses of connectivity may be better tools for evaluation of brain plasticity than evaluation of changes of brain activation triggered by visual or motor input. We cannot determine whether brain activity change is caused by therapy or by changes of examination trigger.

Also it is still unclear whether an increase or decrease of activation is a positive change, as was discussed in our previous study[25]. So it is always necessary to compare results with a healthy control group and try to precisely interpret the fMRI findings with the change of clinical status of participants, as we have done. To have a more robust comparison the control MS group would always be beneficial.

Conclusions

Although there were no changes in general brain activation (by fMRI) after a two-month neuroproprioceptive “facilitation, inhibition” physiotherapy in patients with MS, there were specific brain activity changes in connection with the improvement of the clinical status of individual patients after therapy. This has been shown in areas identified in hypotheses (cerebellum, supplementary motor areas and premotor areas). Increase of activation in connection with better clinical status was also a clear shift to the activation pattern of healthy controls. This effect was shown to be greater in Motor Program Activating Therapy (“active” approach) compared to Vojta reflex locomotion. It seems that neuroproprioceptive “facilitation, inhibition” approaches could involve processes connected with processing of motion activation.

We can conclude that a facilitation approach can modulate brain activity similarly to a task oriented approach, which could be useful for developing of effective physiotherapeutic treatment in moderate MS.

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Notes

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

Authors’ contributions

Marie Prochazkova – Writing – original draft, organization of study, investigation

assoc. prof. Jaroslav Tintera – fMRI data curation, fMRI methodology, fMRI analyses, writing - reviewing and editing

Sarka Spanhelova – Investigation, data curation

Terezie Prokopiusova – Investigation, data curation

Jan Rydlo – Investigation, fMRI data curation, fMRI analyses

Marketa Pavlikova – Investigation, statistical analyses

Antonin Prochazka – Statistical consultation, writing - reviewing and editing

assoc. prof. Kamila Rasova – Supervision, methodology, writing - reviewing and editing

All authors read and approved the final version of the manuscript.

Tables

Table 1. Baseline demographic and clinical characteristics for each group (MPAT – Motor Program Activating Therapy, VRL – Vojta reflex locomotion SD – standard deviation, MS – multiple sclerosis, RR – relaps-remitting, SP – secondary progressive, PP – primary progressive, EDSS – Expanded Disability Status Scale)

	Total	MPAT	VRL	t-test p value
Number of Participants	38	18	20	
Male/female	10/28	2/16	8/12	
Age (mean±SD)	46.9±12.7	51.9±11.6	42.4±12.3	0.0191
Type of MS (RR/SP/PP)	25/12/1	9/9/0	16/3/1	
Disease duration (mean±SD)	12.3±7.2	15.4±7.8	9.3±5.3	0.0073
EDSS (mean±SD)	4.2±1.7	4.6±1.5	4.0±1.9	0.2636
Clinical index (mean±SD)	0.613±0.16	0.574±0.17	0.647±0.14	0.2933

Titles of tables and figures

Table 1. Baseline demographic and clinical characteristics for each group

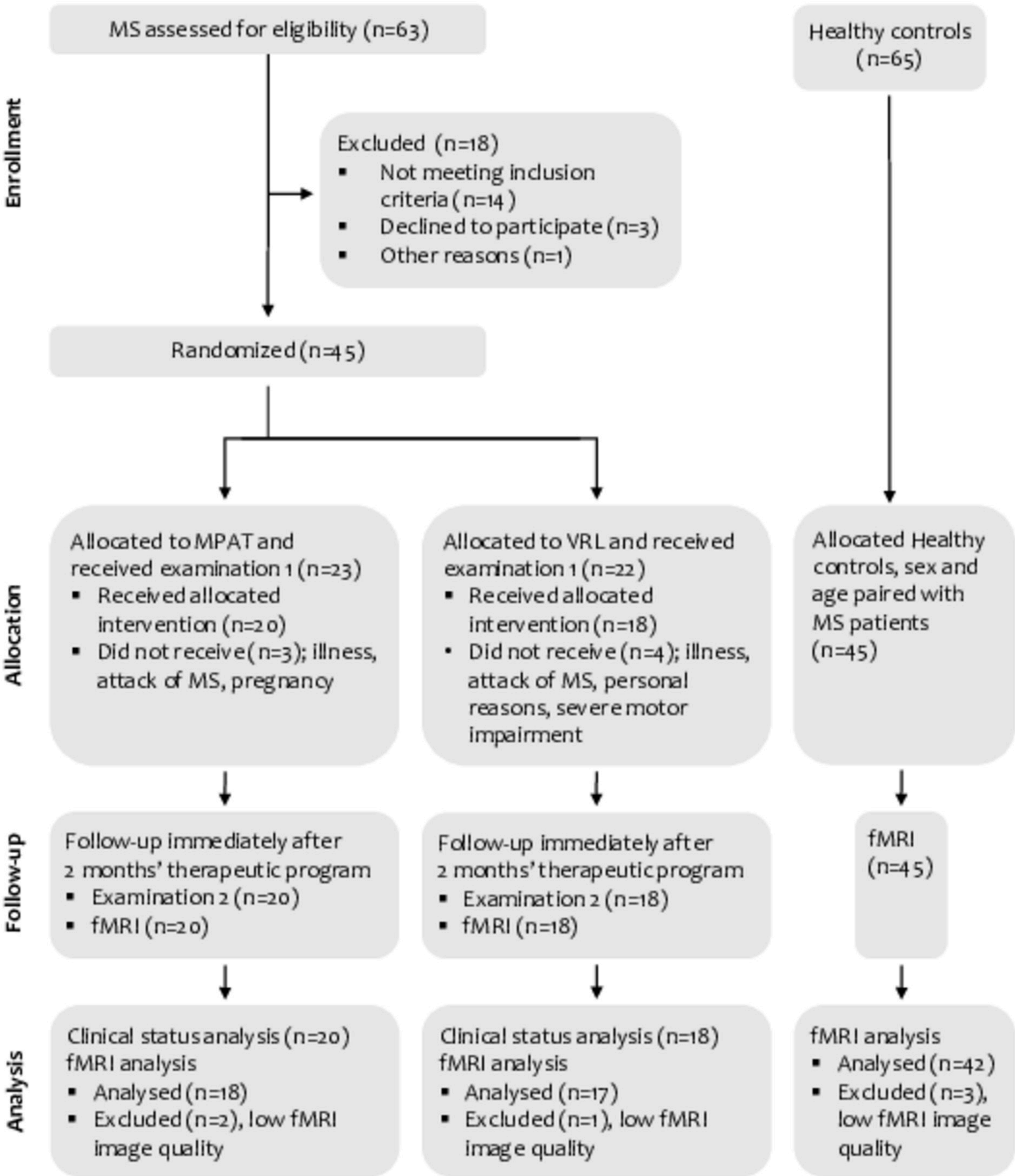
Figure 1. The chart of the flow of participants.

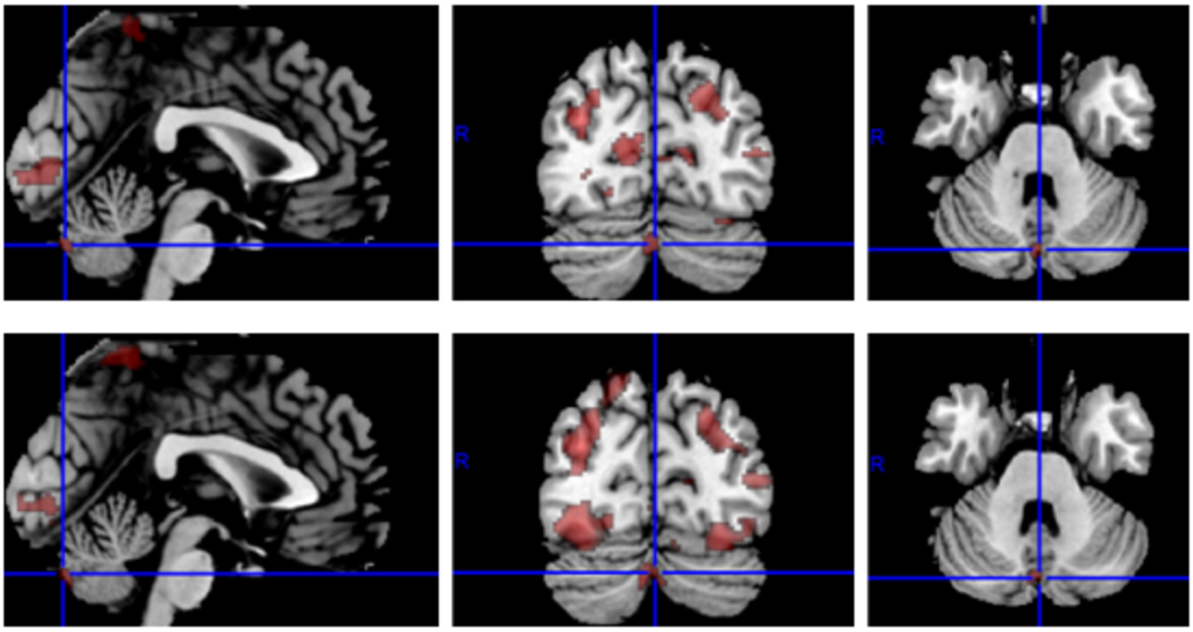
Figure 2. Differences in activation of patients and healthy controls when watching kinetic videos. Examination before the therapy (first line) and after therapy (second line). Colored regions illustrate areas with higher activation in controls than patients (p=0.01) in the sagittal section – left column, frontal section– middle column and transversal section – right column.

Figure 3. Activation pattern (in sagittal – left column, frontal – middle column and transversal section – right column) by kinetic video in patients before therapy (top) and after therapy (bottom), p=0.001 FWE.

Figure 4. Activation differences (in cerebellum and right frontal lobe) between MPAT and VRL groups after therapy (p=0.001). Colored regions illustrate areas with higher activation in MPAT group in sagittal section – left column, frontal section – middle column and transversal section – right column.

Figure 5. Increase in cerebellar (left image) and supplementary motor and premotor areas (right image) activation (p = 0.05) after physiotherapy in conjunction with a positive change in clinical index. In sagittal section – top left, frontal section – top right and transversal section – bottom left.


Enrollment
MS assessed for eligibility (n=63)
Healthy controls (n=65)
Excluded (n=18)
Not meeting inclusion criteria (n=14)
Declined to participate (n=3)
Other reasons (n=1)
Randomized (n=45)
Allocation
Allocated to MPAT and received examination 1 (n=23)
Received allocated intervention (n=20)
Did not receive (n=3); illness, attack of MS, pregnancy
Allocated to VRL and received examination 1 (n=22)
Received allocated intervention (n=18)
Did not receive (n=4); illness, attack of MS, personal reasons, severe motor impairment
Allocated Healthy controls, sex and age paired with MS patients (n=45)
Follow-up
Follow-up immediately after 2 months' therapeutic program
Examination 2 (n=20)
fMRI (n=20)
Follow-up immediately after 2 months' therapeutic program
Examination 2 (n=18)
fMRI (n=18)
fMRI (n=45)
Analysis
Clinical status analysis (n=20)
fMRI analysis
Analysed (n=18)
Excluded (n=2), low fMRI image quality
Clinical status analysis (n=18)
fMRI analysis
Analysed (n=17)
Excluded (n=1), low fMRI image quality
fMRI analysis
Analysed (n=42)
Excluded (n=3), low fMRI image quality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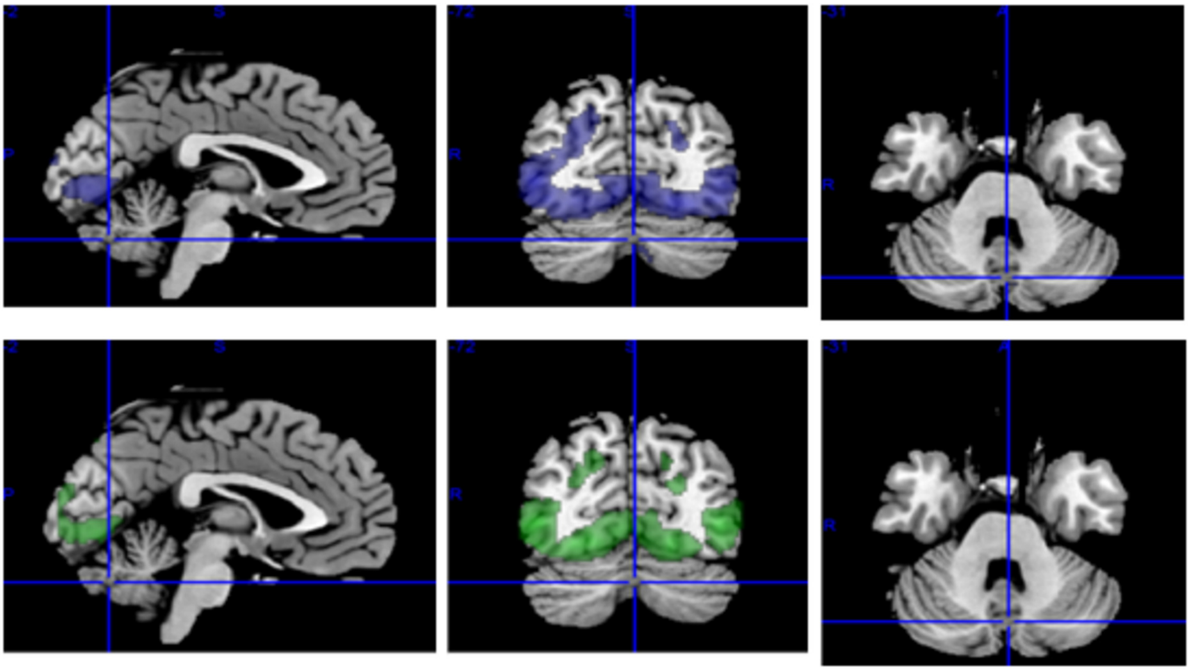

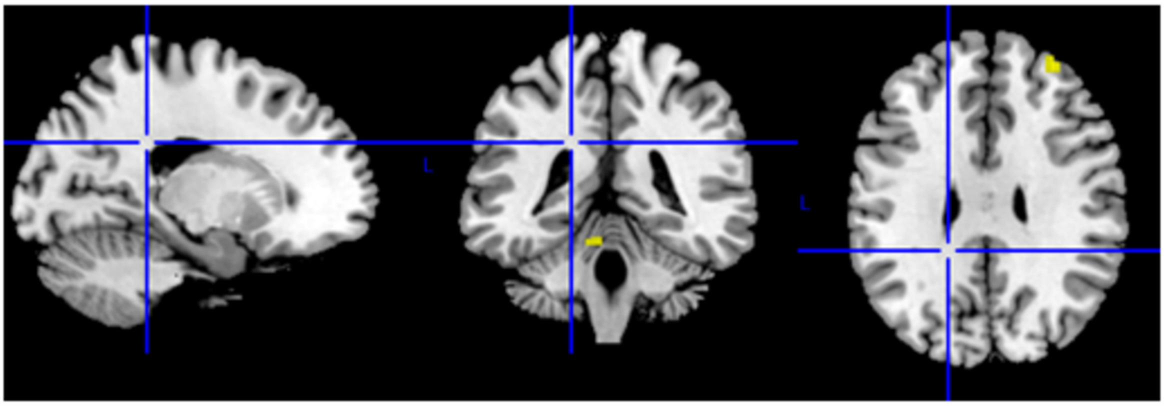

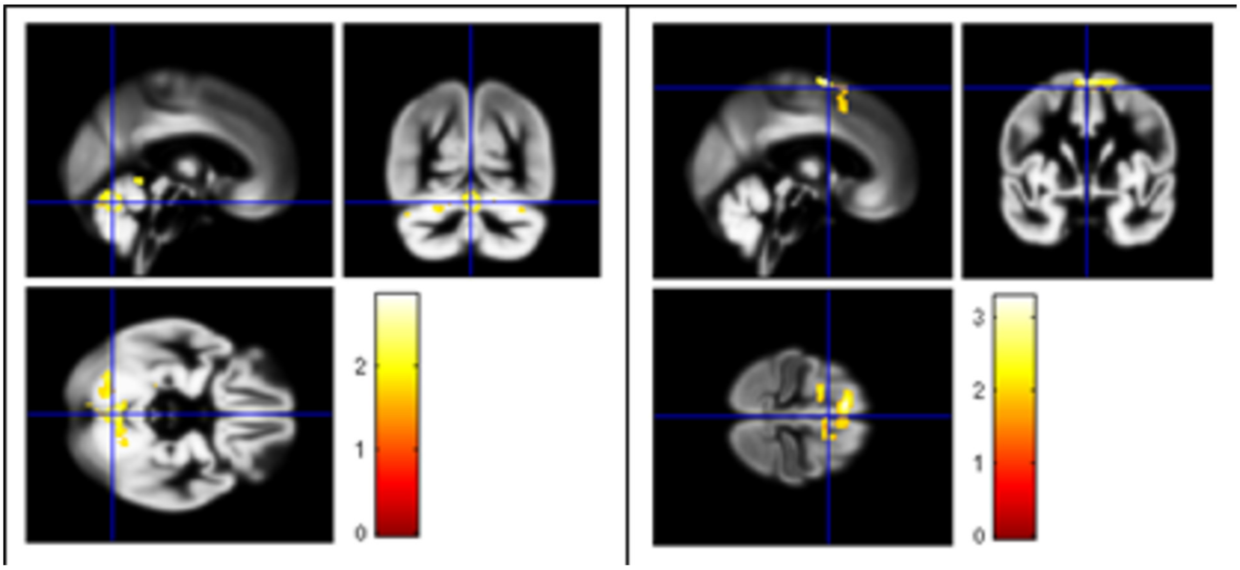

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