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A Three-Arm Parallel-Group Exploratory Trial documents balance improvement without much evidence of white matter integrity changes in people with multiple sclerosis following two months ambulatory neuroproprioceptive "facilitation and inhibition" physical therapy

Physical therapy and white matter integrity

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ABSTRACT

BACKGROUND:

Changes of white matter integrity in people with multiple sclerosis (MS) were documented following mainly motor/skill acquisitions physical therapy, while following neuroproprioceptive ”facilitation, inhibition” (neurofacilitation) only by two pilot studies. Neurofacilitation has potential to induce white matter changes due to possibility to interfere with the neuronal tactility threshold, but stronger evidence is missing.

AIM: This study investigates whether neurofacilitation (three physical therapy types) induce white matter changes and if they relate to clinical improvement.

DESIGN: The Three-Arm Parallel-Group Exploratory Trial (NCT04355663)

SETTING: Each group underwent different kind of two months ambulatory therapy (Motor Program Activating Therapy, Vojta's reflex locomotion, and Functional Electric Stimulation in Posturally Corrected Position).

POPULATION: MS people with moderate disability

METHODS:

At baseline and after the program, participants underwent magnetic resonance diffusion tensor imaging (DTI) and clinical assessment. Fractional anisotropy maps obtained from DTI were further analyzed using tract-based spatial statistic exploring the mean values in the whole statistic skeleton. Moreover, additional exploratory analysis in 48 regions of white matter was done.

RESULTS: 92 people were recruited. DTI data from 61 were analysed. The neurofacilitation (irrespective type of therapy) resulted in significant improvement on the Berg Balance Scale (p=0.0089), mainly driven by the Motor Program Activating Therapy. No statistically significant change in the whole statistic skeleton was observed (only a trend for decrement of fractional anisotropy after Vojta's reflex

locomotion). Additional exploratory analysis confirmed significant decrement of fractional anisotropy in the right anterior corona radiata.

CONCLUSIONS: Neurofacilitation improved balance without much evidence of white matter integrity changes in people with MS.

CLINICAL REHABILITATION IMPACT: The study results point to the importance of neuroproprioceptive "facilitation and inhibition" physical therapy in management of balance in people with multiple sclerosis and the potential to induce white matter changes due to possibility to interfere with the neuronal tactility threshold.

Key words: adaptive plasticity, neural plasticity, multiple sclerosis, physical therapy, diffusion tensor imaging, and functional recovery

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease that causes a wide range of clinical dysfunctions and limits the quality of life and active participation within it. Many people with MS (pwMS) thus have a lifelong need[1] for rehabilitation that supports functional recovery by repair or compensation of the structural damage through adaptive and plastic processes of the central nervous system (CNS)[2,3].

One of the options to investigate processes following functional recovery is fractional anisotropy (FA), a metric derived from diffusion tensor imaging (DTI), used to evaluate the degree of anisotropy or directional diffusion within the white matter fibers in the brain tissue (a biomarker for myelin-axon integrity). DTI investigates brain properties and functionality at a microstructural level and as such can help to determine structural changes in the white matter following rehabilitation[4,5].

Physical therapy (PT) treats physical functions with the aim of promoting functional independence, preventing complications, and enhancing the overall quality of life. It uses a variety of techniques and methods that can be broadly divided into four categories: physical activity training, motor/skill acquisition, neuroproprioceptive "facilitation, inhibition", and technology-based PT[6]. Each PT category can influence processes of the CNS, but in a different way. Up to now, a handful of studies have monitored the microstructural changes of the brain after PT in pwMS[5, 7-12], however, the patterns and paradigms underlying functional recovery following PT still remain unclear.

Physical activity (fitness/endurance/resistance) training acts as an acute stress that enhances neurobiological processes, for example mediates brain-derived neurotropic factor and nerve growth factor that likely play roles in neuronal survival, activity-dependent plasticity, mood

states, learning and memory. Important is also anti-oxidant effect that could attenuate CNS vulnerability to neuronal degeneration[13-16]. Physical activity training influences the CNS non-specifically – it induces new angiogenesis and increases cerebral blood flow without cortical reorganization[17] and it exerts a prophylactic influence on the cerebral atrophy observed earlier while preserving neuronal integrity[18].

Motor/skill acquisitions and Technology based PTs are interventions that systematically train damaged function. The repetition of new and complex movements induces a substantial cortical network reorganization topographically closely related to the trained movement that leads to a synaptogenesis process[17,19]. In MS, white matter changes have already been documented following several different motor/skill acquisition PTs such as the training of isometric visual-motor tracking task[12], visual feedback training with a video game balance board[10], active and passive motor rehabilitation[8] or constraint-induced movement therapy[7].

Neuroproprioceptive "facilitation, inhibition" (neurofacilitation) PT enhances the effectiveness of the synaptic connections among neurons forming functional networks, which leads to the evocation of movement by some otherwise weak and insufficient stimuli. A suitable combination of afferent stimuli modulates interneuronal systems, repeatedly activates motor programs at the subcortical level, and as such induces adaptive and plastic processes of the CNS[11,20] . Only few studies have investigated cortical network reorganization following neurofacilitation PT, however, they showed that such approach affects various brain structures involved in motor control[11,20-22]. This could lead to the structural changes that were investigated only in our two pilot studies, which both documented a significant increment of FA following Motor Program Activating Therapy (MPAT)[9,11]. The exploration of whether also other neurofacilitation PT influences white matter integrity could help to understand the mechanism of the treatment and develop more effective therapeutic application for the future.

Moreover, it is important whether there is a correlation between the clinical improvement and white matter changes. Until now, only two studies[7,10] found such association, although several studies[8-12] looked for it.

This study investigates whether neurofacilitation PT induces white matter integrity changes (increased FA) and whether these changes relate to clinical improvement.

Based on previous research, we hypothesised that neurofacilitation PT would have positive effect on clinical outcomes (decrease of symptom severity)[9, 11, 22-24] and white matter integrity (increased FA)[9, 11]. Our pilot studies[9, 11] explored FA changes only in one region of interest – in corpus callosum. Such approach used to be standard, but now there is technically easier to explore white matter integrity changes in the whole brain (global white matter integrity) and explore more regions of interest (in this study, 48 regions were additionally analysed). Functional magnetic resonance studies documented a network reorganisation in multiple brain structures following neurofacilitation PT[11,20,22], so changes in global white matter integrity and more regions of white matter were expected in this study.

Further, we expected that the three different types of neurofacilitation PT (Vojta's reflex locomotion - standard neurofacilitation approach, and MPAT and Functional Electric Stimulation in Posturally Corrected Position - newly developed approaches, used in the Czech republic) will not differ in their effect on both clinical outcomes and white matter integrity, because they use the same principles - interfere with the neuronal tactility threshold by combining different stimuli and repeatedly activate global motor programs[9,11,20].

Finally, we hypothesized that the effect of neurofacilitation PT on clinical outcomes and white matter integrity would correlate.

Materials and methods

Study design

The Three-Arm Parallel-Group Exploratory Trial (NCT04355663) was realized between May 2015 and May 2017. MS patients were divided into three groups by an independent study coordinator according to availability of each therapist (in Groups 1 and 2) and the amount of FES devices to borrow (in Group 3) (according to the 'real-life' personalized rehabilitation process), and underwent three kinds of neurofacilitation PT. At baseline and after the end of the two months' ambulatory therapeutic program, white matter integrity was estimated from DTI and a blinded assessor evaluated clinical outcomes.

Participants

Patients with defined MS[25] were recruited from the MS Centers of Hospitals in the Czech Republic in accordance with the following inclusion criteria: prevailing spastic paraparesis, stable clinical status and treatment in the preceding 3 months determined by a neurologist, Expanded Disability Status Scale score (EDSS)[26] $\leq$ 7.5. The study was powered in order to provide 80% power for weak to moderate effect size (Cohen's d=0.2-0.5). All subjects signed an informed consent form approved by the Ethics Committee of Kralovske Vinohrady University Hospital in Prague (full trial protocol EK-VP/22/0/2014 is available there).

Interventions

All groups underwent two months' ambulatory neurofacilitation PT led by well-educated (MSc.), experienced (at least two years' practice with pwMS) therapists specially trained in each method. Treatments were individually designed according to patient status. The therapists offered their full help and adopted the schedule, so each patient was able to

complete the whole program. To increase adherence, therapists provided effective reminders and established confidential relationships.

Motor program activating therapy (Group 1)

In this therapy, participants underwent 16 face-to-face sessions (1 hour, twice a week for two months). They were corrected into a postural position where the joints were 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 lying, sitting, standing up or moving forward[11].

The duration and intensity of treatment was modified according to the response to the stimuli. A set of stimuli was 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 the 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 were continuously changing 7-10 times in each position. The complete stimulation usually took 10-20 minutes[22].

Activated programs were repeated under various conditions and in different situations and environments to teach the patients to automatically use the acquired motor skills in daily life[11]. Therapy was realized at Faculty Hospital Royal Vineyard.

Vojta's reflex locomotion (Group 2)

In this therapy[27],participants underwent 16 face-to-face sessions (1 hour, twice a week for two months).

Patients were 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 the process of verticalization (kneeling position). Most of activation zones (trunk zone, acromion, scapula, epicondylus medialis humeri, processus styloideus radii, spina iliaca superior anterior, musculus gluteus, epicondus medialis femoris, calcaneum) and their combination were stimulated with precise localization and pressure direction. The pressure was applied manually by a therapist using his/her thumb placed on one of the predefined zones. This sustained manual pressure stimulation of specific points on the skin surface ("stimulus points" or "stimulation/reflex/trigger zones") gradually evoked 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 was activated[22]. Therapy was realized at Motol University Hospital.

Functional Electric Stimulation in Posturally Corrected Position (Group 3)

In this therapy, participants first underwent individual two-hour session consisting of postural correction using MPAT and the device (The WalkAide® System, Innovative Neurotronics Inc., 4999 Aircenter Circle, Suite 103 Reno, NV 89502, USA) programming to produce electrical stimuli to the common peroneal nerve and anterior calf muscles through surface adherent electrodes to induce muscle contractions that mimic normal voluntary gait movement (lifting the foot during the swing phase of gait and achieving correct placement on the ground). Then patients received the device to be used as much as they felt able to during their normal daily activities. After fourteen days, the patients received the second individual two-hour session and underwent one hour of the postural correction by MPAT. The patients then continued to use the device daily for the next six weeks. The number of applied stimuli per day (1190.5 on average) and hours of using the device per day (6.5 hours on average) was monitored by the WalkAide® System[24]. All sessions were led individually face to face at the ambulatory unit of the Department of Neurology, Kralovske Vinohrady University Hospital in Prague.

Examination

Clinical outcomes

Demographic and anamnestic data were collected by a neurologist, namely gender, age, length of disease, type of MS (relapsing-remitting, primary or secondary progressive) and EDSS.

The balance (Berg Balance Scale, BBS[28], and Timed up and go – TUG[29]) was examined and patient-reported outcomes (the 12-item Multiple Sclerosis Walking Scale, MSWS-12[30], and MS impact with the 29-item Multiple Sclerosis Impact Scale, MSIS-29[31]) were collected.

White matter integrity

All participants underwent magnetic resonance imaging on a 3T magnetic resonance scanner (Siemens Trio Tim, Erlangen, Germany) using a 12-channel phased-array head coil. The acquisition protocol consisted of T1-weighted and T2-weighted anatomical scans, and diffusion weighted imaging using spin echo epi sequence with the following parameters: TR=9100 ms, TE=96 ms, FOV=260x211 mm, 64 contiguous axial slices with 2 mm thickness, b=0 and 1100 s/mm2, 64 gradient directions.

For the DTI pre-processing, a combination of FSL tools (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fslwiki, version 5.0) and MRtrix3 was used. The data was initially de-noised and corrected by applying the MRtrix dwidenoise function and Gibbs ringing correction[32]. The resulting images were visually controlled, and the volumes with substantial motion artefacts or signal dropout were discarded. Subsequently, the 'Eddy current correction' was applied[29,33].

FA global change and changes in 48 regions of interest

Using FSL bet function and MRtrix3 function dwi2tensor the images were skull-stripped and a diffusion tensor was fitted to each voxel of the brain, and a fractional anisotropy (FA) map

was created for each subject[34]. The default parameter values were used in the procedure. Fractional anisotropy is a standard DTI measure, which is described by a scalar value between 0-1. It represents a fraction of diffusivity that is anisotropic. While 0 signifies anisotropic diffusion, one implies the diffusion is entirely restricted to a single direction; higher FA values are generally observed in white matter tracts that have dominant direction of water diffusion along the axonal fibres, while the decrease of FA can be interpreted as the decrease of integrity of white matter. The images were further analysed using tract-based spatial statistics (TBSS)[35]. The TBSS routine consisted of three steps: 1) non-linear registration of all FA images to a chosen template – we chose the FMRIB58_FA standard-space image as a target. This step ensures that the images are spatially aligned across patients. 2) application of the non-linear registration identified in the first step, affine registration of each subject to MNI152 space and skeletonization of the mean image. The skeletonization, i.e. creation of the mean skeleton, consists in finding a smaller set of voxels positioned along the core of each tract, and serves to reduce the number of voxels on which the subsequent analysis is carried out. 3) thresholding of the mean skeleton (we used 0.3 as a threshold) and a projection of individual subjects FA maps onto the mean skeleton. Primarily, the (global) mean of the projected FA values over the whole skeleton were compared among subjects.

The resulting skeletonized images were parcellated using the ICBM-DTI-81 white- matter labels atlas consisting of 48 regions[36], and the mean FA value for each region was computed (regions are listed in Table 3).

Statistical analysis

The resulting dataset was further analysed using the non-parametric Wilcoxon test for assessing the difference between visits. Differences between the treatment groups were identified using the Kruskal-Wallis test. All statistical analyses were performed using Matlab

(MATLAB version R2018b). Note that the region-wise analysis was considered exploratory so that there was used an uncorrected significance threshold of 0.05 to select the strongest effects for description. Due to the multiple undertaken tests, many of the presented localized effect results can constitute false positive findings, and thus the observed effects serve rather as initial findings calling for independent validation in a follow-up study. The conservative Bonferroni-corrected threshold across 48 regions would correspond to 0.05/48~=0.0001, which was not reached by any single one of the effects. However, this is to be expected, as the study sample size was not designed for confirmatory testing of such a large set of hypotheses, but rather for global effect testing. This additional exploratory analysis is intended to provide the reader with further information on the presence/absence and spatial distribution of any potential localized effects outside the global hypotheses testing.

Results

Baseline characteristics

120 people were initially assessed for eligibility, 92 were allocated into three groups; from these 71 participants finished their therapeutic programs (Figure 1). Data of ten patients were discarded upon the visual control, due to the low quality of DTI acquisition resulting in 61 participants entering the central analysis. Their distribution into groups and baseline characteristics see in Table 1.

The effect of the neurofacilitation therapy (irrespective of the type of therapy)

A significant improvement of balance measured by BBS (p=0.0089) (Table 2) was followed by a decrement of FA in the right anterior corona radiata (p=0.0081, without correction for multiple testing) (Figure 2, Table 3). No global FA change (p=0.9687) (Table 2) was detected.

Differences between groups

There were differences between the groups in the treatment effect.

MPAT showed the highest effect on clinical outcomes, with the improvement of BBS (p=0.0016) (the difference between groups was significant, p=0.0330).

VRL was associated with the strongest FA change, in particular with a statistically not significant decrease of global FA (p=0.0942) (the difference between groups was not significant p=0.1947),

Moreover, the exploratory analysis (uncorrected statistical threshold) suggested tentative FA changes among the treatment groups in the left stria terminalis (p=0.0217) and right superior longitudinal fasciculus (p=0.0381). In both regions, FA increased after MPAT and FES therapy, whereas a slight decrease was observed after VRL.

Correlations between clinical function changes and fractional anisotropy changes

Exploratory analysis for specific correlates of clinical function changes revealed several effects, however, none of them survived the correction for multiple testing.

In particular, the improvement of MSIS was followed by an increment of FA in the right superior fronto-occipital fasciculus (a part of the anterior internal capsule) (r=0.2959, p=0.0283) and by a decrement of FA in left posterior thalamic radiation (including optic radiation) (r=-0.2720, p=0.0446).

The improvement of MSWS was followed by an increment of FA in the left posterior limb of the internal capsule (r=0.3815, p=0.0040) and by a decrement of FA in the pontine crossing tract (r=-0.3061, p=0.0231) and left medial lemniscus (r=-0.2836, p=0.0359).

Significant correlations between clinical function and global FA changes were not observed.

Adverse events

An increased number of falls in one participant potentially related to the use of FES (five falls per day when using FES while any without FES) was reported in Group 3, which resulted in his drop out from the study.

Discussion

The effect of neuroproprioceptive ”facilitation, inhibition” PT on clinical outcomes

Until now, only a few studies have defined their intervention as a neuropropriceptive “facilitation, inhibition” approach (previously named as neurotherapeutic facilitation) and documented its effectiveness[9,11,22-24]. Also in this study, the positive effect on clinical outcomes was confirmed. BBS improved significantly, similarly as in other studies[23,24], however, it did not reach a minimal clinically important change (MCID) set as an increase of 2 points or more in outpatients[37]. Moreover, participants felt subjectively better; there was a trend for the improvement in MSIS-29, unfortunately again without MCID (that was set as the decrement of 8 points)[38] .

The improvement on the Berg Balance Scale was mainly driven by the MPAT and this time it also reached MCID. MPAT also led to the improvement in TUG that reached MCID (set as the decrement of 2 seconds and more[37]) similarly to our previous study[23].

Neuroproprioceptive “facilitation, inhibition” approach improved balance outcome probably due to following physiological explanation. An appropriate combination of afferent stimuli in precisely given postural positions activates the motor programs that lead to a motor reaction of the whole body. We can see the muscle synchronization (the co-contraction of an agonist and an antagonist), the functional centration (the best possible distribution of the load at the articular surfaces), the postural stabilisation in the sagittal plane in the whole body in each of the activated motor functions similarly as in the ontogenesis[39].

Considering the above, it seems that any of neuroproprioceptive approaches can improve different kind of clinical and functional outcomes.

The effect of neuroproprioceptive "facilitation, inhibition" PT on white matter integrity

In this study, we did not observe a global change of FA in MS patients after two months of PT except for a trend for the of FA after VRL. The analyses of the global changes (microstructural changes in the whole brain) are unique in this study and as such they are incomparable with other studies.

The consequent investigation of 48 regions of JHU atlas found a significant decrement only in the right anterior corona radiata (p=0.0081, without the correction for multiple testing). Apart from this study, all regions in the whole brain were monitored only in the next two studies[7,12], and only Barghi et al. 2018[7] described significant changes (in the ipsilateral posterior corpus callosum and contralateral superior occipital gyrus). The majority of studies have investigated changes in the chosen regions of interest – in the corticospinal tract[9], cingulum[5], corpus callosum[5,8,9,11], superior longitudinal fasciculi[8] and cerebellum[10]; they were only confirmed in the corpus callosum[8, 9], corticospinal tracts[8] and cerebellum[10]. Any other study found changes in anterior corona radiata as we did in this study. It could be either a random finding or a change connected with PT, because this region plays a role in motor control. Anterior corona radiata namely consists of the descending efferent fibres from the frontal and prefrontal motor cortices that mainly projects by fronto-pontine projection to the precerebellar nuclei of the brain stem, but may also constitute the cortico-bulbar part of extrapyramidal motor systems[40].

Most previous studies[5,7,9,11] documented an increment of FA following PT that was interpreted as an improvement. In this study, we found significant decrement of FA in the right anterior corona radiata. Similarly Bonzano et al., 2014[8] described a decrement of FA in

the superior longitudinal fasciculi, but they interpreted it as a lack of treatment effects on this structure; showing damage progression was likely due to a demyelination process.

In this study, we did not exactly know where in the CNS the acute inflammatory process (that would manifest with a decrease in FA) and where the chronic degenerative process (that would manifest with an increase in FA) was in time of therapy located. In the phase where inflammation and demyelinization prevails[41], we could expect re-myelinization processes followed by an increase in FA, while in the phase where axonal loss prevails[(42)], axonal reorganization connected with a decrease in FA could be expected following PT.

We also did not know, where in the CNS pathological processes prevail. Although it is known that FA varies depending on lesion localization[43], studies have only evaluated microstructural changes following PT in MS in the brain[5,7-12]. No one has documented the consequences of spinal cord lesions on brain white matter integrity (an increment of FA is expected). Based on high contemporary research that confirmed spinal cord recovery following targeted neurotechnologies[44], an effect of PT on both the spinal cord and terminal brain could be expected. In this case, FA in the brain could decrease.

Further, microstructural changes would probably be dependent on which phase of motor learning each participant in our study was situated. While in the early motor control phase (characterized by synthesis of various proteins), changes of FA are not expected; in the later phase, an increase of synapse numbers and motor map reorganization has been documented[2,45], and so, FA changes would be expected.

Finally, each participant in this study could react to the therapy differently. The therapy could support repair or compensatory strategies or stimulate adaptive responses, and as such it could influence the recovery differently. Repair refers to molecular and cellular changes that can restore functions of the damaged system by itself (e.g. new oligodendrocytes from progenitors and remyelinization, restoration of normal conduction and glial trophic support for axons).

Compensation involves behavioural changes leading to an altered strategy for task completion (e.g. better postural strategy improves upper extremity function). Adaptation involves recruitment of the same pathway that is being used prior to the damage, or undamaged parallel pathways that could manifest as existing latent corticocortical connections, synaptic rearrangements, and axonal growth coupled with new synapse formation[45, 46].

It was expected that all neurofacilitation PTs in this study would induce white matter integrity changes similarly, because they all use the same principles, but there was no significant difference in the FA global change among treatment groups. Only an FA decrease trend after VRL was observed, while no substantial change was observed after FES or MPAT. In exploratory analysis in 48 regions of interest, we observed differences among treatment groups in the left stria terminalis and right superior longitudinal fasciculus. Differences could be either a random finding or caused by PT, because afferent stimuli induce plastic changes via transient peripheral[20] stimuli (MPAT and VRL by manual, mainly proprioceptive, FES in PCP by electrical stimuli) and the repetition of an activated motor program, a basic premise for learning and re-learning[45].

Therefore, it seems that clinical improvement following neuroproprioceptive PT could change FA in both directions depending on acute or chronic brain pathophysiological processes, the localization of damage throughout different levels of the CNS, different phases of motor learning and different processes in the neural networks following a recovery process (repair, compensation or adaptation).

Changes in clinical outcomes and their correlations with FA changes

In this study, the improvement of MSIS correlated with the increment of FA in the right superior fronto-occipital fasciculus (a part of the anterior internal capsule) and the decrement of FA in the left posterior thalamic radiation (including optic radiation). The improvement of

MSWS was correlated with the increment of FA in the left posterior limb of the internal capsule and the decrement of FA in the pontine crossing tract and left medial lemniscus. Only next two studies[7,10], confirmed correlations between the clinical improvement and microstructural changes, Prosperini et al., 2014[10] in the left and right superior cerebellar peduncles, and Barghi et al., 2018[7] in ipsilateral posterior corpus callosum and contralateral superior occipital gyrus. The next two studies[5,12], did not confirm any correlations and others[8,9,11,47,48], found only an association between the clinical improvement and microstructure changes. Correlations in our study look inconsistent, similarly as in other studies[7-12], however, further verification is necessary, because as follows from post-stroke rehabilitation study[44], such correlation could be a good descriptor of functional recovery.

Study contributions and limitations

The investigation of microstructural changes of white matter tracts remains challenging. Studies monitoring structural brain plasticity enhanced by PT in MS[5, 7, 9-12] differ for example in design, sample size, participant characteristics, as well as the analyses used.

Studies looking for white matter integrity changes following PT were three randomized controlled trials[5, 7, 8] and one randomized, two-period crossover pilot study[10], while the others were non-randomised pre-post comparison studies[9, 11, 12]. This study was designed as Three-Arm Parallel-Group Exploratory Trial with the aim to address more than one research question – to verify an effect of neurofacilitation PT (three therapy types increase amount of participants) and to find correlations between white matter changes and the clinical improvement. Although somebody could criticize missing control group, we are convinced that, for our purpose, the chosen design was sufficient.

In comparison to other studies[5,7,9-12], this study has the largest sample size, even at the end of the study after the drop out. This sample provides 80% power to detect at $p<0.05$ effects of

minimal size d=0.36 (weak to moderate effect size). Yet, together with the heterogeneity of MS patients, it is also a limitation of this study. In particular, while the study is adequately powered to detect the clinical effects of the treatment and is larger than those conducted previously[9, 11], still the sample size may not be sufficient for: i) detecting potential weak changes in individual treatment subgroups, ii) small differences among the treatments and iii) for confirmatory analysis of a large set of localization hypotheses for the FA changes. Although we provide the results of exploratory analysis for all 48 white matter regions using the uncorrected statistical significance threshold of 0.05, they should be interpreted with care and used to provide more specific hypotheses for further validation.

Although all participants fulfilled inclusion criteria and were divided into groups independently, they differed at baseline characteristics (except for EDSS) and at clinical outcomes. Participants in Group 1 were older, had longer disease duration and almost half of them had secondary MS, while participants in Group 3 had more balance impairment. On the other side, all groups had comparable white matter integrity. The non-uniform distribution of participants within groups caused by different availability to undergo therapy and limited supply of the FES device may decrease the comparative power among the methods (particularly for the FES device). Moreover, groups differed in compliance with the treatment (95.23% to MPAT, 51.72% to VRL and 81% FES in PCP). On the other hand, this study brings information about personalized rehabilitation in 'real-life' settings.

FA is not the only parameter available for the identification of white matter changes, other measures (e.g. mean, axial or radial diffusivity) could have also been used for the purpose, however, since the regional analysis of the white matter integrity was only considered exploratory, we decided to use only FA as it belongs to the most widely reported one[5,7,9-12].

Conclusion

Neuroproprioceptive "facilitation/inhibition" PTs (led mainly by Motor Program Activating Therapy) were confirmed to induce clinical improvement (Berg Balance Scale), but not global white matter integrity changes (only a trend for decrement of fractional anisotropy after Vojta's reflex locomotion). Additional exploratory analysis confirmed significant decrement of FA in the right anterior corona radiate, trends for correlations between the clinical improvement and fractional anisotropy in several regions (the right superior fronto-occipital fasciculus, the left posterior thalamic radiation, the left posterior limb of the internal capsule, the pontine crossing tract and left medial lemniscus), and differences among treatment groups in the left stria terminalis and right superior longitudinal fasciculus.

Therefore, neuroproprioceptive "facilitation and inhibition" PTs improved balance without much evidence of white matter integrity changes in people with multiple sclerosis. Of course, given the moderate sample size and limited sensitivity of neuroimaging measurements of white matter integrity, it is important to point out that the absence of evidence does not constitute the evidence of absence.

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NOTES

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TABLES

Table I. —Participant characteristics

	all PT	MPAT	VRL	FES	p-value
female/male (sum)	38/23 (61)	25/10 (35)	7/6 (13)	6/7 (13)	0.2144
Age in years (std; min; max)	48.11 (11; 22;70)	51 (10.7; 29; 70)	42.3 (10.5; 22; 63)	46.15 (10.1; 29.0; 60)	0.0368
Type of MS (RR, SP, PP)	34; 20; 6	17; 15; 2	11; 1; 1	6;4;3	0.0622
Length of MS in years (std; min; max)	12.72 (7.0; 1; 38)	14.2 (7.4; 4; 38)	8.38 (5.1; 1.0; 15)	13.15 (6.1; 2.0; 21)	0.0379
EDSS (min; max)	4 (1.0; 7)	4 (1.0; 7)	4 (1.0; 6)	4 (2.0; 7)	0.5571

RR relaps-remitent MS, SP secondary progressive MS, PP primary progressive MS, EDSS Expanded Disability Status Scale score, MPAT Motor Program Activating Therapy, VRL Vojta reflex locomotion, FES Functional electric stimulation, all PT Neuroproprioceptive "facilitation and inhibition" interventions (MPAT+VRL+FES)

Table II.—**An immediate effect of neuroproprioceptive "facilitation and inhibition" interventions on clinical functions and global FA**

	All PT			
	before mean (SD)	**after mean (SD)**	**the absolute difference**	**p-value**
BBS	41.44 (12.72)	41.44 (12.72)	1.26	0.0089
TUG	16.11 (16.42)	16.11 (16.42)	-1.15	0.144
MSIS-29	70.66 (18.92)	70.66 (18.92)	-3.32	0.0638
MSWS-12	36.75 (12.08)	36.75 (12.08)	-1.6	0.2565
global FA	0.5089 (0.0293)	0.5089 (0.0293)	-0.0005	0.9685
	MPAT			
BBS	50.54 (7.18)	49.85 (7.53)	2	0.0016#
TUG	9.62 (4.01)	9.00 (3.49)	-2.7	0.1262
MSIS-29	63.15 (15.40)	58.08 (15.11)	-4.6	0.0583
MSWS-12	29.38 (14.04)	32.15 (12.30)	-2.6	0.132
global FA	0.5233 (0.0266)	49.85 (7.53)	0	0.6002
	VRL			
BBS	50.54 (7.18)	49.85 (7.53)	-0.69	0.2266
TUG	9.62 (4.01)	9.00 (3.49)	-0.62	0.3799
MSIS-29	63.15 (15.40)	58.08 (15.11)	-5.07	0.1309
MSWS-12	29.38 (14.04)	32.15 (12.30)	2.77	0.6758
global FA	0.5233 (0.0266)	0.5207 (0.0284)	-0.0026	0.0942

	FES			
BBS	34.15 (11.07)	35.38 (11.56)	1.23	0.1641
TUG	15.92 (8.82)	17.85 (12.82)	1.93	0.8672
MSIS-29	69.46 (19.60)	71.38 (22.79)	1.92	0.5693
MSWS-12	42.62 (13.04)	39.31 (14.94)	-3.31	0.7178
global FA	0.5027 (0.0293)	0.5028 (0.0305)	0.0001	0.946

BBS Berg Balance Scale, TUG Timed Up and Go, MSIS-29 Multiple Sclerosis Impact Scale, MSWS-12 The Multiple Sclerosis Walking Scale-12, FA Fractional anisotropy, MPAT Motor Program Activating Therapy, VRL Vojta's reflex locomotion, FES Functional electric stimulation, NA not applicable, all PT Neuroproprioceptive "facilitation and inhibition" interventions (MPAT+VRL+FES), SD standard deviation

#significant difference between groups

Table III.— Changes of FA in 48 regions of interest

ROI name	Before mean (SD)	After mean (SD)	difference	p-value
Anterior corona radiata R	0.464 (-0.043)	0.462 (-0.043)	-0.003	0.008*
Superior longitudinal fasciculus L	0.509 (-0.034)	0.511 (-0.033)	0.002	0.073
Sagittal stratum R	0.523 (-0.055)	0.526 (-0.054)	0.003	0.093
Uncinate fasciculus L	0.506 (-0.064)	0.500 (-0.061)	-0.006	0.096
Posterior limb of internal capsule R	0.673 (-0.030)	0.676 (-0.028)	0.002	0.117

Fornix	0.420 (-0.104)	0.428 (-0.107)	0.007	0.127
Inferior cerebellar peduncle R	0.566 (-0.039)	0.562 (-0.036)	-0.005	0.136
Anterior limb of internal capsule L	0.602 (-0.029)	0.600 (-0.028)	-0.002	0.167
Genu of corpus callosum	0.731 (-0.054)	0.730 (-0.054)	-0.001	0.202
Stria terminalis L	0.533 (-0.052)	0.536 (-0.052)	0.003	0.232
Superior fronto-occipital fasciculus L	0.482 (-0.041)	0.488 (-0.043)	0.006	0.240
Tapetum L	0.548 (-0.117)	0.551 (-0.115)	0.003	0.264
External capsule L	0.461 (-0.031)	0.462 (-0.030)	0.001	0.306
Anterior corona radiata L	0.452 (-0.042)	0.451 (-0.043)	-0.001	0.313
Splenium of corpus callosum	0.773 (-0.054)	0.772 (-0.053)	-0.001	0.323
Cerebral peduncle R	0.690 (-0.036)	0.688 (-0.036)	-0.002	0.371
Uncinate fasciculus R	0.552 (-0.060)	0.548 (-0.057)	-0.005	0.419
Pontine crossing tract	0.515 (-0.038)	0.519 (-0.038)	0.004	0.440
Medial lemniscus R	0.603 (-0.038)	0.606 (-0.039)	0.003	0.484
Sagittal stratum L	0.516 (-0.050)	0.515 (-0.050)	0.000	0.516
Posterior thalamic radiation R	0.548 (-0.060)	0.548 (-0.062)	-0.001	0.534
Inferior cerebellar peduncle L	0.549 (-0.040)	0.551 (-0.038)	0.002	0.554
Corticospinal tract R	0.568 (-0.044)	0.570 (-0.041)	0.002	0.558
Posterior corona radiata L	0.449 (-0.047)	0.448 (-0.048)	-0.001	0.558
Cingulum R	0.561 (-0.056)	0.562 (-0.055)	0.001	0.563
Cingulum L	0.618 (-0.056)	0.617 (-0.056)	-0.001	0.618
Posterior corona radiata R	0.464 (-0.053)	0.463 (-0.053)	-0.001	0.638
Superior longitudinal fasciculus R	0.513 (-0.034)	0.512 (-0.035)	0.000	0.643

Medial lemniscus L	0.606 (-0.036)	0.603 (-0.036)	-0.002	0.654
Cingulum R	0.570 (-0.059)	0.570 (-0.057)	0.000	0.659
Posterior limb of internal capsule L	0.670 (-0.030)	0.671 (-0.027)	0.001	0.696
Retrolenticular part of internal capsule R	0.593 (-0.041)	0.594 (-0.039)	0.001	0.696
Posterior thalamic radiation L	0.531 (-0.056)	0.530 (-0.057)	-0.001	0.701
Tapetum R	0.467 (-0.108)	0.465 (-0.107)	-0.002	0.728
Superior cerebellar peduncle R	0.677 (-0.044)	0.677 (-0.049)	0.000	0.755
Superior fronto-occipital fasciculus R	0.543 (-0.040)	0.542 (-0.045)	0.000	0.755
Corticospinal tract L	0.569 (-0.046)	0.571 (-0.043)	0.003	0.793
Retrolenticular part of internal capsule L	0.598 (-0.039)	0.599 (-0.041)	0.001	0.804
Superior corona radiata R	0.472 (-0.031)	0.472 (-0.031)	0.000	0.804
Superior cerebellar peduncle L	0.685 (-0.046)	0.685 (-0.047)	0.000	0.827
Stria terminalis R	0.527 (-0.053)	0.526 (-0.053)	0.000	0.832
External capsule R	0.455 (-0.033)	0.456 (-0.034)	0.000	0.855
Cingulum L	0.541 (-0.057)	0.542 (-0.055)	0.001	0.889
Middle cerebellar peduncle	0.581 (-0.030)	0.581 (-0.028)	0.000	0.923
Body of corpus callosum	0.691 (-0.061)	0.689 (-0.062)	-0.002	0.940
Anterior limb of internal capsule R	0.614 (-0.033)	0.614 (-0.031)	0.000	0.969
Cerebral peduncle L	0.679 (-0.041)	0.679 (-0.039)	0.000	0.986
Superior corona radiata L	0.476 (-0.032)	0.476 (-0.033)	0.000	0.986

Mean and standard deviation (SD) of average FA in each region of interest before and after treatment, together with the difference, sorted by the corresponding p-value

(Wilcoxon test); R: right; L: left. Note: p values are not corrected for multiple comparisons; * marks $p<0.05$

TITLES OF FIGURES

Figure 1.— Flow chart diagram

Figure 2.— Right anterior corona radiata, region where FA significantly decreased immediately after neuroproprioceptive "facilitation and inhibition" rehabilitation

Right anterior corona radiata (as defined by the JHU white matter atlas) is highlighted in red: in this region, the FA significantly decreased after the neuroproprioceptive "facilitation and inhibition" physical therapy. The MNI coordinates of the cross-hair and of the visualized sagittal (left), coronal (middle) and axial (right) sections are [21,30,18] mm.