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Is it possible to actively and purposely make use of plasticity and adaptability in the neurorehabilitation treatment of multiple sclerosis patients? A pilot project

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Objective: To investigate whether neurorehabilitation is able to influence clinical parameters and brain function measured radiologically.
Design: A group of healthy probands was compared with two groups of multiple sclerosis (MS) patients, one of which received rehabilitative therapy.
Setting: Outpatient in a university hospital.
Subjects: Twenty-eight patients with multiple sclerosis (MS), 17 of whom received rehabilitative therapy, and 13 healthy controls.
Interventions: Two months of rehabilitative eclectic therapy based on principles of sensorimotor learning and adaptation.
Main measures: Multiple Sclerosis Functional Composite, Modified Fatigue Impact Scale, Beck Depression Inventory Score, Barthel Index, Environment Status Scale and Multiple Sclerosis Quality of Life – 54, and functional magnetic resonance imaging (fMRI).
Results: Patients who underwent neurorehabilitation showed a greater drop in fatigue, depression, impairment, disability and handicap and more improvement in quality of life than those who did not receive therapy. Correlation of brain activity between the right and the left hemisphere is greater in healthy individuals than in MS patients. Neurorehabilitation resulted in a trend for increased correlation between the left and the right hemisphere in patients (approaching the standard). In comparison with control groups, signal amplitudes in anatomical areas did not show any significant changes.
Conclusion: Clinical changes seen with neurorehabilitation were not associated with any detectable changes in fMRI observations.

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Introduction

The central nervous system is plastic and therefore capable of adaptation to the changing conditions of the internal as well as external environment. Such adaptive changes may contribute to functional recovery. The adaptive changes may occur spontaneously or they can be initiated therapeutically, with the help of medication or rehabilitation treatment.[1] The pathological processes of multiple sclerosis (MS), such as demyelinization and axonal loss, cause structural damage to the central nervous system but the central nervous system is able to reduce their impact by adaptive reorganization at the level of axon, neurone, synapse or system.[2,3]

Research looks for links between brain activity changes caused by rehabilitation and the changes that indirectly characterize brain adaptation processes. These links have already been demonstrated in animal[4] and human models.[5–7] Based on the literature, it seems that stroke is a better human model for studying plasticity and adaptability of the central nervous system than MS, which is a very unstable and variable disease. It is clear at the present time that the training of a disabled limb in patients after stroke leads to changes in brain activity. However, the pattern of these changes differs in localization and size between individual studies.[8–10] In addition, it was demonstrated that these changes are dynamic and that they change with the period of time from the brain damage.[11]

The potential to make use of the plasticity and adaptability of the central nervous system in order to influence brain activity and consequently to improve clinical symptoms by means of neurorehabilitation sounds very promising. Unfortunately, there is still no scientific basis for these possibilities.

The majority of authors who have tried to evaluate the effects of neurorehabilitation of central paresis by means of functional magnetic resonance imaging (fMRI) monitored brain activity changes in response to movement training that corresponded to the movement paradigm used during the imaging examination.[12,13] However, in neurorehabilitation treatment of MS it is impossible to concentrate only on the training of an isolated movement. It is not only the muscles of the thumb and index finger that participate in the opposition of the thumb to the index finger (the movement chosen as a paradigm for fMRI examination), but also the muscles of the trunk.[14] That is why we have chosen to investigate therapy based on sensorimotor learning.[15,16] Sensorimotor learning can be perceived as a form of synaptic plasticity where the changes in synaptic connection become a physiological substrate for retaining a piece of information in one's memory. Motor learning influences the interconnection of neural networks according to the theory of information processing.[17]

First, this study tested the hypothesis that a neurophysiologically based rehabilitation that makes use of known principles of sensorimotor learning and adaptation can lead to improvement of fatigue, depression, impairment, disability, handicap and quality of life.

Secondly, we tested the hypothesis that a healthy population differs from patients with MS in the amplitude of signal in four anatomical areas that participate in sensorimotor learning. This would imply that evaluation of the amplitude of signal on fMRI is a good tool for the assessment of plasticity and adaptability of the central nervous system. We also tested whether a healthy population differs from patients with MS in the interdependence between the right and the left hemisphere.

Thirdly, we tested the hypothesis that neurorehabilitation in patients with MS could lead to the normalization of the amplitude of signal and interdependency between the left and the right hemisphere (brain function approaches to standard).

Methods

Subjects

The 41 probands were divided into three groups. The first group (experimental) consisted of 17 patients with MS who went through the physiotherapeutic programme; the second group (control group 1) comprised 11 patients with MS who did not do any special exercise. The third group (control group 2) included representatives of the healthy untrained population (13 probands) and did not do any special exercise.

The patients were chosen at random from 2500 patients of MS Centre at Department of Neurology, 1st Medical Faculty, Charles University and

VFN in Prague. The patients were all clinically stabilized outpatients with MS who came to regular medical examinations (patients with MS without any complications regularly visit the MS centre every six months), were able to move independently and walk at least 20 m with two canes (Expanded Disability Status Scale ≤ 6.5) and were indicated to and able to undergo neurorehabilitation (e.g., agreement with participation on the study, motivation to co-operate actively, ability to transport to the centre regularly).

Patients were divided into groups. The patients of the experimental group were chosen on the basis of prevalent clinical symptoms (spastic paraparesis, ataxia, tremor, fatigue, etc.) as well as on the basis of the degree of movement impairment. Patients with the most similar clinical symptoms and impairment were chosen as a counterpart to the control group 1.

Examination

fMRI

All subjects were scanned twice. For the experimental group scans were acquired before and after therapy (the therapy went on for two months). For the two control groups scans were acquired on two occasions, approximately two months apart. We used a 1.5 T Philips Gyroscan NT Scanner (Philips, The Netherlands) to acquire echoplanar images (EPI) of the whole brain in transverse 4-mm slices without gaps and overlapping with parameters: TR 3000 ms, TE 50 ms, EPI factor 50, basic matrix 64×64 reconstructed to 128×128 using field of view (FOW) 256 mm, voxel size $4 \times 4 \times 4$ mm.[18]

The oscillation of the signal in the course of alternation between rest and activity was recorded and further investigated by means of the amplitude size of the change of signal intensity in the chosen brain areas (where the changes were expected as a consequence of sensorimotor learning): primary sensorimotor cortex, supplementary motor cortex, cerebellum (ncl. dentatus) and basal ganglia (putamen).

Subjects viewed the light using an obliquely placed mirror situated on the coil above their head at the eye level, while synchronizing it with a controlled, fluent and simultaneous movement of the index finger and thumb forming a 'pinch grasp' at a frequency of one movement per 3 s.

We acquired 60 dynamic scans with a total duration of 6 m 12 s (pure time of acquisition was 6 m, preparation pulses takes 12 s). Thirty-second periods of rest alternated with 30-s periods of movement. We acquired dynamic scans for the right hand followed by the left hand. This was followed by a morphologic T1-weighted gradient fast field echo (FFE) sequence, lasting 90 s and with the same geometric parameters as the functional sequence.

The obtained data were processed using image processing software.[18] To carry out the group assessment of different probands, we transformed the magnetic resonance images of every proband from the group in question into the standard space of the Talairach brain (several tens of transformed and subsequently averaged brains from the Czech Republic). To achieve better comparability between the first and the second examination of the same proband, only the first examination was transformed to Talairach space, whereas the second one was transformed into the space of the first scan. Furthermore, on the brains averaged in this way, the fMRI signal was standardly assessed. The fMRI signal was smoothed by a spherical Gaussian filter (kernel $5 \times 5 \times 5$), the correction of slow signal change during dynamic scans was done by means of high pass filter, and the correction of fast changes caused by noise or shooting effects was carried out with a low pass filter. Using these two time filters (high and low) the signal was maximized with the frequency of 10 dynamics. This 'adjusted' signal was statistically evaluated using Pearson's correlation coefficient. The values of Pearson's correlation coefficient were plotted into the T1-weighted morphologic image.

In addition to the absolute values of amplitude of signal in the individual areas, the so-called relative values were worked out as well. For example, the relative value for supplementary motor cortex, PSMOrv, was obtained according to the following formula: PPMO – PSMO/PPMO, where PPMO is the value in the right sensorimotor cortex, PSMO is the value in the right supplementary motor cortex.

To integrate the results, we added the evaluation of group level activation. We created group average images for each of the three subject groups at each

scanning session and for left and right hand movements, making a total of 12 group average images. We calculated summary values from the group average images. We counted the volume of the brain that was activated and we defined the co-ordinates of the centre of the area. The brain activity area in the primary sensorimotor cortex and supplementary motor cortex was counted from slice 23, while the brain activity in ncl. dentatus was counted from slice 5 and putamen from slice 7. We used the co-ordinate values of the centre of the activated area prior to and after therapy to calculate the vector length of the shift of the centre.

Clinical examination

In the groups of rehabilitated and nonrehabilitated patients measures of impairment, disability, handicap and quality of life were examined by an independent therapist. Impairment was examined by means of the Multiple Sclerosis Functional Composite,[21] which assesses the function of upper extremities (nine-hole peg test) and of lower extremities (timed 25-foot walk) as well as cognitive functions (PASAT 3). It was also examined by a physiotherapist who, apart from other things, evaluated postural reactions.[19] Fatigue was evaluated by means of Modified Fatigue Impact Scale,[21] depression by the Beck Depression Inventory Score,[20] disability by Wade and Collin's modified version of the Barthel Index (we scored it from 0 to 100), Environment Status Scale[21] and Multiple Sclerosis Quality of Life-54.[21]

Therapy

Twice a week over a period of two months, the probands went through the therapy, each session lasting approximately 1 h. The neurophysiologically based therapy worked on known principles of sensorimotor learning and adaptation. Facilitation elements for each of the probands were chosen individually, according to the prevailing symptoms of the disease. Individual facilitation techniques were combined so as to achieve the best function. We employed various elements of several treatment methods in an eclectic way (Vojta's reflexive locomotion, Bobath concept, sensorimotor stimulation, proprioceptive neuromuscular facilitation, Brüger concept and yoga).[15,16]

Statistical analysis

Considering the number of performed tests it is appropriate to apply the Bonferroni correction for multiple comparisons. Each difference was considered statistically significant if the level of significance of the test was lower than or equal to 0.05 divided by the number of performed tests in the batch (k). Such a level of significance was highlighted. Using this approach, the overall significance level of the whole batch of tests is 0.05.

Before comparing groups in terms of clinical and brain activity variables, first we used the Shapiro–Wilk test to test the normality of these variables. Because the normality assumptions were not satisfied in the case of many variables (especially in the case of clinical parameters), for further analysis we preferred nonparametric tests.

To compare two independent groups (healthy volunteers and patients) as far as clinical variables or variables related to brain activity are concerned, we employed the two-sample Wilcoxon test.

The comparison of the three groups in relation to brain activity variables was carried out with the help of the Kruskal–Wallis ANOVA.

The one-sample Wilcoxon test was used to evaluate changes in parameters after the therapy or after two months for the groups without treatment.

The dependence of values corresponding to brain activity parameters in the right and in the left hemisphere was evaluated within the individual groups by means of Pearson's correlation coefficient. The correspondence of the degree of dependency between healthy volunteers and the MS patients was tested using the Fisher z-transformation.

Results

Clinical parameters

Comparison of the baseline values

Comparison of the baseline values of clinic parameters allows us to state that two groups of patients (experimental and control 1) do not differ (Table 1).

Table 1 Influence of neurorehabilitation treatment on clinical parameters

	Prior to the study					Changes (increase in values) after the study						
	Experimental		Control 1		2-sample Wilcoxon test	Experimental			Control 1			2-sample Wilcoxon test
	Mean	SD	Mean	SD	*p*-value	Mean	SD	*p*-value	Mean	SD	*p*-value	*p*-value
9 HPT right (s)	43.60	36.61	45.13	41.44	0.817	−5.81	7.18	**0.001**	1.26	3.41	0.050	< **0.001**
9 HPT left (s)	39.18	25.48	35.90	17.78	0.981	−5.26	7.84	< **0.001**	1.80	5.39	0.201	< **0.001**
T 25 FW (s)	12.26	20.73	8.03	5.16	0.888	−2.66	7.64	**0.002**	0.05	0.16	0.329	**0.001**
PASAT 3	39.12	16.81	41.45	16.82	0.778	6.41	5.41	**0.001**	−0.27	1.19	0.492	< **0.001**
PR – seat	0.53	0.80	0.91	1.14	0.420	0.94	0.24	< **0.001**	0.00	0.00	0.999	< **0.001**
PR – stand	0.53	0.80	0.91	1.14	0.420	0.88	0.49	< **0.001**	0.00	0.00	0.999	< **0.001**
MSQOL phys.	48.25	13.31	52.75	17.23	0.371	9.41	7.86	**0.001**	−2.96	4.28	0.010	< **0.001**
MSQOL psych.	58.26	18.51	58.22	20	0.890	10.18	11.57	**0.002**	−7.73	13.43	0.010	< **0.001**
MFIS	43.71	13.86	41.64	14.48	0.724	−6.03	4.69	< **0.001**	1.73	2.41	0.035	< **0.001**
BDIS	10.26	8.67	7.18	7.05	0.131	−3.50	3.66	**0.001**	−0.50	1.50	0.371	**0.001**
BI	93.53	5.80	95.00	5.00	0.572	4.56	4.70	0.007	0.00	0.00	0.999	0.005
ESS	8.03	6.06	4.50	4.64	0.119	−2.47	2.90	0.009	0.00	0.00	0.999	0.005

9 HPT, nine-hole peg test; T 25 FW, timed 25 foot walk; PR, postural reaction; MSQOL, Multiple Sclerosis Quality of Life – 54; BDIS, Beck Depression Inventory Score; BI, Barthel Index; ESS, Environment Status Scale.
Bold indicates statistically significant difference at $p < 0.05/12$, thus at the overall level of significance $p < 0.05$.
On average, there were patients with moderate neurological impairment in both groups (experimental group: mean EDSS 4.1 ± 1.4, range EDSS from 2 to 6.5, control 1 group: mean EDSS 2.8±1.8, range EDSS from 0 to 5).
Two patients groups (experimental and control 1) do not differ in the examined clinic parameters at baseline (two-sample Wilcoxon test).
Changes after the neurorehabilitation treatment are significant in the experimental group (one-sample Wilcoxon test). The amount of change in the experimental group is statistically different from the amount of change in the control group (two-sample Wilcoxon test).

Effect of neurorehabilitation on the examined clinical parameters

The members of the group participating in the rehabilitative programme displayed a significant decrease in fatigue, depression, impairment, handicap and an improvement in quality of life. In contrast, the probands of the group not participating in the rehabilitative programme did not display any significant changes in clinical parameters–only some of the clinical parameters got worse. Moreover, the amount of change in the experimental group is statistically different from the amount of change in the control group. We confirmed the hypothesis that neurorehabilitation in patients with MS leads to an improvement in the examined clinical parameters (Table 1).

Brain activity parameters

Comparison of the baseline values

Comparison of the baseline values of the amplitude of signal in four anatomical areas did not allow us to state that the mean values of the individual groups significantly differed (Table 2).

Difference between healthy people and patients with MS in brain activity

It could be seen (see Table 3) on the basis of the baseline evaluation that in some brain areas the interdependence between the right and the left hemisphere is greater in healthy individuals than in patients with MS. This means, in most cases, that the bigger the amplitude of signal in a certain area in the left hemisphere, the bigger it is in the right hemisphere. Nevertheless sometimes the correlation is negative (e.g., i PSMC rv).

We did not confirm the hypothesis that the healthy population differs from patients with MS in the amplitude of signal (Table 2).

Effect of neurorehabilitation on the amplitude of signal in anatomical areas

In the experimental group, the therapy based on neurophysiology resulted in a trend for

Table 2 Input brain activity values of all the three groups

Brain areas	Experimental		Control 1		Control 2		K-W
	Mean	SD	Mean	SD	Mean	SD	*p*-value
k PSMC r	7.21	3.42	7.24	4.23	8.73	4.04	0.408
k SMC r	6.62	2.89	6.17	4.40	4.73	3.92	0.218
k PSMC l	6.36	2.93	6.79	3.97	5.51	3.88	0.532
k SMC l	6.08	2.77	5.81	4.61	4.72	3.14	0.525
i PSMC r	1.32	1.44	0.93	1.64	1.14	1.70	0.849
i SMC r	1.48	1.89	1.40	2.25	1.91	2.64	0.967
i PSMC l	1.28	2.31	2.08	3.18	1.24	2.59	0.816
i SMC l	1.57	2.09	2.92	4.21	0.69	2.10	0.218
k PUT r	1.25	2.42	1.12	1.79	1.65	2.29	0.970
k PUT l	2.48	2.04	2.26	2.55	2.29	1.94	0.953
i CRBL r	5.49	4.71	3.05	3.41	4.25	2.89	0.329
i CRBL l	5.75	4.46	6.06	3.84	6.11	3.10	0.874
k CRBL r	3.12	4.09	0.77	3.63	2.42	2.67	0.701
i PUT r	1.54	2.35	1.40	2.23	1.87	3.31	0.908
k CRBL l	3.28	4.01	3.13	4.16	1.81	2.63	0.267
i PUT l	1.69	2.55	1.82	2.25	1.79	1.83	0.889
k SMC r rv	−0.03	0.58	0.11	0.43	0.50	0.35	0.005
i PSMC r rv	0.81	0.18	0.91	0.43	0.84	0.19	0.719
i SMC r rv	0.80	0.26	0.88	0.72	0.73	0.32	0.939
k PUT r rv	0.77	0.45	0.96	0.57	0.82	0.25	0.946
i CRBL r rv	0.26	0.60	0.66	1.12	0.50	0.28	0.302
k CRBL r rv	0.55	0.53	1.13	1.30	0.74	0.29	0.421
i PUT r rv	0.70	0.49	0.97	0.82	0.77	0.34	0.909
k SMC l rv	0.00	0.40	0.08	0.61	1.00	3.18	0.388
i PSMC l rv	0.83	0.36	1.17	1.74	−1.33	5.69	0.753
i SMC l rv	0.75	0.36	0.92	1.57	1.96	3.21	0.154
k PUT l rv	0.61	0.28	0.69	0.64	0.26	0.95	0.507
i CRBL l rv	0.12	0.49	−0.03	0.92	5.15	20.36	0.881
k CRBL l rv	0.53	0.42	0.81	1.24	1.24	2.29	0.861
i PUT l rv	0.76	0.32	0.91	0.73	1.13	2.82	0.858

K-W, Kruskal–Wallis ANOVA; PSMC, primary sensorimotor cortex; SMC, supplementary motor cortex; CRBL, cerebellum; PUT, putamen; k, contralateral; i, ipsilateral; r, during performance of right hand; l, during performance of left hand; rv, relative values.
Example: i PSMC r rv–amplitude of signal in ipsilateral primary sensorimotor cortex during performance of right hand, relative value.
No statistically significant difference at $p < 0.05/30$.

increased dependency between the left and the right hemisphere (thus approaching the standard). On the other hand, the change of interhemispheric dependence was also observed after two months in control group 1 and control group 2 (variable i PSMC in the healthy volunteers showed a large drop in dependence) (Table 4). Consequently, it is questionable whether these changes provide meaningful evidence for adaptive change.

We did not reject the equality of the mean values of the parameters before and after the therapy (or after two months) in any group (Table 5) and did not confirm the hypothesis that neurorehabilitation in patients with MS could lead to the normalization of the amplitude of signal.

We did not confirm any relationship between brain activity changes and clinical parameter changes (9-hole peg test, walking, PASAT 3). Similarly, it was not shown that the type of hand handicap could influence brain activity changes after the therapy (i.e., it is not important whether it is paresis or paralysis that is prevailing).

Table 3 Comparison of the dependency degree of corresponding parameters in the right and in the left hemisphere

Brain areas	Pearson's correlation coefficient		Fisher's *z*-transformation
	Experimental and control 1	Control 2	*p*-value
k PSMC	0.110	0.588	**0.003**
k SMC	0.234	0.533	0.057
i PSMC	0.355	0.647	0.104
i SMC	0.385	0.859	< **0.001**
k PUT	0.063	0.797	< **0.001**
i CRBL	0.343	0.59	0.087
k CRBL	0.186	0.363	0.431
i PUT	0.129	0.904	< **0.001**
k SMC rv	0.021	−0.026	0.802
i PSMC rv	0.146	−0.592	**0.001**
i SMC rv	0.131	0.447	0.153
k PUT rv	0.088	0.573	**0.003**
i CRBL rv	0.165	0.171	0.976
k CRBLrv	0.029	0.163	0.581
i PUT rv	0.069	0.354	0.219

PSMC, primary sensorimotor cortex; SMC, supplementary motor cortex; CRBL, cerebellum; k, contralateral; i, ipsilateral; rv, relative value.
Bold indicates statistically significant difference at $p < 0.05/15$, thus at the overall level of significance $p < 0.05$.

Evaluation of group level activation in the experimental group

As the probands of the three groups did not differ in the values of the amplitude of signal in anatomical areas, we complemented this method by fMRI evaluation of the co-ordinates of the centre and the surface of an activated area (Table 6) and by visual description of group level fMRI before and after therapy in the experimental group (Figure 1).

When carrying out the paradigm with the right hand, the cerebellum displayed bilateral enlargement of the activated area after therapy. When carrying out the paradigm with the left hand, the cerebellum displayed an ipsilateral decrease in activated area and a contralateral enlargement.

When carrying out the paradigm with the right and the left hand, the basal ganglia showed increased bilateral activation.

When carrying out the paradigm with the right hand, we observed reduction of the activated area in the primary sensorimotor cortex as well as in the supplementary motor cortex after therapy. When carrying out the paradigm with the left hand, we

Table 4 Change of the dependence degree of corresponding parameters in the right and in the left hemisphere after two months

Brain areas	Pearson's correlation coefficient					
	Experimental		Control 1		Control 2	
	Prior to the therapy	After the therapy	Entrance (input)	After 2 months	Entrance (input)	After 2 months
k PSMC	0.232	0.345	−0.007	0.265	0.588	0.651
k SMC	0.462	0.716	0.086	0.342	0.533	0.739
i PSMC	0.417	0.653	0.348	0.166	0.647	0.003
i SMC	0.524	0.680	0.337	0.477	0.859	0.032
k PUT	0.292	0.333	−0.328	0.425	0.797	0.361
l CRBL	0.676	0.743	−0.418	0.869	0.590	0.782
k CRBL	0.642	0.412	−0.597	0.782	0.363	0.381
i PUT	0.434	0.714	−0.450	0.456	0.904	0.329
k SMC rv	0.224	0.160	−0.282	0.089	−0.026	0.372
i PSMC rv	0.287	0.441	0.105	0.002	−0.592	0.112
i SMC rv	0.510	0.489	0.075	−0.037	0.447	0.270
k PUTt rv	0.254	−0.018	−0.026	−0.085	0.573	0.387
i CRBL rv	0.722	0.338	−0.044	−0.104	0.171	0.483
k CRBLrv	0.767	0.340	−0.197	−0.196	0.163	0.544
i PUT rv	0.456	0.410	−0.130	−0.092	0.354	0.740

PSMC, primary sensorimotor cortex; SMC, supplementary motor cortex; CRBL, cerebellum; k, contralateral; i, ipsilateral; rv, relative value.

Table 5 Difference in brain activity (the amplitude of signal in four anatomical areas) before and after the therapy (after two months of the experiment)

Brain areas	Experimental			Control 1			Control 2		
	Mean		Wilcoxon	Mean		Wilcoxon	Mean		Wilcoxon
	Before	After	*p*-value	Before	After	*p*-value	Before	After	*p*-value
k PSMC r	7.21	7.63	0.747	7.24	6.93	0.831	8.73	8.48	0.413
k SMC r	6.62	6.60	0.611	6.17	4.78	0.278	4.73	4.12	0.320
k PSMC l	6.36	5.42	0.059	6.79	5.85	0.123	5.51	5.03	0.374
k SMC l	6.08	5.31	0.065	5.81	4.25	0.102	4.72	3.27	0.032
i PSMC r	1.32	1.47	1.000	0.93	0.64	0.577	1.14	1.24	0.945
i SMC r	1.48	2.14	0.263	1.40	1.19	0.831	1.91	1.56	0.844
i PSMC l	1.28	1.67	0.579	2.08	−2.02	0.067	1.24	−0.41	0.109
i SMC l	1.57	2.53	0.190	2.92	0.89	0.206	0.69	−0.35	0.547
k PUT r	1.25	2.58	0.174	1.12	1.75	0.898	1.65	2.64	0.946
k PUT l	2.48	2.01	0.712	2.26	2.17	0.966	2.29	1.36	0.505
i CRBL r	5.49	5.98	0.963	3.05	4.15	0.765	4.25	3.91	0.946
i CRBL l	5.75	5.42	0.712	6.06	4.98	0.206	6.11	4.18	0.003
k CRBL r	3.12	3.23	0.963	0.77	2.79	0.320	2.42	1.62	0.742
i PUT r	1.54	2.26	0.611	1.40	1.56	0.638	1.87	3.40	0.844
k CRBL l	3.28	2.84	0.782	3.13	2.41	0.248	1.81	0.82	0.250
i PUT l	1.69	1.53	1.000	1.82	1.68	0.638	1.79	0.93	0.183
k SMC r rv	−0.03	−0.01	0.927	0.11	0.57	0.018	0.50	0.51	1.000
i PSMC r rv	0.81	0.80	0.795	0.91	1.11	0.563	0.84	0.87	0.688
i SMC r rv	0.80	0.71	0.190	0.88	1.04	0.365	0.73	0.74	0.106
k PUT r rv	0.77	0.55	0.098	0.96	0.71	0.477	0.82	0.50	0.413
i CRBL r rv	0.26	0.17	0.670	0.66	0.08	0.577	0.50	0.49	0.123
k CRBL r rv	0.55	0.51	0.963	1.13	0.52	0.102	0.74	0.80	0.752
i PUT r rv	0.70	0.60	0.431	0.97	0.73	0.689	0.77	0.04	0.688
k SMC l rv	0.00	0.03	0.691	0.08	2.34	0.102	1.00	0.29	0.765
PSMC l rv	0.83	0.75	0.551	1.17	−2.29	0.320	−1.33	1.11	0.156
i SMC l rv	0.75	0.56	0.231	0.92	−3.98	0.465	1.96	1.15	1.000
k PUT l rv	0.61	0.64	0.365	0.69	0.11	0.765	0.26	0.79	0.929
i CRBL l rv	0.12	−0.07	0.706	−0.03	−1.07	0.831	5.15	0.16	0.465
k CRBL l rv	0.53	0.49	0.821	0.81	−3.37	0.700	1.24	0.83	1.000
i PUT l rv	0.76	0.75	0.717	0.91	−1.78	0.831	1.13	0.88	1.000

PSMC, primary sensorimotor cortex; SMC, supplementary motor cortex; CRBL, cerebellum; PUT, putamen; k, contralateral; i, ipsilateral; r, during performance of right hand; l, during performance of left hand; rv, relative values.
Example: i PSMC r rv–amplitude of signal in ipsilateral primary sensorimotor cortex during performance of right hand, relative value.
No statistically significant difference at $p < 0.05/30$.

observed enlargement in the primary sensorimotor cortex and decrease in the supplementary motor cortex after therapy.

Discussion

The evidence that rehabilitation (in inpatient and outpatient settings) has beneficial effects on MS has already been provided by Patti *et al.*,[22] Lord *et al.*[23] and Freeman *et al.*[24] The results of the current research study are in agreement with these authors and confirm that neurorehabilitation treatment making use of the motor learning theory has a significant positive impact on the clinical parameters of patients with MS. However, our research only observed immediate effects after therapy. For future research, it would be necessary to find out how long the clinical parameter changes remain, and if and to what extent patients are able to apply rehabilitation exercises independently. This would be important for the formulation of neurophysiologically based therapy that is effective in the long term.

Table 6 Shift of the centre of the activated area and change of the surface of the activated area in the experimental group

	Right hand			Left hand		
	Vector length of the shift	Angle of the shift (degree)	Change of the surface (mm^2)	Vector length of the shift	Angle of the shift (degree)	Change of the surface (mm^2)
Primary sensorimotor cortex	2.00	90.00	−1.89	8.06	82.87	0.47
Supplementary motor cortex	3.74	15.52	−1.13	21.18	82.54	−0.65
Ncl. dentatus ipsilaterally	3.16	341.57	4.67	2.24	206.57	0.51
Ncl. dentatus contralaterally			4.30	4.12	75.96	−4.15
Putamen ipsilaterally			0.00			0.53
Putamen contralaterally			0.67			1.06

The comparison of the group of healthy probands and the two groups of patients with MS, out of which one group went through the neurorehabilitation treatment and the other did not, led to the finding that the groups did not differ in brain activity parameters and that there is no relationship between brain activity changes and clinical parameter changes either. This can probably be explained by the variability of MS, the selection and number of probands, method of evaluation (Is the fMRI method sensitive enough for the evaluation of the plasticity of the central nervous system? Is evaluation of changes of signal amplitude in anatomical areas an appropriate method?) or by the variable execution of the paradigm.

In addition, the statistical conclusiveness of the changes in the signal amplitude in anatomical areas after therapy is made more difficult by the

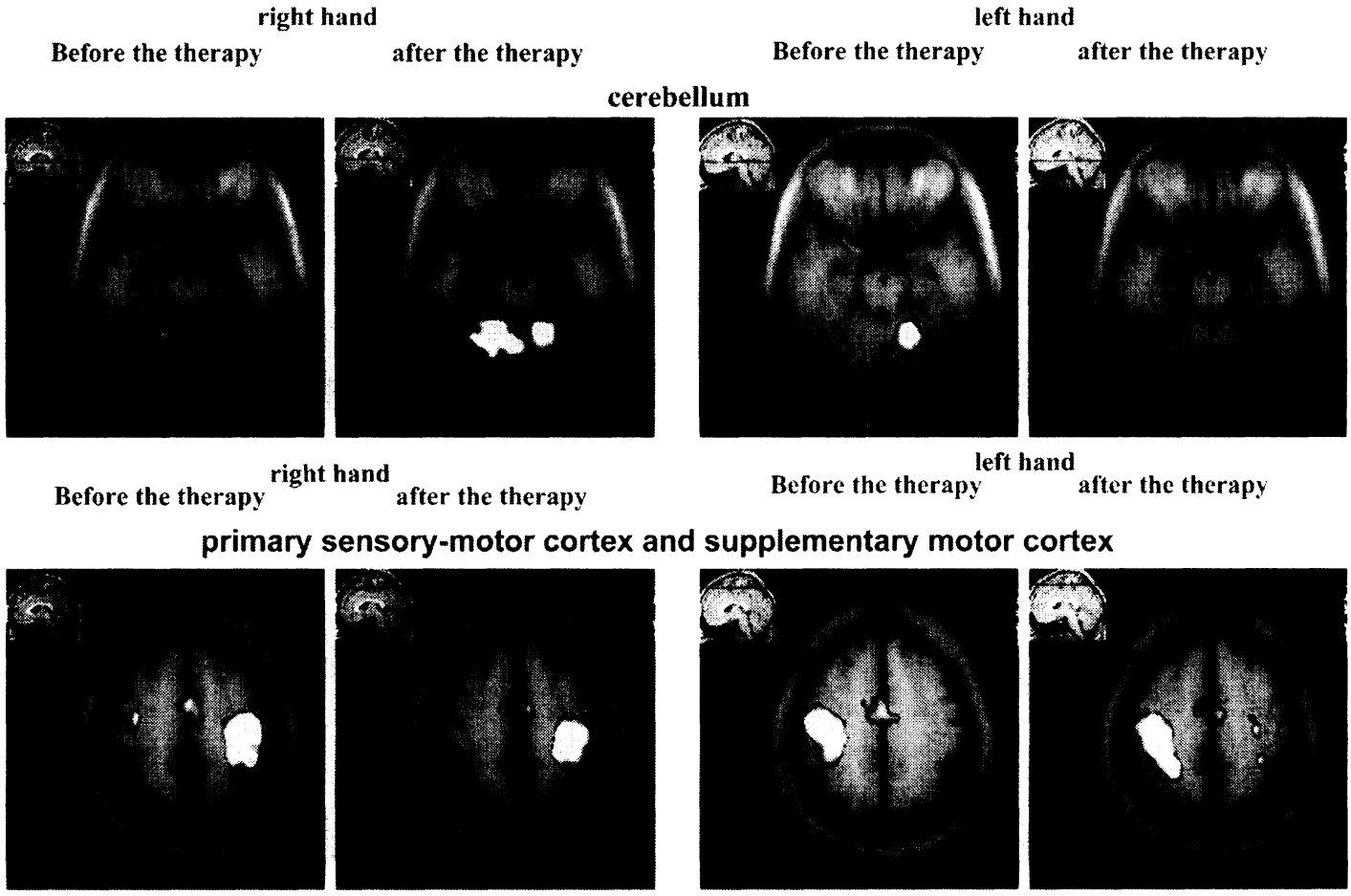

Figure 1 Group level activation in the experimental group.

fact that its increase as well as its decrease can be interpreted as improvement. Augmentation of the signal amplitude may represent compensation of a function or the renewal of impaired conduction in the examined area.[1] Therefore, it would be better to evaluate the changes individually. For the probands whose brain activity prior to therapy was abnormally high, the reduction of brain activity could be perceived as improvement. By contrast, for probands whose brain activity prior to the therapy was too low, augmentation could be perceived as improvement.

The group magnetic resonance images taken after therapy show that in certain areas the activated area increased and in other areas it was smaller. It is extremely difficult to interpret which activation changes are connected with the improvement of brain function. The activated brain area of an average population in the course of the execution of the paradigm is smaller and located more anteriorly in comparison with patients with MS.[3,25] The enlarged activated area in the brains of patients with MS is interpreted by spontaneous compensation mechanisms. Consequently, when evaluating the effect of the therapy, the further enlargement of the activated area could be perceived as the reinforcement of compensation mechanisms, whereas the reduction of an activated area could be the normalization of brain activity (the movement is mastered to such an extent that less feedback is needed for its control and so the brain consumes less energy, or the function is restored at the place of correct anatomic localization, or fewer but more efficient neurones are employed during the execution of a movement).[1] The majority of research studies demonstrate that the activated area after the therapy is enlarged;[8] some of them also demonstrate the shift of an activated area.[9] Nevertheless, some of them demonstrate the reduction of an activated area.[10]

Clinical message

- We have shown a clinical change associated with rehabilitation, but no specific changes in functional magnetic resonance imaging.

The positive effect of symptomatic rehabilitation treatment has been proved in various research studies.[26–28] The influence on a specific symptom (e.g., spasticity) can secondarily lead to influence on the execution of an impaired function (e.g., walking).[26] However, we prefer a holistic approach,[15,16] as we perceive it to be more effective. In our research study we concentrated on improvement of control over the whole body,[14] and on the stimulation of interplay between the postural system, righting mechanisms and phase movements. We made use of reflexive relations between individual systems that can be explained by the existence of global genetically coded movement patterns.[29] From our point of view, this was the origin of the improvement of functions (e.g., delicate motor movements and cognitive functions), on which we did not purposely concentrate in our research. The therapy was primarily holistic and it also caused holistic changes of clinical functions. We presupposed similar changes also in the brain.[4,30,31] We presupposed on the basis of the theory of information processing[17] that the higher the amplitude of signal in one hemisphere in the course of the execution of the paradigm, the higher it is in the opposite hemisphere. At baseline, we found higher inter-hemispheric dependence in controls than patients. For patients receiving therapy there was a trend towards increasing inter-hemispheric dependence after therapy, approaching the normal pattern. This suggests that changes in inter-hemispheric dependence may provide a useful marker of adaptive brain changes with therapy.

Evaluation of the therapeutic effect on brain activity is difficult because the therapy differed in individual probands (the therapy was adjusted to the clinical symptoms of individual probands), and also over the course of the neurorehabilitation of individual probands (the therapy was adjusted to the development of the disease symptoms over time). We worked on the assumption that the influence of isolated movement training on brain activity had already been demonstrated[4–7] and therefore we concentrated on proving the relationship between effective neurorehabilitation treatment and the change of brain activity.

Furthermore, the interpretation of results is influenced by the fact that the therapy combined aspects of various types of motor learning (proce-

dural and declarative learning). Each type activates different brain structures.[32] Different areas are also activated in the course of different phases of sensorimotor learning.[15,16] From our point of view, the differences in the activation of brain areas of the individual probands could have been caused by the fact that the probands were in different phases of sensorimotor learning.

Therefore, variability in therapy and motor learning strategy may have reduced our sensitivity to group level changes in fMRI activation with therapy.

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