Brain Research Bulletin 135 (2017) 98–104

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

Follow up study: The influence of rTMS with high and low frequency stimulation on motor and executive function in Parkinson's disease

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ARTICLE INFO

Keywords:
Repetitive transcranial magnetic stimulation (rTMS)
Parkinson's disease
Executive function

ABSTRACT

Background: rTMS may influence on both cognitive and motor function in PD but the daily routine and the predictors of responders to rTMS are not known.
Objective/hypothesis: We hypothesized that the frequency and intensity of stimulation somehow relate to each other. Our goal was to select the optimal frequency with low intensity for PD. We clarified the importance of age in the effect of rTMS.
Methods: A total sixty-six patients with PD were included in the study. In an open investigation, randomly selected patients were divided into three groups. The effects of 1 Hz (N = 28), 5 Hz (N = 13) and 5 + 1 Hz (N = 25) frequency at low intensity over each DLPFC and the brain stem for 7 days were compared. Patients were followed for six months. UPDRS, the Trail Making Test, and dual tasks were applied. Patients ≤65 years > 65 yrs were compared. Data were analyzed by repeated measure ANOVA.
Results: Only 1 Hz had an effect on motor scores. Before the trial patients ≤ 65 yrs had UPDRS total scores of 30.3 ± 16.9, after 1 month: 17.8 ± 8.9 $p < 0.001$, after 6 months 18.3 ± 8.8 $p < 0.001$. Improvement of patients > 65 yrs was observed after one month ($p < 0.01$). Executive function > 65 yrs (N = 16) was significantly worse compared with C (N = 15) and it was improved temporarily by 1 Hz. Five Hertz and 5 + 1 Hz did not cause improvement.
Conclusion: One Hertz with proper intensity has a good outcome in PD. Patients > 65 yrs show deterioration in their executive function and they have shorter duration in their therapeutic effect of rTMS. This study draws attention to the importance of stimulation intensity and age as a predictor of the effect of rTMS.

1. Introduction

Nearly 20 years ago repetitive transcranial magnetic stimulation (rTMS) was recommended for the treatment of Parkinson's disease (Mály and Stone, 1998,1999). The pharmacokinetic effect of antiparkinsonian drugs and the physical intervention of rTMS deeply differ from each other. While the antiparkinsonian drugs have a faster and shorter effect, rTMS has a delayed effect after the stimulation. Furthermore, its effect is maintained for months (Mály and Stone, 1998, Dragasevic et al., 2002Shirota et al., 2013Mály and Stone, 1998, Dragasevic et al., 2002; Shirota et al., 2013). These characteristics of physical intervention with rTMS need a longer follow-up period after the stimulation, than those for antiparkinsonian drugs. Therefore, time is very critical when we examine patients after their treatment with rTMS. After the first observations, the favorable effect of low frequency stimulation was confirmed (Dragasevic et al., 2002; Shirota et al., 2013; Li et al., 2015), but in contrast, a Jack of effect from 1 Hz stimulation was also published (Arias et al., 2010; Filipovic et al., 2010a; Flamez et al., 2016). In the first part of the 21st century, the high-frequency stimulations entered the therapeutic protocols (Khedr et al., 2003; Khedr et al., 2006; Lomarev et al., 2006; Pál et al., 2010; Brys et al., 2016). Despite numerous publications, there is no full agreement about which frequency for stimulation is the most favorable improving the behavior of PD patients. However, there is agreement on having the period of stimulation last for 7–10 days. A shorter period (4 days) had no effect in Parkinson's disease (Filipovic et al., 2010b). One session of stimulation was not effective in PD (Tergau et al., 1999) nor was a single stimulation. However, Pascual Leone published a short after-effect on reaction time after both a single stimulation and a one-session stimulation (Pascual-Leone et al., 1994), and this was confirmed by Siebner (Siebner et al., 1999). The intensity of the stimulation has shown great variation in different publications, which may reflect the diversity of the results in PD with rTMS stimulation. Lately, meta-analyses have compared the lower frequency and higher frequency stimulations, but their conclusions were contradictory. The first meta-analysis confirmed the superiority of high-frequency stimulation over

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http://dx.doi.org/10.1016/j.brainresbull.2017.10.002
Received 7 August 2017; Received in revised form 22 September 2017; Accepted 3 October 2017
Available online 05 October 2017
0361-9230/

low-frequency stimulation (Elahi et al., 2009), while the next meta-analysis preferred low-frequency stimulation in PD (Zhu et al., 2015). The latest meta-analyses concluded that either the low- or high-frequency stimulation may be effective in PD (Chou et al., 2015; Wagle et al., 2016). Evidence-based studies have confirmed the usefulness of the stimulation over both hemispheres in a graded level "C" (Lefaucheur et al., 2014).

Finally, the demand arose to clarify the most important criteria by which the effect of stimulation is weaker or amplified. What are the predictors of non-responders or responders to rTMS in PD? In this study, we focused on the age of recruited patients and examined the effect of different frequencies with low intensity.

2. Materials and methods

2.1. Patients

The study was approved by the Regional Ethics Committee of University Hospital of Petz Aladár in Győr, Hungary. Sixty-six patients with PD were enrolled into the study from 2011 to 2015. They were randomly separated into three different groups according to the frequency of the stimulation with 1 Hz (N = 28), 5 Hz (N = 13) or 5 + 1 Hz (N = 25). They were followed for half a year in an open study. The patients with PD belonged to Hoehn-Yahr stages I–III. The groups were divided into subgroups according to their age (≤ 65yrs <). Baseline demographic data are shown in Table 1. At the baseline of the study, their states did not differ significantly from each other, but the patients > 65 yrs had a more advanced state of disease. Their executive function was compared with that of an age-matched healthy control group. Persons under 65 yrs (N = 11) and above 65 yrs (N = 15) were involved in the control study groups.

2.2. The applied methods

The patients were tested with the Unified Parkinson Disease Rating Scale (UPDRS) (Fahn et al., 1987), Trail Making Test (Reitan, 1992) and a dual test. The dual test had three parts. The time to walk a distance of 25 m was measured. The measurement was repeated counting back from 100 by 3 and 7. We measured the distance walking for 6 min and the time for a distance of 10 m. A Mini Mental Rating Scale excluded the patients with dementia from the study. Patients were tested before the study and then one week, one month and six months after the rTMS treatment. The examinations were performed during the effect of medication. Patients were taking levodopa with dopamine decarboxylase and cathecol ortho-methyl transferase inhibitors.

2.3. Protocol for stimulation with rTMS

One-Hertz stimulation was applied over both dorsolateral-prefrontal cortices (DLPFC) and over the brain stem. Each DLPFC was marked with an EEG cap. The brain stem was labeled 2 cm over the edge of the occipital bone. The intensity was 25% of the maximum output of the device (2.3 T) (Magstim 220). The intensity was chosen according to a dose-response curve where the optimal intensity for treatment in PD was determined (Mály and Stone, 1999a, 1999b Mály & Stone, 1999a, 1999b). Fifty stimuli with 25% of 2.3 T were given over each DLPFC. One hundred stimuli with 40% of maximum output were applied over the brain stem. Twelve sessions were done for 7 days.

Five-Hertz stimulation was applied over both DLPFC. Four hundred stimuli were given to each of them. The intensity was 30% of the maximum output of the device (Magventure Pro) (Maximum output 2.0 T). The brain stem stimulation with 1 Hz was same as the former description.

Five + one Hertz stimulation was given over both DLPFC one after the other according to the previous descriptions. The brain stem was stimulated with 1 Hz.

2.4. Statistical analysis

Results are expressed as the mean ± standard deviation of mean (S.D.) and sample size (N) for each treatment group. The normality of data was checked by applying Shapiro-Wilk's test. When non-normality of data could not be rejected, homogeneity of variances was assessed through the Levene's test. Means were compared by a *t*-test or by separate repeated measures analysis of variance (ANOVAs) with Tukey's correction for multiple comparisons applied where appropriate.

Analysis was two sided, with a level of significance of $\alpha = 0.05$. All statistical analyses were done using the SAS 9.4. (SAS Institute Inc., Cary, NC, USA.) software package.

3. Results

The 1-Hz stimulation with low intensity for 7 days had the most favorable behavior in PD. The rTMS with 1 Hz caused a significant improvement in motor symptoms as assessed by UPDRS total after one month (before trial (BF) ≤ 65 UPDRS total score 30.3 ± 16.9, after 1 month: 17.8 ± 8.9 $p < 0.001$, > 65 BF: 26.3 ± 16.8, after 1 month: 19.3 ± 10.1 $p < 0.01$). It was maintained for six months in the group ≤ 65yrs (N = 12, 18.3 ± 8.8 $p < 0.01$) (Fig. 1).

However, in the group > 65 yrs (N = 16) a better outcome was observed only after one month (BF: 26.3 ± 16.8, 1 month later 19.3 ± 10.1 $p < 0.01$, after 6 months: UPDRS total score: 22.1 ± 12.3 $p = 0.06$). While stimulation with 5 + 1 Hz decreased the scores assessed by UPDRS, stimulation with neither 5 Hz nor 5 + 1 Hz caused significant changes in PD after 6 months. The clinical data are shown in Tables 2 and 3. The dose of levodopa in the groups was maintained at the same level for the next half year (See Tabl. 2 and 3).

Results of the Trail Making Test and dual tests in PD ≤ 65 yrs did not differ from those in controls (C) below 65 years. However, the executive function of patients over 65 yrs (N = 16) was significantly worse compared to controls (N = 15) (C: Trail B-A: 50.0 ± 25.1 s, PD: Trail B-A > 65 yrs: 76.0 ± 45.1 s $p < 0.01$). One month after rTMS treatment with 1 Hz, an improvement was observed in the Trail Making

Table 1
Demographic data of the study. The table presents the data of the patients involved in the study. Patients with Parkinson's disease were divided into three groups according to the frequency being applied. The main three groups of patients were divided into two subgroups: ≤65 and 65 < years.

	1 Hz		5 Hz		5 + 1 Hz	
	≤ 65	> 65	≤ 65	> 65	≤ 65	> 65
Number	12	16	6	7	17	8
Age	56.1 ± 9·5	72.3 ± 4.2	62.1 ± 2·3	72.7 ± 3.2	60.0 ± 3.4	70.6 ± 3.0
Duration of disease	4.08 ± 2.08	3.9 ± 2.7	6.0 ± 3.1	6.2 ± 2.0	5.0 ± 3.5	4.6 ± 2.8
F/M	5;7	5;11	5;1	1;6	7;10	1;7
Years of education	16.6 ± 2.95	15.8 ± 2.8	15.0 ± 3.8	14.4 ± 2.1	16.3 ± 3.0	16.7 ± 2.4
Tremor or akinesis dominance	6T;6A	11T;5A	4T;2A	5T;2A	11T;6A	4T;4A

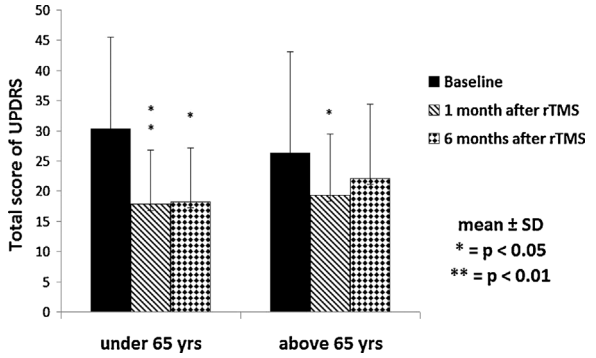

Fig. 1. The effect of rTMS with 1 Hz in PD. The columns represent the values of the UPDRS total score. The baseline is fully filled, 1 month after stimulation is striped and 6 months after stimulation is dotted. The first three columns show the patients with Parkinson's disease ≤65 yrs. The second three columns show the results of patients > 65 yrs. The one-Hz stimulation with low intensity for 7 days caused highly significant improvement in the symptoms of PD assessed by UPDRS, which was maintained for a half year. The alleviation of motor disability in PD > 65 yrs appeared in shorter time and smaller amount.

Table 2
Clinical data of motor scores of patients with Parkinson's disease taking levodopa ≤65 years. The table presents the data after rTMS treatment with low intensity and with different frequencies for a week. Patients ≤65 years with Parkinson's disease improved in a highly significant way ($p < 0.01$) one month after stimulation, and they maintained this improvement for half a year. None of the other frequencies altered the parkinsonian motor symptoms.

	Baseline of the study	After one month of rTMS	After six months of rTMS
1 Hz (N = 12)			
H-Y	1.90 ± 0.94	1.68 ± 0.71	1.54 ± 0.52
UPDRS Total	30.3 ± 16·9	17.8 ± 8·9**	18.3 ± 8·8*
UPDRS Motor	15.2 ± 8·5	10.9 ± 6·2*	10.3 ± 5.6*
Levodopa (mg)	345.45 ± 246.42	390.90 ± 228.93	395.45 ± 255.39
5 Hz (N = 6)			
H-Y	1.66 ± 0.81	1.66 ± 0.81	2.0 ± 0.89
UPDRS Total	21.6 ± 9·0	17.6 ± 10.2	19.8 ± 8.5
UPDRS Motor	11.5 ± 4·4	10.4 ± 5·9	10.6 ± 4.1
Levodopa (mg)	391.66 ± 159·42	400 ± 164.31	466.66 ± 147·19
5 + 1 Hz (N = 17)			
H-Y	1.43 ± 0.62	1.5 ± 0.63	1.56 ± 0.62
UPDRS Total	16.61 ± 7.79	13.41 ± 6.00	16.73 ± 6·78
UPDRS Motor	8.65 ± 4·13	7.37 ± 3·59	9.42 ± 3·57
Levodopa (mg)	400 ± 247.65	396.87 ± 259.78	400 ± 237.34

Test compared with data at the baseline of treatment (PD: 48.70 ± 21.4 s $p < 0.05$) (Fig. 2).

The dual test results deteriorated in the group over 65 years compared to age-matched controls. The 1-Hz stimulation did not reverse their values. (C: counting back (CB) −3: 50.0 ± 25.9 s, > 65 yrs PD CB −3: 57 ± 21, 1 month after rTMS CB −3: 69 ± 20, 6 months after rTMS: 60 ± 19 s; PD BF CB-7 100 ± 45 s, 1 month 102 ± 32 s, 6 months: 82 ± 23 s).

4. Discussion

In this study, low intensity rTMS treatment was studied with different frequencies. The stimulation affected both sides of the hemispheres and the brain stem. The low intensity treatment combined with low frequency influenced motor function as assessed by UPDRS in both subgroups according to their ages. The long-lasting effect was more significant in the younger group of patients with PD after a half year than in patients with over 65 yrs. The UPDRS motor score showed a similar tendency as the UPDRS total score. The study confirmed the age dependency of the effect of rTMS on motor function because the group of patients above 65 yrs had a shorter effect on their reaction to rTMS

Table 3
Clinical data of motor scores of patients taking levodopa with Parkinson's disease > 65 years. The table shows the data after different frequencies of rTMS with low intensity for one week. Patients with Parkinson's disease > 65 years were followed for half a year. The dose of levodopa was not changed. A significant temporarily reduction in the score of UPDRS and motor score of UPDRS was observed after the treatment with 1 Hz. Neither 5 Hz nor 5 + 1 Hz caused improvement in the symptoms assessed by UPDRS. The low intensity rTMS is effective only with 1 Hz stimulation.

	The baseline of the study	After one month of rTMS	After six months of rTMS
1 Hz (N = 16)			
H-Y	1.85 ± 0.77	1.71 ± 0.72	1.64 ± 0.74
UPDRS Total	26.3 ± 16.8	19.3 ± 10.1*	22.1 ± 12.3
UPDRS Motor	13.1 ± 8.0	10.0 ± 4.8*	11.7 ± 6.7
Levodopa (mg)	210.71 ± 203.97	225 ± 183.71	242.85 ± 178.51
5 Hz (N = 7)			
H-Y	2.5 ± 0.54	2.5 ± 0.54	2.5 ± 0.54
UPDRS Total	27.1 ± 9.4	27.0 ± 6.9	30.8 ± 5.8
UPDRS Motor	13.5 ± 4.5	12.3 ± 3.8	14.8 ± 2.9
Levodopa (mg)	500 ± 181.65	475 ± 175.35	475 ± 175.35
5 + 1 Hz (N = 8)			
H-Y	1.66 ± 1	1.55 ± 0.88	1.66 ± 0.86
UPDRS Total	19.2 ± 7.95	15.55 ± 4.39	18,0 ± 7.34
UPDRS Motor	10.8 ± 4.68	9.44 ± 3.16	9.83 ± 4.83
Levodopa (mg)	272.22 ± 148.13	272.22 ± 148.13	316.66 ± 180.27

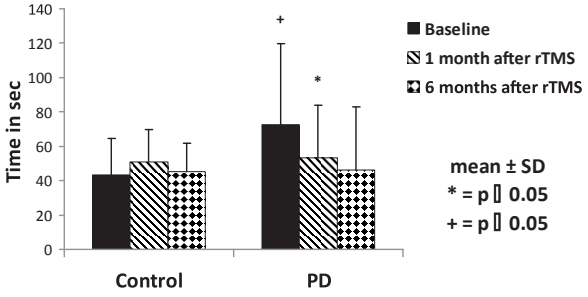

Fig. 2. The effect of rTMS with 1 Hz on the executive function assessed by Trail Making Test (B–A). Persons were above 65 years. The columns represent the Trail Making Test (B–A) values in sec. B–A shows the executive function without slowed movement. Patients with PD > 65 years were compared with age-matched healthy controls. The baseline values were significantly different from controls (+ = $p < 0.05$). The rTMS with 1 Hz and low intensity for 7 day temporarily improved the executive function in patients > 65 years (* = $p < 0.05$).

than the patients below 65 yrs. This new observation of the study may be taken into account in future studies.

In the present study, the intensity was much lower than the motor threshold, although it was effective in the group stimulated with 1 Hz but not in the 5 Hz and 5 + 1 Hz stimulations. Although, low intensity seems unusual in the therapeutic studies with rTMS, previously published studies showed that low-intensity stimulation with rTMS has an effect on brain activity according to TMS-evoked brain response assessed by EEG (Komssi 2004). In this study, rTMS stimulation at 60% of motor threshold produced a distinct change in amplitudes assessed by EEG (Komssi et al., 2004). Another study proved that there was an optimal intensity for reducing the amplitude of MEP after rTMS with 2 and 6 Hz for 10 min (Todd et al., 2006). Neither the 70% nor the 90% of the maximum output caused a significant reduction in the amplitude of MEP or even induced a great variation in the facilitation or inhibition, but the low intensity stimulation evoked a consistent reduction in the amplitude of MEP (Todd et al., 2006). Not only did this study confirm the favorable effect of low intensity, but an animal study with evoked LTP in the hippocampus further confirmed the superiority of low intensity (0.75 T) over the 1 T (Ogiue-Ikeda et al., 2003). The inhibitory effect of rTMS with 1 Hz was demonstrated after stimulation for one session over the later I-waves in humans (Di Lazzaro et al., 2008). There was a significant suppression in the amplitude of MEP detected in the

cervical epidural space. The low-intensity stimulation evoked a dopamine release on both sides of the striatum, while the high intensity around the motor threshold elevated the dopamine level only on the contralateral side of stimulation with 10 Hz (Strafella et al., 2006). The authors declared the effect of low intensity stimulation to be a placebo effect, but in the present study it may be caused by the real low-intensity stimulation of rTMS. The importance of intensity at different frequencies was also confirmed by our study. When the intensity was elevated up to the motor threshold, there was no favorable effect of 1-Hz stimulation (Arisen et al., 2010). It seems that the low frequency is more effective with low intensity. However, a high frequency connected with higher intensity around the motor threshold is much more favorable to produce a good outcome in PD, as was published in earlier studies (Khedr et al., 2003; Khedr et al., 2006; Lomarev et al., 2006; Hamada et al., 2008; Kang et al., 2010; Brys et al., 2016). However, elevation of the frequency up to 50 Hz did not cause a good outcome in PD (Benninger et al., 2012). The different clinical effects of high- and low-intensity stimulations with rTMS for one session were published in a study. While, the high-intensity stimulation over the primary motor cortex evoked changes only in the symptoms on the contralateral side of stimulation, the low frequency induced alteration in the symptoms on both sides of the brain of PD patients after one session of rTMS (Lefaucheur et al., 2004). We can not say that low- or high-frequency stimulation is effective in PD, but we can say that the proper intensity with adoptive frequency can alleviate Parkinsonian symptoms.

The present study also reveals the importance of age in PD with rTMS treatment. The therapeutic effect was significant even after half a year in the group treated with 1 Hz rTMS in the group of patients ≤ 65 yrs. This does not mean that rTMS is ineffective in patients with over 65 yrs, but they react to rTMS for a shorter time, which may indicate more frequent treatment with rTMS for better outcomes. In this study, we observed a significant improvement after stimulation that lasted for half a year. The same observation was made by Brys, who noted a positive effect at 21 weeks after stimulation with rTMS with 10 Hz (Brys et al., 2016). Despite high-frequency stimulation with rTMS, the improvement in parkinsonian symptoms was missed in a follow-up period for 14 days (del Olmo, 2007). The observation time was only two weeks, which seems too short to detect a better outcome in PD. In contrast, when the follow-up period was 12 months with rTMS treatment at 5 Hz, a favorable improvement in articulatory dysfunction of PD was detected by the end of the observation (Murdoch et al., 2012). The age dependency of the effect of rTMS and a delayed effect of stimulation may be partly responsible for the different results in the previous publications.

In the present study, the mental function in patients over 65 yrs assessed by the Trail Making Test and dual tests showed significant deterioration compared with age-matched healthy controls. The reversion was detected after one month of treatment with 1 Hz rTMS, however, it did not last for half a year. The other studies published earlier, observed improvement in cognitive function after one session of rTMS over DLPFC on the right side but not on the left side (Srovnalova et al., 2012; Sedlácková et al., 2009). Lately, one publication revealed that context-dependent learning was influenced by one session of rTMS with 1 Hz over DLPFC (Lee and Fisher, 2017). The same observation was made by Solé-Padullés, who found that memory performance in elderly patients whose memory was slightly disturbed presented a temporary improvement after treatment with rTMS using 5 Hz stimulation (Solé-Padullés et al., 2006). Reviews have summarized the contribution of non-invasive brain stimulation to improving disturbed cognition (Miniussi and Rossini, 2011; Floel and Cohen, 2007; Lawrence et al., 2017). In this study, motor and mental effects of rTMS were detected after rTMS with l Hz stimulation in PD with patients of different ages, but the high-frequency stimulation had no effect on symptoms of PD.

The crucial question is how we can explain the effects of rTMS. The site of action of rTMS may cover many mechanisms, which may be partly important to develop the therapeutic effect in PD or even in any other disease of the central nervous system. We briefly look over the brain plasticity, dopamine release, change in the microcirculation, in the elevation of BDNF, induction of progenitor cells and non-synaptic spread of the neurotransmitters from the focal stimulation site of rTMS.

Even the first publications revealed the effect of rTMS on brain plasticity. The intracortical excitability is changed in PD as detected by a shorter silent-period (SP) and a reduced short intracortical inhibition (SICI) (Priori et al., 1994; Ridding et al., 1995; Elleway et al., 1995; Chen et al., 1997; Beraradelli et al., 1996; Tsuji and Rothwell, 2002; Wu et al., 2007; Golaszewski et al., 2016), which are reversed by dopaminergic drugs (Pierantozzi et al., 2001; Mir et al., 2005). The transcranial magnetic stimulation influences intracortical excitability as do dopaminergic drugs. The shorter silent period in PD and decreased long interval intracortical inhibition (LICI) mediated by GABA B transmission are characterized for PD (Chen, 2004; Ni and Chen, 2015). There is deterioration in cortical LTD-like plasticity in PD. Presynaptic inhibition is impaired in PD, and it is not recovered by dopamine (Ni and Chen, 2015). Alterations assessed by electrophysiological parameters last for hours or even a day (Peinemann et al., 2004; Bagnato et al., 2005; Filipovic et al., 2010a,b). Brain plasticity can be changed by one session of rTMS. This means a rapid alteration in facilitation or inhibition in the intracortical connections, but its after-effect is too short to explain the therapeutic effect of rTMS lasting for a number of months (Chen et al., 1997; Romero et al., 2002; Schambra et al., 2003; Gorsler et al., 2003; Di Lazzaro et al., 2011). The two effects, the brain plasticity and the therapeutic effect, are partly connected with each other, but do not give a full explanation for the long-lasting therapeutic effect of rTMS in PD. The different mechanisms have been collected in a study (Rajan et al., 2016). Furthermore, there is great variation among people in excitability after stimulation with 1 Hz, 5 Hz or theta burst stimulation, but the therapeutic effect in PD is a much greater consequence after the stimulation for 7 days than the effect on brain plasticity (Gangitano et al., 2002; Romero et al., 2002; Hamada et al., 2013). Following focal stimulation with rTMS, the electrophysiological effects appear not only locally, but also far from the stimulation site and can be detected on both sides of the brain (Bagnato et al., 2005; Schambra et al., 2003; Chen, 2004; Gorsler et al., 2003). Focal stimulation with rTMS affects both hemispheres, as well as the deeper areas of the brain (Kim et al., 2008).

Increased dopamine release was shown after one session of stimulation with rTMS over the motor cortex and DLPFC (Strafella et al., 2005; Ko et al., 2008; Strafella et al., 2001). Even today, everything revolves around dopamine in PD. rTMS over the DLPFC or primary motor cortex induces dopamine release in the striatum (Strafella et al., 2006; Ko et al., 2008; Kim et al., 2008). It relates to the stimulation and it does not have a long-lasting effect. This temporarily favorable effect of rTMS does not explain the therapeutic effect of rTMS after one month of stimulation.

The remote effect of rTMS was confirmed not only by the electrophysiological observations, but also by changes in circulation in different areas of the brain (Park et al., 2017). Alterations in the microcirculation in different areas of the brain after rTMS may further confirm the general effect of focal stimulation with rTMS. Furthermore, the general change in amplitudes of waves assessed by EEG after TMS stimulation (TEP), less than 48 msec over both sides of the brain was found to be involved in the effect of one session of TMS (Chung et al., 2015). Despite the focal nature of stimulation with rTMS, both electrophysiological and microcirculation assessments have proved a broad effect in the brain thereafter.

The remote effect of rTMS after focal stimulation may induces non-synaptic transmission mechanism: transmitters are released into the extrasynaptic space. This effect was first published by Vizi (Vizi, 1984; Vizi et al., 2010). This non-synaptic transmission mechanism spread over the brain may increase or decrease the GABA and glutamate transmission in different areas of the brain, which may explain the effect of non-invasive brain stimulation (Vizi, 2000; Ardolino et al.,

2005). It should be noted that the effect of rTMS is similar to that of field stimulation: both are able to produce action potentials in the axons and release transmitters (Di Lazzaro et al., 2001). Neurochemical evidence has been obtained that field stimulation releases GABA (Lőrincz et al., 2016) noradrenalin/dopamine (Vizi et al., 1993; Milusheva et al., 1996; Sircuta et al., 2016; Borbély et al., 2017) serotonin (Vizi et al., 1981) and ATP (Vizi and Burnstock, 1988).

Finally, the non-synaptic transmission mechanism may be explained by the remote effect of focal stimulation with rTMS, but the long-term effect of rTMS may relate to the elevated brain derived nerve factor (BDNF) and the enhanced production of progenitor cells from the subventricular zone and the hippocampus gyrus dentatus region. According to animal studies, BDNF is increased after rTMS (Müller et al., 2000; Cheeran et al., 2008). The BDNF polymorphisms (Val66Met, Val66Val, Met66Met alleles) have a definitive impact on brain plasticity in humans and on the effect of rTMS and tDCS (Cheeran et al., 2008; Antal et al., 2010). There is no regeneration in the central nervous system without BDNF, it may contribute to synaptic plasticity, and it relates to learning, memory and the improvement of sensory and motor decline (Lipsky and Marini, 2007; Schäbitz et al., 2007; Hariri et al., 2003; Coelho et al., 2012). In a long-term study, polymorphism of BDNF was confirmed as a main genetic factor in the deterioration of executive function (Erickson et al., 2008). According to animal experiments, the effect of BDNF is realized through AMPA receptors (Clarkson et al., 2011). BDNF increases the production of progenitor cells.

rTMS not only elevates the concentration of BDNF but also induces the production of progenitor cells (stem cells) from the subventricular zone and the dentate gyrus of the hippocampus, which migrate into striatum and contain thyrosine hydroxylase enzyme (Arias Carrión, 2008; Yuan et al., 2014). Further studies confirmed that rTMS promotes neuronal stem cells in both the subventricular zone and the hippocampus (Guo et al., 2014; Ueyama et al., 2011; Liu et al., 2015; Luo et al., 2017). Stimulation with 1 Hz was compared with 30 Hz of stimulation in the brains of adult mice (Abbasnia et al., 2015). The effect of 1 Hz stimulation started earlier, and more cells were induced than from the stimulation with 30 Hz. Both stimulation levels increased the differentiation of stem cells. The clinical studies and animal experiments were reviewed by Winner and later Radad (Winner et al., 2011; Radad et al., 2017). If BDNF and neurogenesis are involved in the site of action of rTMS for days in humans, rTMS is not only symptomatic, it may be the etiological treatment of the disease. The physical interventions more frequently involved in therapy for central nervous diseases and their various of stimulation types produce a wide range to influence on motor programming and cognition (Santarnecchi et al., 2017).

5. Conclusions

In this study, we confirmed the importance of the intensity of treatment with rTMS, which may differ according to the frequency of stimulation. The effect of rTMS develops slowly, and its effect is maintained for months. We observed strong age dependence in the effect of rTMS, which may indicate the need for more frequent treatment with rTMS in patients over 65 yrs than in the younger age group. The longevity of the effect is not solely explained by the modification of brain plasticity or the induction of dopamine release in the striatum by rTMS. However, the role of the prolonged elevation of BDNF and the production of progenitor cells in the brain may be important mechanisms in the effect of rTMS.

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