

Research report

Recovery of motor disability and spasticity in post-stroke after repetitive transcranial magnetic stimulation (rTMS)

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Abstract

Lately it has been indicated that the stimulation of both sides of the motor cortices with different frequencies of rTMS can improve the behaviour of a paretic arm. We studied the effect of rTMS in severe cases of post-stroke after nearly 10 years. They had wide hemispheric lesion and their paresis had not changed for more than 5 years. The majority of patients could not move their fingers on the affected side. In our study we examined whether the active movement could be induced by rTMS even several years after stroke and which hemisphere (affected or unaffected) stimulated by rTMS would be the best location for attenuating the spasticity and for developing movement in the paretic arm.

Sixty-four patients (more than 5 years after stroke in a stable state) were followed for 3 months. They were treated with rTMS with 1 Hz at 30% of 2.3 T 100 stimuli per session twice a day for a week. The area to be stimulated was chosen according to the evoked movement by TMS in the paretic arm. That way, four groups were created and compared. In group A, where both hemispheres were stimulated (because of the single stimulation of TMS could induce movement from both sides of hemispheres) the spasticity decreased but the movement could not be influenced. A highly significant improvement in spasticity, in movement induction and in the behaviour of paresis was observed in group B, where before treatment, there was no evoked movement in the paretic arm from stimulating either hemispheres of the brain. For treatment we stimulated the unaffected hemisphere from where the intact arm is moved (ipsilateral to the paretic side). In both groups C (contralateral hemisphere to the paretic arm) and D (ipsilaterally evoked movement in the paretic arm), the spasticity decreased during the first week, but the movement of the paretic arm improved only in group C. It seems that spasticity can be modified by the stimulation either the affected or the unaffected hemisphere, but the induction of movement can be achieved only by the stimulation of an intact motor pathway and its surrounding area (groups B and C). The improvement in paretic extremities can be achieved with rTMS even after years of stroke when the traditional rehabilitation has failed.

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1. Introduction

In spite of the improvement in the acute treatment of stroke, which means that mortality is reduced, the recovery of post-stroke has not changed much for decades. The remaining symptoms of the motor system and cognitive dysfunction mean that about two-third of patients are unable to continue their profession after stroke [15,48]. The traditional methods in neuro-rehabilitation are based on the direct electric stimulation of peripheral nerves and training of muscles [40,38,19]. The

improvement is mainly expected within a year after the stroke. Introducing transcranial magnetic stimulation (TMS) into the rehabilitation made it possible to directly stimulate the nervous system through the scalp [3]. It may lead to a faster recovery because of the better reinnervation of paretic extremities [14] and the change in the brain plasticity (intracortical excitability) affecting behaviour [30,23]. This theory was partly proven by the studies published lately in which both sides of the brain, the one affected by a lesion and the unaffected hemisphere were separately stimulated by rTMS. The unaffected hemisphere was stimulated by rTMS with 1 Hz to elevate the intracortical inhibition [37,50], and the affected hemisphere was stimulated by high frequency of rTMS to increase the intracortical facilitation [27,52] or by low frequency but high intensity to help the recovery in a paretic side [26]. It resulted in a faster move-

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ment of fingers and an improvement in disability of the affected hand. Lately it was reviewed in different aspects [51,35,45]. Researchers declared that the stimulation of rTMS was safe [33,7]. The previous studies involved relatively slight cases with motor disability and the treatment with rTMS was within 1 year after stroke and the etiology of hemiparesis was a subcortical infarct. Although, the great challenge for rehabilitation is to induce active movement in the paretic extremities, even years after the stroke, and release the spasticity, which is hardly influenced at all by traditional spasmolytic drugs. We wanted to study whether the active movement could be induced by rTMS several years after stroke, and which hemisphere should be stimulated by rTMS to be the best location for attenuating the spasticity, and for developing movement in a paretic arm in severe cases with a large hemispheric lesion.

2. Materials and methods

2.1. Patients

Sixty-four patients (age: 57.6 ± 10.8 years; duration of the disease: 10.0 ± 6.4 years; females: 27; males: 37) with one lesion after stroke were enrolled in this study and they were followed for 3 months. The criterion for inclusion was that their movement state had not changed for 5 years. Except for drug-controlled hypertension, they had no other disease. Forty-six patients had occlusions in a big artery supplying the brain—either the cerebri media artery or the carotid internal artery. Eighteen patients had haemorrhages in their ganglion basale. There was no subject with a subcortical infarct among the recruited patients with hemiparesis.

The local ethical committee approved the trial. Every patient signed an agreement for the treatment.

2.2. Stimulation protocol

A MagStim 220 device was used with a 13 cm diameter circular coil. Patients were treated with rTMS with 1 Hz at sub-threshold intensity of MEP (30% of 2.3 T) twice a day for a week. One hundred stimuli were given in each session on the area which was marked. The area to be stimulated was chosen according to the evoked visible movement by TMS in the paretic arm. An EMG recording was not used. The maximum intensity of single stimulus of TMS was not beyond 85% of 2.3 T. That way four groups were created: A (movement in the paretic arm could be evoked from both sides of the brain, both hemispheres were stimulated), B (before treatment no induction of movement in the paretic arm from either sides of the brain (the intact pathway to the healthy extremities was stimulated from where visible movement could be evoked in them), C (the stimulation of the contralateral hemisphere to the paresis could induce movement in the paretic arm, so that side was stimulated), D (stimulation of the ipsilateral side of paresis could induce movement in a paretic arm, so that side was stimulated). A circular coil was used to stimulate the area of the brain which innervates the major part of the affected upper and lower extremities (Fig. 1). Four groups were compared in our study where the stimulated area differed from each other, but the intensity and frequency were same. This arrangement is suitable for controlled trials.

2.3. Methods

Internationally accepted self-rating scales were not used in patients with post-stroke beyond 5 years, because they became accustomed to live with one hand. Motor score system based on the Fugl-Meyer scale [18]. Expenditure of the movements in paretic extremities and detection of movements reappearing again in the affected arm and leg were measured. We simplified and decreased the points detected from different joints compared to Fugl-Meyer scale to grade the onset of movement in the paretic extremities. Furthermore we separated the movement score from the behaviour score. We took account of spasticity in the fingers, the most affected part of hemiparesis. The spasticity was scored

The Selection Groups According to the Areas of Evoked Movement in a Paretic Hand

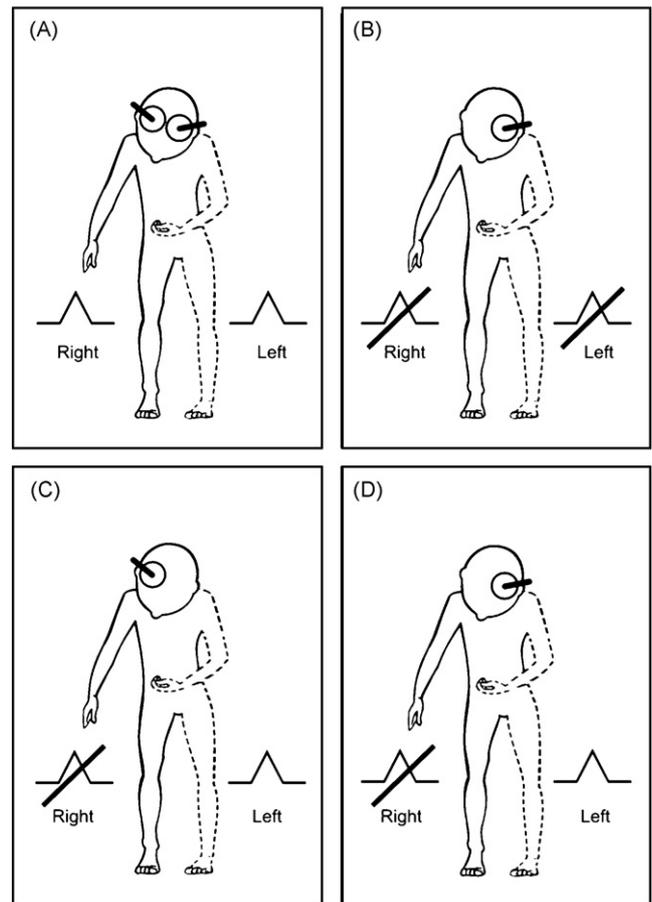


Fig. 1. (A–D) The selected groups according to the areas of evoked movement in a paretic hand. The area to be stimulated was chosen according to the evoked visible movement by single TMS in the paretic arm. That way four groups were created: (A) (movement in the paretic arm could be evoked from both sides of the brain, both hemispheres were stimulated), (B) (before treatment no induction of movement in the paretic arm from either sides of the brain (the intact pathway to the healthy extremities was stimulated from where visible movement could be evoked in them), (C) (the stimulation of the contralateral hemisphere to the paresis could induce movement in the paretic arm, so that side was stimulated), (D) (stimulation of the ipsilateral side of paresis could induce movement in a paretic arm, so that side was stimulated).

according to state of the fingers at rest which represented the rate of spasticity without any intervention. However, the Asworth scale [2] has spread all over the world, but its validity is questionable [29] and the subjectivity in the decision was high. Furthermore, the spasticity could be increased immediately after active effort. Therefore we preferred to observe the resting state, in the view of spasticity which was stable and well controlled and therefore this state can be compared with any stage of therapies.

The scores of their spasticity, the expenditure of movement in different joints on the paretic side were summarized as the movement score, and the functional improvement (walking, catching, dressing) was taken into account in the mathematical statistical analysis.

Score system:

1. Score of spasticity at rest

- Spasticity in the upper extremity (0 = none, 1 = slight, the fingers partly extended, 2 = the fingers are in flexion and passive extension of the elbow is difficult, 3 = expressive flexion).

- Spasticity in the lower extremity (0 = none, 1 = minimal resistance in passive movement, 2 = difficulty in the passive flexion of the knee and ankle, 3 = great difficulty to bend the knee).
2. Score of movement
- Shoulder (0 = none, 1 = movement starting, 2 = abduction 90°, 3 = more than 90°).
 - Elbow (0 = none, 1 = minimal flexion, 2 = flexion 90°, 3 = part extension, 4 = forward extension is complete).
 - Wrist (0 = none, 1 = there is dorsal flexion).
 - Fingers (0 = none, 1 = flexion, 2 = part extension, 3 = extension in every finger).
 - Hip (0 = none, 1 = part movement in one direction).
 - Knee (0 = none, 1 = extension 180°, 2 = part flexion, 3 = flexion 90°).
 - Ankle (0 = none, 1 = part dorsal flexion).
3. Behaviour of the paretic extremities
- The paretic arm takes part in dressing (0 = none, 1 = it can be put into the sleeve of a pullover, 2 = buttoning is possible).
 - Catching (0 = cannot grip, 1 = grasp an object but cannot release, 2 = grasp an object and let it slip out, 3 = catch and release an object).
 - Walking (0 = none, 1 = walking with a walker or cane, 2 = walking with one cane, 3 = walking without an aid).

2.4. Statistical analysis

The results were given by a descriptive method (i) for continuous data as the means \pm S.D., median, sample size, S.E.M., minimum and maximum values, (ii) for categorical data were given by median, sample size, minimum and maximum values for each treatment group.

We have adopted a generalized linear model (GLM) method for comparisons within treated groups. In this model the base line value was a covariate variable. A Tukey's honestly significant difference (HSD) test post-hoc procedure (adjustment) was used after ANCOVA to screen the significant differences between time pairs for multiple comparisons. Analysis was two sided with a level of significance of $\alpha = 0.05$. All statistical analyses were done using an "SAS 8.2" software package.

3. Results

A group: The spasticity was decreased significantly ($p = 0.0007$), the movement ($p = 0.1931$) and the behaviour of paretic extremities ($p = 0.9203$) were not changed. **B group:** The most expressive improvement was observed in this group either in spasticity ($p < 0.00001$), or movement ($p = 0.00081$) and the functional improvement ($p = 0.0204$). **C group:** Spasticity was decreased significantly ($p = 0.0043$), the movement was changed significantly ($p = 0.0481$) and the behaviour was not altered ($p = 0.2005$). **D group:** The spasticity was modified slightly ($p = 0.0628$), but there was no detected alteration in the movement or in the behaviour (Figs. 2–4).

The most expressive improvement was observed in group B, where the ipsilateral (intact motor pathway) was stimulated. Here there was significant improvement in spasticity, in movement induction and in behaviour. After 1 month there was a significant reappearance in movement of the upper extremity (Fig. 5A and B). We summarized the new movements and the expenditure of movements in different joints of upper extremities in group B (Table 1).

After treatment, movement began, but the controlled function in everyday life was delayed. None of the patients was able to use his or her hand before the treatment in group B, and after 1 month four subjects in this group could catch and release an

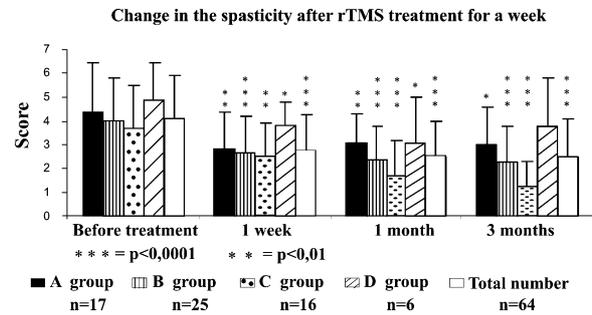


Fig. 2. Change in the spasticity after rTMS treatment for a week. Columns show the mean \pm S.D. The values represent the summarized spasticity scores of the upper and the lower paretic extremities; $n = 64$. The spasticity was scored by a 0–3-point system, where 0 meant a lack of spasticity. The release of spasticity developed after rTMS treatment for a week independently of the stimulated hemisphere of the brain; *** $p < 0.0001$; ** $p < 0.01$.

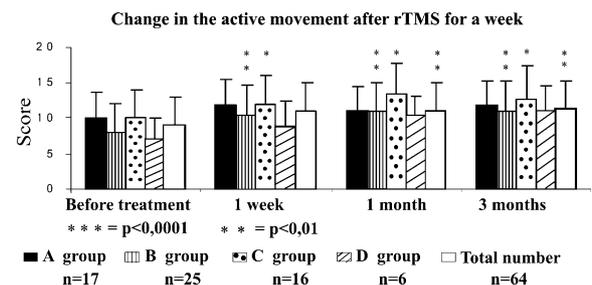


Fig. 3. Change in the activity movement after rTMS for a week. The columns show the mean \pm S.D. The values represent the summarized movement scores of the upper and the lower paretic extremities; $n = 64$. There was no change in the movement of patients with post-stroke if the both hemispheres were stimulated by rTMS (A group) ($p = 0.1931$). The movement induction was highly significant in group B, where the non-lesioned hemisphere (intact motor pathway) was stimulated ($p = 0.00081$). Similarly, active movement was improved in group C, where the reorganized motor pathway was stimulated in the hemisphere with lesion ($p = 0.0481$); *** $p < 0.0001$; ** $p < 0.01$.

object. The functional changes in details in group B: cannot grip: 22 (before (B)), 15 (1 month later (M)); grip: 1 (B), 3 (M); grasp an object and let it slip: 2 (B), 3 (M); catch and release an object: 0 (B), 4 (M).

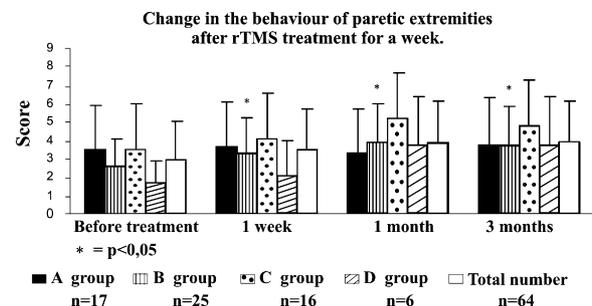


Fig. 4. Change in the behaviour of the paretic extremities after rTMS treatment for a week. The columns show the mean \pm S.D. The values represent the summarized movement scores of the upper and the lower paretic extremities; $n = 64$. The behaviour of the paretic extremities significantly improved in group B, where the non-lesioned hemisphere (ipsilateral motor pathway) was stimulated by rTMS ($p = 0.0204$). However, in the other groups a positive change was observed which did not reach a level of significance. The average of all the patients was higher than the level before treatment ($p = 0.03444$); * $p < 0.05$.

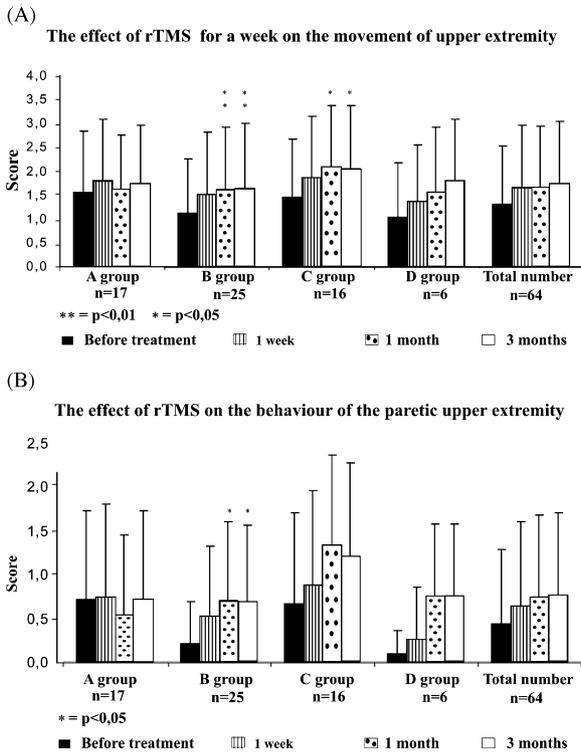


Fig. 5. (A and B) The effect of rTMS for a week on a movement of upper extremity; ** $p < 0.01$; * $p < 0.05$ (A). The effect of rTMS on the behaviour of the paretic upper extremity; * $p < 0.05$ (B). The columns show the mean \pm S.D. The values represent the summarized movement scores of the upper paretic extremities; $n = 64$. There was no change in group A, where both hemispheres were stimulated by TMS. Significant changes were observed in groups B and C. The functional improvement was detected only in group B, where the intact hemisphere was stimulated.

Table 1
Changes in the movement of upper extremities after rTMS treatment

Joints	Before rTMS	1 month after rTMS
Shoulder		
No movement	4	0
Movement starting	7	7
Abduction 90°	9	4
More than 90°	5	14
Elbow		
No movement	3	1
Minimal flexion	9	8
Flexion 90°	0	2
Part extension	11	4
Extension is total forward	2	10
Wrist		
No movement	19	14
Onset of dorsal flexion	6	11
Fingers		
No movement	12	7
Flexion	10	12
Part extension	3	1
Extension in every finger	0	5

This table represents group B ($n = 25$). The first column shows the number of patients and the movement they can do with different joints before treatment with 1 Hz rTMS. The second column shows the number of patients, and the start and spread of movement in different joints after 1 month. Change in the movement of upper extremities after rTMS treatment.

4. Discussion

In this study the reduction in spasticity, induction and spread of the movement were demonstrated in 64 patients with post-stroke after 1 Hz rTMS for a week. They had stable neurological symptoms for more than 5 years before they were recruited into the study. After the treatment period using rTMS with 1 Hz, the movement reappeared in different joints most expressively 1 or 2 weeks after stimulation over the cortical area, which may be involved in the reinnervation of paretic extremities. Groups B and C were particularly improved, where the intact motor pathway or the reorganised contralateral pathway was stimulated together with their nearby areas. The most affected part was the upper extremity in the patients several years after stroke, and the expanded movement led to an improved behaviour of the paretic arm. In group B before treatment with rTMS, 12% of patients could grip, and after 1 month 48% of patients could catch and release an object. The most surprising observation in our study was that the movement could be induced in paretic extremities more than 10 years after the stroke. Last year a case report was published which also detected a newly appeared movement in paretic fingers after 1 Hz stimulation with rTMS over the unaffected hemisphere [4]. In contrast, the high-frequency stimulation of rTMS (20 Hz) could not further improve the movement achieved by constrained-induced therapy [34].

One of the explanations of the effectiveness of the treatment with rTMS in post-stroke is based on the observation that there is an immediate change assessed by functional methods in both hemispheres [10,16,61]. After stroke, the balance in the counterpart inhibition between the two hemispheres is destroyed. An elevated inhibitory drive was demonstrated with TMS from the intact hemisphere to the lesioned hemisphere during the process of generation of a voluntary movement by the paretic hand, which might adversely influence the recovery of a paresis [39]. However, it was partly discussed by Büterfisch et al. [6]. Furthermore a disinhibition was assessed by a paired-TMS method in both hemispheres. Facilitation was mainly characteristic of the unaffected hemisphere; conversely an inhibition was recorded in the primary motor cortex in the affected part of brain [11,36,31,32,5,47]. Thus the transcallosal inhibitions became important in the treatment of the motor symptoms of post-stroke. Excitability of the intracortical connections in the intact motor area was demonstrated with the elevated amplitude of motor evoked potential (MEP) in the intact side and it was decreased by 1 Hz rTMS in correlation with the faster finger movement in the paretic arm [17]. It was confirmed by further studies that when elevated facilitation in the intracortical connections decreased in the intact hemisphere and this led to faster finger movement in the paretic arm [37,50]. In contrast to this study, the affected hemisphere was stimulated with high-frequency rTMS, and the amplitude of MEP increased parallel with the behaviour of the affected arm [27,52]. The importance of transcallosal inhibition in the acceleration of movement after rTMS stimulation over the ipsilateral primary motor cortex was also proved in healthy subjects [28].

The previous publications claimed that it is necessary to reverse the intracortical activity in both hemispheres separately and that causes an acceleration of movement.

Those studies involved patients with a subcortical stroke, where the primary motor cortex was not impaired and it was stimulated by rTMS. The common observation was that the paretic fingers could move faster after stimulation over the intact motor cortex in both sides of brain. Similar observations were made in Parkinson's disease [43] and even in healthy subjects [28] where the motor cortical area was stimulated by rTMS and the consequence was a shorter reaction time and an increased speed of movement. The results may confirm that the wide range of stimulation over the primary motor cortex can induce faster movement independently of the pathological state. Besides the correction of disinhibition, by either high or low frequency of rTMS, its influence on the primary motor cortex (if it is not damaged) may be taken account in the acceleration of movement in post-stroke.

Contrary to the lately published studies we involved patients nearly 10 years after their strokes where the affected paretic arm had not been used for years. In our study we concentrated on the induction of movement in the affected arm after the treatment with rTMS. It was interesting that the induction of movement in a paretic arm with a single TMS was relatively independent of the onset of movement after rTMS. Instead it was connected with the stimulation of the intact motor pathway plus its nearby area (group B) or an area around the reorganised motor pathway (group C). Our results show that the intact motor cortex influenced by 1 Hz rTMS may play role in the reorganization or the reinnervation of the paretic extremities or the intact portion of the affected hemisphere helps this reinnervation. Earlier published studies said that if the MEP could be evoked from the contralateral hemisphere of paresis, patients showed a better recovery than without it [54,55,13]. In contrast, in our study a highly significant recovery ($p = 0.00081$) appeared after 1 Hz stimulation over intact cortical areas where the evoked movement by single TMS in paretic extremities could not be performed from either hemisphere (group B) before treatment with rTMS. Lately the high-frequency rTMS at 10 Hz [27] and excitatory theta-burst stimulation [52] were applied over the affected hemisphere to cause enhanced facilitation parallel with faster movement in a paretic arm. In contradiction to these observations (which were based on the elevated excitability in the intracortical connections in the affected hemisphere) we also presented here a significant improvement in movement and behaviour of a hemiparesis, although the frequency and intensity of rTMS were low (group C). This inhibitory rTMS [9,53] caused a similar effect as did the high-frequency stimulation. Similar observations were made by Pomeroy et al. [44] when they used 1 Hz rTMS to stimulate the affected hemisphere in patients with a subcortical infarct, they could increase the MEP frequency in the muscles of biceps and triceps of the upper paretic limb [39]. The improved reinnervation of a paretic arm after 1 Hz rTMS partly confirms our results. However the behaviour of a paretic upper limb was not significantly changed compared to the placebo group by the end of treatment period of 8 days. We suppose according our results that the recovery in the secondary outcome is delayed. That is

why they could not detect a change in the behaviour of paretic arm after rTMS.

Treatment failed to promote the improvement in motor score or behaviour score in group D, where the ipsilateral motor cortex was stimulated, because the evoked movement in the paretic upper extremity appeared after a single TMS. Similar results were published in agreement with our observation that the reappearance of an ipsilateral response to the hemiparesis might not be beneficial for rehabilitation for the stroke, because it was mainly recorded in poorly recovered patients [56]. Similarly, the continuous stimulation of both hemispheres (from one part to another) by 1 Hz rTMS (group A) failed to cause any recovery in patients with post-stroke.

In earlier studies the treatment protocol in post-stroke was based on the hypothesis that the correction of disinhibition in intracortical connections might help in the recovery from hemiparesis. However, our observations, presented in this study, where the frequency and the intensity of stimulation were low and the same over both hemispheres, did not support the hypothesis that the improvement was the consequence of revised disinhibition. We hypothesize that an intact cortical area may play a role in the induction of movement in post-stroke, no matter which hemisphere was stimulated. In both groups, group C where we supposed there was a newly reorganized pathway and in group B where the original intact motor pathway was not damaged, the treatment was effective in inducing movement. Furthermore, our results may indicate that the stimulation of area near the intact motor pathway with 1 Hz rTMS may accelerate the improvement of movement even years after the stroke. The importance of intact regions of the brain in the development of rehabilitation process was indicated by the neuro-imaging studies. The conclusion that the reorganisation after stroke might occur in structurally and functionally intact brain regions [60] as based on the observation that the increasing damage in the corticospinal system led to a wider shift in the activation of the normal primary motor system to a secondary motor system to cause attach a recovery [62,63]. There was a renewed movement in paretic extremities when activated intact regions of the brain might be available to generate motor output to spinal cord. In contrast to our results where the importance of intact cortical regions was supposed in the recovery, Werhahn et al. could not prove the involvement of an intact hemisphere in the reinnervation of paretic extremities [64]. They applied high-frequency stimulation of rTMS over intact primary motor cortex to delay the reaction time in the paretic arm, but it failed. They concluded that an intact hemisphere probably did not help to reinnervate the paretic arm [64].

The effect of 1 Hz rTMS is hardly explained in this paper only by the inhibitory effect of rTMS on cortical areas. An alternative explanation would be that low-frequency rTMS develops a new plasticity (excitation in cortical areas) called a homeostatic-like effect which promotes the involvement of the intact primary and secondary motor areas in the restoration.

Ziemann et al. published results showing that the ischemic block of the arm could not change the excitability of the brain, but if they pre-treated the brain with low-frequency rTMS with 0.1 Hz, the facilitation in the contralateral intracortical connec-

tions was increased and the inhibition in the ipsilateral cortical areas also increased. They supposed a homeostatic-like effect of rTMS [68]. In another study, this homeostatic-like effect was aroused after applying 1 Hz rTMS over the motor cortex which was activated by free finger movement. After rTMS the wider areas in both hemispheres were activated [30]. Not only stimulated area was affected by rTMS, but also the area surrounding the site of the stimulation, as well as the opposite regions of the stimulated cortex [30]. It seemed that the contralateral pre-motor cortex had a special contribution to the restoration of hemiparesis [63,25].

It was hypothesized in the previous studies that rTMS with low-frequency not only had an isolated effect, but also a homeostatic-like effect which might play a role in the improved behaviour of the patients.

It seems according to our results that the spasticity which appeared after stroke was also independent of the imbalance of transcallosal inhibition, because the stimulation over both hemispheres together or separately resulted in the release of spasticity during the treatment period using rTMS with 1 Hz at the intensity of 30% of 2.3 T. The reduction in spasticity was independent of the intact motor pathway or the site of the stimulated hemisphere. In addition, we suppose that the release of spasticity is partly independent of innervation of movement. It seems that spasticity in one half of the body can be influenced from both sides of the brain. This may mean that the development of spasticity includes many neurotransmitter systems from the cortical and subcortical areas of the brain. rTMS may create a homeostatic change in the brain which contributes to the normalization of muscle tone. The role of the spinal cord was shown in an animal model of ischemic paraplegia where that the glutamate receptor 1 (GluR 1) upregulated in astrocyte cells in the spinal cord during the development of spasticity. Its further importance was proved by a knockdown state where the spasticity was not recorded [21]. Our results confirm the published trial in children that the rTMS over the motor area decreases spasticity [58].

Electric stimulation achieves its effect trans-synaptically between cortical neurons [59]. What are the pharmacological substances which are affected by 1 Hz stimulation of rTMS in post-stroke? The simplest answer would be that it is the GABA A [9,53,67,8] but the new imbalance of neurotransmitter systems could also be taken into account. The destroying effect of acute stroke depends on the excitotoxicity of glutamate [20] and the extra-cellular concentration of defending substrates, such as kynurenic acid, and adenosine which may determine the enlargement of infarct in the brain [12,49]. The elevated concentration of GABA can decrease the release of glutamate [42]. Furthermore the toxicity of glutamate can also be decreased by glutamate transporters attenuating the extra-cellular concentration of glutamate. They are respected as a future therapeutic intervention in stroke [46,57].

The excitotoxicity of glutamate is mainly important in acute stroke, but in our study, patients with stroke were treated even after 10 years. Although we do not know the new balance of neurotransmitters, the importance of glutamate arose again, not as a harmful substance, but as a helpful substance in rehabilitation after the stroke.

The long-term potential (LTP) takes place in the formation of neuroplasticity based on the glutamate expression. It was proved that the after-effects of rTMS with high frequency depend on NMDA receptors, because its effect was blocked by NMDA antagonists [22]. We applied 1 Hz stimulant which mainly activated GABAergic neurons in the cortical regions, and this stimulation led to the release of spasticity and the induction of movement in paretic extremities. After that we cannot say that this protocol directly induced NMDA dependent plasticity in either hemisphere. A recently published article says that the primed 6 Hz stimulation continued by 1 Hz stimulation led to prolong inhibitory effect of 1 Hz rTMS [66].

The pharmacologic effect of this phenomena may based on the observation that the primary NMDA reduces long-term potentiation LTP causing an inhibition which may promote the recovery from acute injury [42].

But the belief that GABA is always inhibitory and that glutamate is an excitatory neurotransmitter must be changed. It seems that their effect depends on the situation. In this way a new balance develops between the GABAergic and the glutaminergic systems, which leads to a new equilibrium of LTP/LTD activity in the intracortical neurons. We take into account that there is also a neurogenesis from the subventricular zone to the surroundings of the lesion caused by a stroke which may contribute to the further functional recovery after stroke [41,24]. It was reviewed by Wiltrout et al. [65]. The effect of rTMS on neurogenesis in post-stroke is not known but it was proved in animal studies that after treatment by rTMS in a Parkinsonian animal model that neurogenesis increased parallel with the improvement in movement [1]. Altogether, these effects of rTMS and other things that are not known contribute to the behaviour of central nervous diseases.

In our present study we demonstrated that low-frequency and low-intensity rTMS could provoke new movement in the paretic extremities years after a stroke. Furthermore, a decreased spasticity was observed during the following 3 months. The previous studies and ours indicate that rTMS is becoming an add-on therapy for patients with post-stroke.

Conflicts of interest

We declare that our submitted paper has no conflict of interest with any scientific group.

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