Official Title: Neuroproprioceptive Facilitation and Inhibition Physical Therapy Activates Adaptive and Plastic Changes in the Central Nervous System

Brief Title:Neuroproprioceptive "Facilitation, Inhibition" and Brain Plasticity (NEFAI)

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Methods

1.1. Study design

The Multi-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 amount of FES devices to borrow (in Group 3), and underwent three kinds of PT. At baseline and after the end of the two months' therapeutic program, white matter integrity was estimated from DTI and a blinded assessor evaluated clinical outcomes.

1.2. Participants

Patients with defined MS (13) were recruited from the MS Centers of Hospitals in the Czech Republic in accordance with the following inclusion criteria: prevailed spastic paraparesis, stable clinical status and treatment in the preceding 3 months determined by neurologist, Expanded Disability Status Scale score (EDSS) $\leq$7.5 (14). The study was powered in order to provide 80% power for weak to moderate effect size (Cohen's d=0.2-0.5). 120 people were initially assessed for eligibility, 92 were allocated into three groups; from these 71 participants finished their therapeutic programs. 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. This sample provides 80% power to detect at $p<0.05$ effects of minimal size d=0.36 (weak to moderate effect size). For distribution of participants into groups during the study see Figure 1, for their baseline characteristics see Table 1. 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).

1.3. Interventions

All groups underwent two months' ambulatory neuroproprioceptive 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.
Group 1 underwent 16 face-to-face sessions (1 hour, twice a week for two months) of MPAT (10), method developed and verified by our team. In this therapy, patients are corrected into a postural position where the joints are functionally centered. Afferent stimuli are then 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. Activated programs are repeated under various conditions and in different situations and environments to teach the patients to automatically use the acquired motor skills in daily life. Therapy was realized at Faculty Hospital Royal Vineyard.
Group 2 underwent 16 face-to-face sessions (1 hour, twice a week for two months) of VRL (15), which is a standard approach for patients with MS in the Czech Republic. During the therapy, global patterns of the reflex locomotion are activated by stimulation of specific zones, with the individual placed in a precisely determined initial position (supine, prone and side laying, low kneeling position). These movement patterns have the qualities of the forward movement (locomotion) and the

movement responses are precisely defined. Reflex locomotion (reflex turning and reflex creeping) is used in therapy to activate involuntarily responses of muscle function, which are necessary for spontaneous movements. Therapy was realized at Motol University Hospital.

Group 3 underwent FES in PCP (16), a method developed at our workplace. 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. Patients received the device to be used use as much as they felt able to during their normal daily activities.. After fourteen days, the patients received the second individual two-hour session. The patients then continued to use the device daily for the next six weeks.

1.4. 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 (17) and Timed up and go – TUG (18)] was examined and *patient-reported outcomes* [the 12-item Multiple Sclerosis Walking Scale, MSWS-12 (19) and MS impact with the 29-item Multiple Sclerosis Impact Scale, MSIS-29 (20)] were collected.

1.5. 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 following parameters TR=9100 ms, TE=96 ms, FOV=260x211 mm, 64 contiguous axial slices with 2 mm thickness, b=0 and 1100 s/mm^2, 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 (21) and Gibbs ringing correction (22). The resulting images were visually controlled, and the volumes with low quality were discarded. The 'Eddy current correction' was subsequently applied (23).

In the context of neuroproprioceptive PT, we did not expect changes in a particular area; hence we analyzed FA across the white matter using a global changes of FA as well as FA changes in 48 white matter regions.

FA global change and changes in 48 regions of interest

A diffusion tensor was fitted to each voxel of the brain, and a fractional anisotropy (FA) map was created for each subject (24). The images were further analyzed using tract-based spatial statistics (TBSS) (25). 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; 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; 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- (26) matter labels atlas consisting of 48 regions, and the mean FA value for each region was computed (regions are listed in Table 3).

1.6. Statistical analysis

The resulting dataset was further analyzed 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.