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Self-regulation of brain activity and its effect on cognitive function in patients with multiple sclerosis – First insights from an interventional study using neurofeedback

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HIGHLIGHTS

- Patients with multiple sclerosis are able to self-regulate their brain activity.
- Successful self-regulation of brain activity improves cognitive function.
- A tele-rehabilitation system enables neurofeedback training at home.

ABSTRACT

Objective: To investigate the effects of EEG-based neurofeedback training, in which one can learn to self-regulate one's own brain activity, on cognitive function in patients with multiple sclerosis (pwMS).
Methods: Fourteen pwMS performed ten neurofeedback training sessions within 3–4 weeks at home using a tele-rehabilitation system. The aim of the neurofeedback training was to increase voluntarily the sensorimotor rhythm (SMR, 12–15 Hz) in the EEG over central brain areas by receiving visual real-time feedback thereof. Cognitive function was assessed before and after all neurofeedback training sessions using a comprehensive standardized neuropsychological test battery.
Results: Half of the pwMS ($N = 7$) showed cognitive improvements in long-term memory and executive functions after neurofeedback training. These patients successfully learned to self-regulate their own brain activity by means of neurofeedback training. The other half of pwMS ($N = 7$) did neither show any cognitive changes when comparing the pre- and post-assessment nor were they able to modulate their own brain activity in the desired direction during neurofeedback training.
Conclusions: Data from this interventional study provide first preliminary evidence that successful self-regulation of one's own brain activity may be associated with cognitive improvements in pwMS.
Significance: These promising results should stimulate further studies. Neurofeedback might be a promising and alternative tool for future cognitive rehabilitation.

1. Introduction

Cognitive problems are common in multiple sclerosis (MS) and occur in 50–60% of the patients already at early stages of the disease (Amato et al., 2008; Khalil et al., 2011; Pinter et al., 2014; Pinter et al., 2015; Rosti-Otajarvi and Hamalainen, 2014). Slowed information processing speed, memory and learning dysfunction,

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and reduced executive functions represent the most common MS-related cognitive deficits (Calabrese, 2006; Forn et al., 2008; Pinter et al., 2014; Pinter et al., 2015; Rogers and Panegyres, 2007; Rosti-Otajarvi and Hamalainen, 2014). Cognitive deficits have a strong negative impact on activities of daily living, quality of life, employment status, emotional well-being, and social activities of MS patients (Chiaravalloti and DeLuca, 2008; Cotter et al., 2016; Rosti-Otajarvi and Hamalainen, 2014). Meta-analyses provide low-level evidence that traditional cognitive rehabilitation may reduce cognitive symptoms in MS (das Nair et al., 2016; Rosti-Otajarvi and Hamalainen, 2014).

In this context, EEG-based neurofeedback (NF) represents an appealing alternative tool for cognitive rehabilitation (Hofer et al., 2014; Kober et al., 2015a). In NF applications, brain activity patterns are fed back to the user in real-time for instance via visual or auditory feedback (Enriquez-Geppert et al., 2017). Individuals can learn to self-regulate these brain parameters directly. Consequently, they might gain influence on the cortical substrates, which underlie cognitive functioning. Modulating these cortical substrates voluntarily by means of NF training might support functional cerebral reorganization, highlighting a great potential of NF for cognitive rehabilitation (Kober et al., 2015b; Kober et al., 2015a; Nelson, 2007; Reichert et al., 2016; Ros et al., 2014).

Prior studies showed that especially upregulating the sensorimotor rhythm (SMR, 12–15 Hz) in the EEG, which is strongest pronounced over central areas of the brain, leads to specific cognitive improvements. An increase in SMR activity is associated with a reduction or inhibition of sensorimotor interferences, which might disturb cognitive processing (Kober et al., 2015b; Reichert et al., 2016; Sterman, 1996, 2000). Increase in performance in memory, information processing, and executive functions - including working memory and attentional functions – has been observed in healthy individuals, stroke patients, and patients with traumatic brain injury (Gruzelier, 2014a; Hoedlmoser et al., 2008; Hofer et al., 2014; Kober et al., 2015b; Kober et al., 2015a; Kober et al., 2017a; Reichert et al., 2016; Schabus et al., 2014; Tan et al., 2009). In contrast, similar evidence in MS patients is lacking so far, although a few single case studies provided first evidence of positive effects of NF training on cognition, depression and fatigue in MS (Choobforoushzadeh et al., 2015; Dobrushina et al., 2016; Kober et al., 2016; Mackay et al., 2015).

Aim of the present study was to investigate the effects of SMR-based NF training, in which the amplitude of the SMR rhythm in the EEG had to be increased by means of NF training, on cognitive function in a larger sample of patients with MS. Based on prior findings in healthy individuals as well as neurologic patient groups such as stroke patients (Gruzelier, 2014a; Hofer et al., 2014; Kober et al., 2015b; Kober et al., 2015a; Kober et al., 2016; Reichert et al., 2016), we hypothesized that successful up regulation of the SMR rhythm would lead to cognitive improvements in MS patients.

2. Methods

2.1. Participants

Fourteen patients with relapsing-remitting (RRMS) or secondary progressive (SPMS) MS (Lublin et al., 2014) participated in this pilot study. All patients performed the same NF training and pre-post assessment. After finishing the measurements, patients were divided in two groups depending on their changes in cognitive performance as assessed with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990; Scherer et al., 2004). Patients with significant improvements in the overall score of the BRB-N (post-pre difference in T-scores > critical difference of 4.92, please see section "Statistical analysis" for more details) constituted the so-called "responder" group ($N = 7$), while patients with no significant changes in the overall score of the BRB-N (post-pre difference in T-scores < critical difference of 4.92) formed the "non-responder" group ($N = 7$). The calculation of the critical difference values is described in the section "Statistical analysis" in more detail. Relevant data describing the patient groups are provided in Table 1. All patients were right-handed. They had either normal or corrected-to-normal vision. For inclusion, patients with MS had to have no relapse in the three months prior to the study and no change in medication for at least six months prior to the study.

2.2. Standard protocol approvals and patient consents

This study was approved by the ethics committee of the Medical University of Graz, Austria (27–520 ex 14/15). All volunteers gave written informed consent. The present study is in accordance with the Declaration of Helsinki.

2.3. Neurofeedback training

All patients performed 10 NF training sessions within 3–4 weeks at their home using a tele-rehabilitation system (Kober et al., 2016) (Fig. 1A&B). The tele-rehabilitation system had three components: (1) A patient system including an EEG headset (NeXus EEG HeadSet, Mind Media B.V.), a portable 10-channel EEG amplifier (NeXus-10 MKII, Mind Media B.V.) and a laptop to perform the NF training using the BioTrace + software (Mind Media B.V.). With this system, home-based NF training was possible (Fig. 1A). EEG was recorded by semi-dry Ag/AgCl electrodes over Cz. Reference electrodes were placed on the left and right mastoid position. The ground was placed at C4. EEG signals were digitized at 256 Hz. Vertically moving bars presented on the screen of the laptop provided visual real-time feedback about one's own brain activity (Fig. 1C). Patients had no difficulties with placing the EEG headset on their head, starting the EEG measurement, and performing NF training on their own (Kober et al., 2016). (2) A server: EEG data recorded during NF training was automatically encrypted and uploaded to a server (HASOMED GmbH) ensuring secure data transportation. A standard internet connection as available in the homes of patients was sufficient to connect the NF system with this server. (3) A therapist system, which enabled the experimenter to monitor the NF training and EEG data quality remotely while the patients performed the NF training at home. The experimenter could also contact the patients via a video chat function during the NF training if necessary. Before the first NF training session, the experimenter prepared the setup-up of the NF system (patient system) at the patients' home, instructed and trained the patients in how to use the NF system. NF training sessions 2–10 were performed by the patients alone at their homes (Kober et al., 2016).

During NF training, patients received visual feedback of their own SMR power (12–15 Hz), theta power (4–7 Hz), and beta power (21–35 Hz), which was recorded over Cz. The amplitude of the power values was illustrated by three vertically moving bars, which were shown on the screen of the laptop (Fig. 1C). The aim was to increase the height of the bar in the middle while keeping the height of the outer two bars constant. The smaller bars on the left and right side of the screen showed the power values in the theta and beta frequency range. These two frequency bands were used to assure that patients were not manipulating the SMR amplitude by producing artefacts, e.g., blinking, which would have increased theta power, or tensing their muscles, which would have increased beta power and consequently, also SMR power (Doppelmayr and Weber, 2011; Weber et al., 2011). One NF training session comprised one baseline run (3 min) and six feedback

Table 1
Descriptive statistics (Means ± *SE* or Median ± IQR) for the entire study group of *N* = 14 MS patients, and separately for neurofeedback (NF) responders and non-responders, including results of the statistical subgroup comparisons depending on response.

	ALL	NF Responders	NF Non-Responders	*p*
N	14	7	7	
Sex female (%)	50	57.1	42.9	0.27
Age (years), Mean ± SE	38.9 ± 2.2	36.9 ± 4.2	41.0 ± 1.6	0.37
Education (years), Mean ± SE	14.9 ± 0.9	15.4 ± 1.3	14.4 ± 1.4	0.60
Disease duration (years), Mean ± SE	9.0 ± 1.9	13.4 ± 3	7.2 ± 1.9	0.12
EDSS, Median ± IQR	2.3 ± 3.5	3.0 ± 3.5	2.0 ± 3.5	0.71
T2-LL (cm^3), Median ± IQR	17.42 ± 23.93	19.32 ± 22.49	11.28 ± 23.13	0.32
RRMS (%)	92.9	85.7	100	

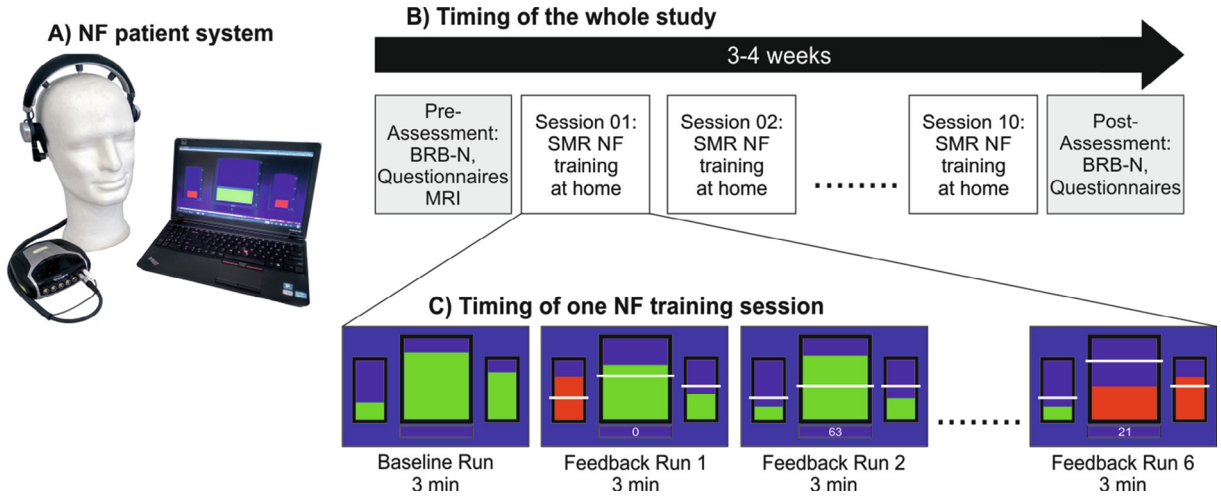

Fig. 1. (A) NF patient system including a semi-dry EEG headset, a small 10-channel EEG amplifier and a laptop on which the NF training program was running. (B) Timing of the whole study including pre- and post-assessments and 10 NF training sessions. (C) Timing of one NF training session including one baseline run and six feedback runs. Visual feedback of changes in one's own EEG activity was presented to patients by vertically moving bars. The height of the bar in the middle of the screen depicted SMR (12–15 Hz) amplitude changes, the bar on the left side amplitude changes in the theta frequency range (4–7 Hz) and the bar on the right side amplitude changes in the beta frequency range (21–35 Hz). The white horizontal lines represented the individually defined thresholds for each bar. The counter at the bottom indicated the number of reward points accumulated during the feedback runs.

runs (3 min each) (Fig. 1C). During the baseline run, patients were instructed to relax and just watch the moving bars without trying to control them. During the feedback runs, patients tried to increase the bar in the middle of the screen above a predefined threshold while keeping the outer two bars below their individually predefined thresholds (indicated by a white horizontal line, Fig. 1C). To do so, all patients received the instruction of being physically relaxed and mentally focused during the feedback runs. If they were successful in steering the bars in the specified direction, they received reward points displayed below the bar in the middle of the screen (Fig. 1C) and the moving bars turned green. If the left and right bar were above and the bar in the middle of the screen was below the corresponding thresholds, the bars turned red. The baseline run was used to individually calculate the thresholds (SMR threshold: mean of SMR power during baseline, theta and beta thresholds: mean + 1 SD of theta or beta power during baseline). No threshold values were shown, the bars were green all the time, and no reward counter was presented during the baseline run. During the six feedback runs, the threshold values and the reward counter were displayed on the feedback screen. After each feedback run, the threshold for the SMR bar was adapted on the basis of the immediate previous runs (mean SMR power of previous runs). The thresholds for the theta and beta bars (control bars) were kept constant over all feedback runs. This SMR-based NF training protocol has successfully been used in previous NF training studies (Gruzelier, 2014a; Hofer et al., 2014; Kober et al., 2015b; Kober et al., 2015a; Kober et al., 2016; Reichert et al., 2016; Strehl, 2014).

We reported the experimental design and the outcome of our neurofeedback training study in line with the Consensus on the Reporting and Experimental Design of clinical and cognitive-behavioural Neurofeedback studies (CRED-nf) best practices checklist 2019 (Ros et al., 2019) (Supplemental Material A). This checklist is intended to encourage robust experimental design and clear reporting for clinical and cognitive-behavioural neurofeedback studies (Ros et al., 2019).

2.4. EEG data analysis

EEG data was preprocessed and analyzed with the Brain Vision Analyzer software (version 2.01, Brain Products GmbH, Munich, Germany). A semi-automatic artifact rejection was performed by a trained EEG expert (criteria for rejection: >50 μV voltage step per sampling point, absolute voltage value >±120 μV, lowest allowed activity in 100 ms intervals: 0.5 μV, maximal allowed difference of values in 200 ms intervals: 80 μV). The expert was blind to the identity of patients as responder or non-responders at the moment of EEG data recording and analysis. All data points with artifacts were rejected from further EEG analysis.

To analyze the NF training data, we extracted absolute power values in the SMR (12–15 Hz), theta (4–7 Hz), and beta (21–35 Hz) frequency range by means of complex demodulation

implemented in the Brain Vision Analyzer software (version 2.01, Brain Products GmbH, Munich, Germany). This filtering module used a Butterworth filter centered at the frequency of interest. A zero-phase shift low-pass filter with high cut-off (f max-f min)/2 was used. The filter order was $N = 4$ (Brain Products GmbH, 2009; Draganova and Popivanov, 1999). Each 3-minute run was segmented into artefact free 1-s epochs. Power values of the artefact free epochs were averaged per run. To be able to compare the strength of learning effects across participants, EEG power values were re-scaled by means of a z-transformation.

2.5. Cognitive assessment

We used the BRB-N (Rao and Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990; Scherer et al., 2004) to assess cognitive functions before (pre-test) and after (post-test) the NF training. The BRB-N is a standardized and sensitive measure of cognitive impairment in MS patients. It consists of tests assessing verbal learning and memory (Selective Reminding Test, SRT), visual-spatial learning (10/36 Spatial Recall Test, SPART), information processing speed, sustained attention, and concentration (Symbol Digit Modalities Test, SDMT; Paced Auditory Serial Addition Test 3-s version, PASAT), executive functions and semantic verbal fluency (Word List Generation Test, WLG). With these tests, one can discriminate cognitively intact from impaired MS patients with a sensitivity of 71% and a specificity of 94% (Rao et al., 1991). We used two parallel versions of the test during the pre- and post-assessment to avoid test repetition and training effects (Boringa et al., 2001). Normative values of the BRB-N for German-speaking countries are available (Scherer et al., 2004). Test-retest reliabilities of the BRB-N are the following: 0.63–0.89 (Erlanger et al., 2014; Strober et al., 2009). Raw values were transferred into norm-values (Z-scores, which were then transferred into T-scores, Mean = 50, $SD = 10$) in accordance to (Scherer et al., 2004). Single subtests were merged into the cognitive constructs short term memory (composite score of SRT immediate recall and SPART immediate recall), long-term memory (composite score of SRT delayed recall and SPART delayed recall), information processing speed and concentration (composite score of PASAT and SDMT), executive functions (score of WLG), and an overall score (composite score of all single subtests) (Scherer et al., 2004). The person who did the pre-post assessment was blind to the identity of patients as responder or non-responders at the moment of the cognitive assessment.

2.6. Structural MRI + Image analysis

MRI was performed on a 3 Tesla TimTrio scanner (Siemens Healthcare, Erlangen, Germany). Structural 3D images with high-resolution were acquired by means of a T1-weighted MPRAGE sequence with 1 mm isotropic resolution (TI = 900 ms, TR = 1900 ms, TE = 2.19 ms, 176 slices). A T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence with $1 \times 1 \times 3\ mm^3$ resolution served for the assessment of the hyperintense T2-lesion load (T2-LL) in the patients (TI = 2500 ms, TR = 9000 ms; TE = 69 ms, 44 slices). Burden of focal white matter inflammation (respective residual footprints of it) was estimated by the T2-lesion load (T2-LL). Lesion identification was performed by a single experienced rater (AD). Afterwards, a semi-automated region growing algorithm was used to assess T2-LL (Plummer, 2016).

2.7. Questionnaires

During the pre- and post-assessment, patients filled out different subjective questionnaires assessing quality of life, fatigue, mood and depression, sleeping quality, and activities of daily living. A complete list of the tests and their results can be found in Supplemental Material B. The responder and non-responder group did not differ in these subjective variables before the start of the NF training. No significant pre-post changes in these subjective variables were observed.

During the post-assessment, patients were asked which mental strategy they have used to control the feedback bars during NF training. In line with prior studies in healthy individuals, patients reported on the use of various mental strategies during NF training (Kober et al., 2013; Kober et al., 2017c). Responders more frequently reported on the use of no specific strategy and relaxation, while the non-responders used more cognitive effortful strategies such as visual imagination and counting/mental arithmetic strategies than the responder group (see Supplemental Material C).

2.8. Statistical analysis

For statistical analysis of cognitive data, T-normative scores of the single BRB-N sub-tests and cognitive constructs were used. Intra-individual comparisons between BRB-N results assessed during pre- and post-assessment were performed by using critical difference analysis (Huber, 1973, 1977). The critical difference for a pair of test scores was established using the test-retest reliability of the test and its standard deviation. The critical difference value describes the smallest difference between two measurements of a single person, which with a probability α is produced by random fluctuations. By choosing a small value for $\alpha = 10\%$ in the present study, one can be confident that the score difference was not produced at random but can be attributed to the efficacy of the intervention. The difference values between the T-scores reached during the post- and pre-assessment were calculated for each BRB-N parameter and compared with their corresponding critical difference values on the single subject level as well as on the group level. For instance, for the overall BRB-N score the critical difference value was 4.92. Hence, the observed difference value in the overall BRB-N score between the post- and the pre-assessment (T-score of the overall BRB-N score assessed during the post-measurement minus T-score of the overall BRB-N score assessed during the pre-measurement) had to exceed this value (4.92) to be statistically significant.

Mixed-effects models with the fixed effect group (responder vs. non-responder) and the linear fixed effects session (NF training session 1–10) and run (baseline run and 6 feedback runs) were calculated for the dependent variables z-transformed EEG power (either SMR, theta, or beta power) to investigate the NF training performance (Type I Analysis of Variance with Satterthwaite's method). Subjects, individual regression slopes across sessions and runs were included in the model as crossed random effects (Baayen et al., 2008). Mixed effect modeling was performed in R (R development core team, 2007), freely available at http://cran.r-project.org. The lme4 package was used (Bates and Sarkar, 2007). As post-analysis, the same mixed-effects models were run separately for the responder and the non-responder group (without the fixed factor group).

3. Results

3.1. Intervention effects on cognitive function

The groups were comparable in their cognitive performance during the pre-assessment as revealed by t-tests (all $p > 0.08$).

After the NF training, the responder group showed a significantly improved performance in the BRB-N subtests verbal long-term memory (SRT), visual-spatial long-term memory (SPART), and executive functions (WLG) compared to the pre-assessment.

The difference values between the post- and pre-test for these subtests were larger than the corresponding critical differences. Consequently, the cognitive constructs long-term memory and executive functions as well as the overall score of the BRB-N were significantly higher during the post- than during the pre-assessment in the responder group.

The non-responder group showed no significant changes in cognitive function when comparing the pre- and post-assessment.

Table 2 summarizes the cognitive results for both groups (mean and *SE* of T-scores) assessed during the pre- and post-assessment.

To test whether the probability that the number of observed significant performance improvements in the overall BRB-N score ($N = 7$) was higher than chance level, we performed a binomial experiment. For that, we assumed measurement independency across participants and determined the probability of one single participant reaching the critical difference at $p = 0.01$. We statistically compared the proportion of successes (performance differences between post- and pre-assessment > critical differences) in relation to the total number of comparisons (Kober et al., 2015a). This binomial experiment showed that it is highly unlikely that $N = 7$ (out of $N = 14$) patients showed a larger post-pre differences in the BRB-N overall score than the critical difference value by chance alone (binomial probability $p = 0.0002$).

3.2. NF training results

The mixed-effects model for the dependent variable z-transformed SMR power revealed a significant interaction effect group * run ($F(1, 89.23) = 6.27$, $p < 0.05$). The post-analysis showed that responders showed a linear increase in SMR activity over the feedback runs (main effect run: $F(1, 25.40) = 20.74$, $p < 0.001$) while non-responders showed no significant changes in SMR activity across feedback runs (main effect run: $F(1,45.32) = 0.07$, *ns*; Fig. 2).

For the control frequency beta, the ANOVA also revealed a significant interaction effect group * run ($F(1, 91.70) = 6.20$, $p < 0.05$). Non-responders showed a linear increase in the beta activity over the feedback runs averaged over all NF training sessions (main effect run: $F(1, 48.55) = 15.94$, $p < 0.001$) while the responder group showed no significant changes (main effect run: $F(1,41.50) = 0.07$, *ns.*, Fig. 2).

The mixed-effects model for the dependent variable z-transformed theta power revealed a significant 3-way interaction group * run * session ($F(1, 822.96) = 7.92$, $p < 0.01$). Posttests revealed that theta power generally increases over the training runs in the responder group (main effect run: $F(1,33.11) = 4.73$, $p < 0.05$). In the non-responder group, theta power decreased only during session 7 and 8 (interaction effect run * session: $F(1, 421.33) = 8.69$, $p < 0.01$) (Fig. 2).

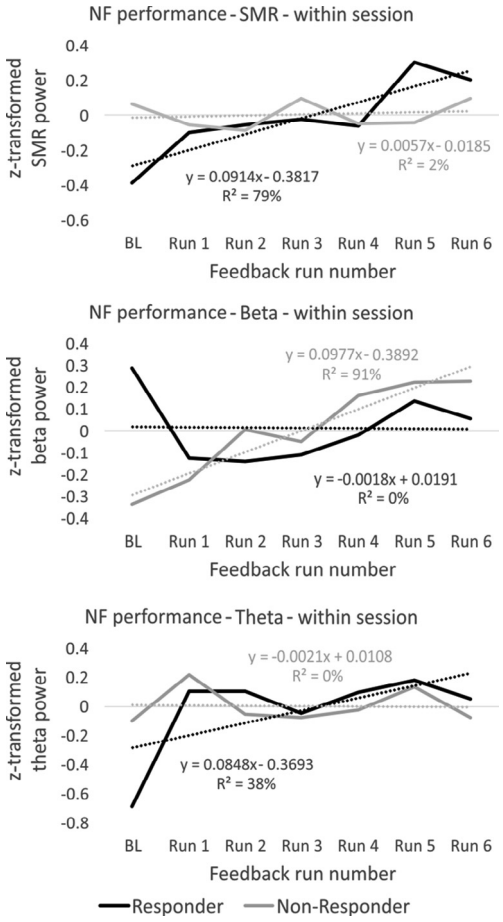

Fig. 2. Neurofeedback training performance. Z-transformed EEG power for the three feedback frequency bands (SMR, theta, beta) over the NF training runs, presented separately for the responder and non-responder group. Values were averaged over all repeated NF training sessions. The regression slopes across runs for each group are indicated by dotted lines. The results of the regression analysis per group and feedback frequency are also added.

4. Discussion

In the present study, we investigated effects of EEG-based NF training on cognitive functions in MS. Fourteen patients with MS

Table 2
Results of cognitive assessment (Mean ± *SE* of T-scores) during the pre- and post-test, presented separately for the responder and non-responder group. Significant results are marked with asterisks.

		NF Responders		NF Non-Responders	
		Pre-Assessment	Post-Assessment	Pre-Assessment	Post-Assessment
BRB-N Subtests					
SRT – Immediate Recall	Verbal Short-Term Memory	50.72 ± 2.73	53.99 ± 3.09	48.10 ± 2.26	46.79 ± 2.27
SPART – Immediate Recall	Visual-Spatial Short-Term Memory	52.53 ± 3.03	58.35 ± 3.80	56.93 ± 3.42	54.67 ± 3.93
SDMT	Information Processing Speed, Concentration	39.23 ± 5.36	43.56 ± 4.97	38.55 ± 6.20	38.53 ± 4.61
PASAT	Information Processing Speed, Concentration	43.79 ± 7.08	47.79 ± 5.29	46.69 ± 3.33	45.73 ± 3.78
SRT – Delayed Recall	Verbal Long Term Memory	43.31 ± 4.37	56.06 ± 2.05*	49.61 ± 3.08	50.53 ± 3.33
SPART – Delayed Recall	Visual-Spatial Long Term Memory	47.57 ± 4.31	56.86 ± 3.85*	56.96 ± 3.84	54.07 ± 4.54
WLG	Executive Functions	46.53 ± 3.71	53.43 ± 4.84*	46.30 ± 4.89	47.27 ± 3.93
Cognitive Constructs					
Short-Term Memory		51.73 ± 2.73	57.26 ± 3.48	51.41 ± 1.80	49.24 ± 3.24
Long-Term Memory		43.96 ± 3.67	58.63 ± 3.45*	54.39 ± 3.90	53.09 ± 4.10
Information Processing Speed & Concentration		39.81 ± 7.13	44.81 ± 5.86	41.17 ± 4.77	40.57 ± 4.24
Executive Functions		46.53 ± 3.71	53.43 ± 4.84*	46.30 ± 4.89	47.27 ± 3.93
Overall Score		44.43 ± 4.24	55.24 ± 4.97*	48.09 ± 3.55	46.60 ± 3.85

were trained to up regulate their SMR activity in the EEG during 10 home-based NF training sessions. The patients were divided into two groups according to their changes in cognitive performance when comparing the overall score of the BRB-N between the pre- and post-assessment. Patients with significant improvements in the overall score built the responder group, patients with no significant changes in the overall BRB-N score formed the non-responder group. Half of all patients showed cognitive improvements after 10 sessions of NF training and half of the patients did not.

In this interventional study in a small group of patients with MS yielding novel and preliminary results, successful self-regulation of patients' own brain activity was associated with cognitive improvements. The responder group that showed significant changes in different BRB-N subscales when comparing the pre-post assessment, was successful in increasing SMR activity during NF training. In contrast, the non-responder group that did not show any cognitive changes when comparing the pre- and post-assessment was not able to increase SMR linearly during NF training. This is in line with findings of prior SMR-based NF training studies in healthy individuals as well as neurological patients that linked successful up regulation of SMR activity to cognitive improvements (Gruzelier, 2014a; Hofer et al., 2014; Kober et al., 2015a; Kropotov, 2009; Reichert et al., 2016). Normally, SMR is most pronounced over the sensorimotor cortex. It is generated in a thalamocortical network and emerges during a motionless but concentrated and attentive state. The SMR amplitude is suppressed during movement (Pfurtscheller, 1981; Sterman, 1996, 2000). This EEG rhythm is assumed to inhibit the conduction of somatosensory information flow to the cortex (Sterman, 1996). Somatosensory or motor activity might interfere with perceptual and integrative components of information processing by disengaging visual processing areas of the cortex. Consequently, sensorimotor interference might disturb cognitive performance (Pfurtscheller, 1992; Sterman, 1996). In this context, increasing SMR activity by means of SMR-based NF training might improve cognitive processing by decreasing sensorimotor interference (Sterman, 1996). In line with this assumption, earlier own work showed that SMR-based NF training could reduce sensorimotor interference and thereby foster cognitive processing in healthy individuals (Kober et al., 2015b). This result could be replicated with stroke patients (Reichert et al., 2016). The present findings provide first indications that successful SMR up regulation also might foster cognitive functioning in patients with MS.

MS patients belonging to the responder group showed significant improvements in verbal and visuo-spatial long-term memory functions as well as in executive functions. The responders' post-pre difference value of 5 T-scores for the cognitive construct "Information Processing Speed & Concentration" was slightly smaller than the critical difference values of 5.44 T-scores. Hence, it slightly failed the significance level. These results indicate that SMR-based NF training has relatively unspecific effects on cognitive functions of MS patients. Prior studies in healthy individuals also report on positive effects of SMR-based NF training on cognitive function such as verbal and visual-spatial memory, working memory, attention and concentration, information processing, or executive functions (Doppelmayr and Weber, 2011; Gruzelier, 2014a; Hoedlmoser et al., 2008; Kober et al., 2015b; Schabus et al., 2014; Kober et al., 2017b). In prior studies with stroke patients, especially memory functions improved due to SMR-based NF training (Hofer et al., 2014; Kober et al., 2015a; Reichert et al., 2016). NF training even led to stronger cognitive improvements in stroke patients than treatment as usual (Kober et al., 2015a). The stroke patients of these prior NF studies showed deficits in memory functions prior to the training. The strongest improvements after NF training were found in cognitive functions, which were most impaired during the pre-assessment (Hofer et al., 2014; Kober et al., 2015a). In the present sample of MS patients, no severe cognitive deficits in any cognitive function were observed during the pre-assessment. Only in the BRB-N subscale SDMT and the corresponding cognitive construct "Information Processing Speed & Concentration" patients were slightly below average (T-score < 40). However, no significant cognitive improvements in these cognitive functions were observed. Instead, we found significant improvements in cognitive functions, which were in an average range before the start of the NF training. This is in line with prior findings in healthy individuals (Doppelmayr and Weber, 2011; Gruzelier, 2014a; Hoedlmoser et al., 2008; Kober et al., 2015b; Schabus et al., 2014; Kober et al., 2017b) and indicates that even participants with only subtle cognitive deficits can benefit from NF training. Our results are in accordance with the assumption that reducing sensorimotor interferences by increasing SMR activity leads to an improved stimulus processing capability, which should have positive effects on maintaining perceptual and memory functions at the same time (Kober et al., 2015b; Sterman, 1996). SMR-based NF training seemed to improve overall cognitive functioning in patients with MS.

MS Patients belonging to the non-responder group showed no significant pre-post changes in any cognitive function after 10 sessions of NF training. It remains open whether these patients might have shown some cognitive improvements when receiving more than 10 NF training sessions. For instance, up to 50 NF training sessions are necessary to obtain any training effects in patients with attention deficit-hyperactivity disorder (ADHD) (Arns et al., 2009). Instead of increasing the amount of NF training sessions, changing the EEG feedback frequency might have been useful in this group of MS patients. It might be that these MS patients would have been able to modulate other EEG frequencies than SMR, such as the Theta/Beta ratio or upper alpha, which can also affect cognitive performance positively (Doppelmayr and Weber, 2011; Gruzelier, 2014a; Hanslmayr et al., 2005; Hofer et al., 2014; Kober et al., 2015a; Kober et al., 2017a; Zoefel et al., 2011). This clearly should be a matter of future investigations.

Furthermore, it is important to note that NF training had no negative effects on cognitive functions in this sample of patients with MS. Neither the responder nor the non-responder group showed significant decreases in cognitive performance when comparing the post- and pre-assessment. This is in line with prior NF training studies in stroke patients, in which NF training had no negative impact on EEG parameters or associated cognitive functions in neurologic patients (Hofer et al., 2014; Kober et al., 2015a; Reichert et al., 2016).

The theta and beta frequencies, which were used as control frequencies during NF training to prevent patients from producing artifacts by blinking, eye movements, or muscle artifacts (Doppelmayr and Weber, 2011; Kober et al., 2015b; Weber et al., 2011), did not change in the same linear fashion than SMR power across feedback runs in the responder group (Fig. 2). This indicates that the responder group did not systematically increase artifact activity across the feedback runs to modulate SMR.

SMR activity only changed linearly within NF training sessions but not between the ten NF training sessions. This is in line with our prior NF training studies, in which we also found within session changes in the trained EEG frequency band but no changes in baseline power between training sessions (Hofer et al., 2014; Kober et al., 2015b; Kober et al., 2015a; Reichert et al., 2016). Voluntary modulation of EEG activity during NF training does not necessarily imply that the EEG baseline levels have to change. In our studies, we could successfully show that participants are able to modulate their EEG activity voluntarily at a given time (within a NF training session) (Kober et al., 2015b). To identify changes resulting from NF training it is assumed that within session changes in EEG parameters might be a more useful approach

(Dempster and Vernon, 2009). The definition of NF learning indices is generally a disputed topic in the NF literature (Enriquez-Geppert et al., 2017; Gruzelier, 2014b).

The tele-rehabilitation system turned out to be practicable and worked flawlessly. The patients had no problems with placing the EEG headset on their head and starting the NF training protocol on their own at home. NF training results of the present sample are also comparable to prior NF training studies, which were performed in a lab environment, where a trained EEG expert mounted standard EEG equipment (Hofer et al., 2014; Kober et al., 2015b; Kober et al., 2015a; Reichert et al., 2016). Such a home-based NF training system can reduce monetary and time-related efforts associated with NF training. Tele-rehabilitation systems might be valuable tools for future cognitive rehabilitation (Kober et al., 2016).

In this first proof of concept study with MS patients, we included a wide range of patients willing and capable to undergo this training, without further selection except the exclusion criteria mentioned above. The sample was therefore relatively heterogeneous regarding disease related parameters, cognitive function, disease phenotype and age (Table 1). This might to some extent limit the interpretation of the results. However, our patient groups did not differ significantly in these variables and in our attempt to test for the feasibility of the methodological approach it made sense to investigate a broader range of patients in a first step. Based on the present promising findings, future studies including different control groups (e.g., waiting list control groups, sham-feedback control groups, treatment as usual), different patient groups (e.g., RRMS vs. SPMS, MS patients selected by cognitive impairment) as well as baseline and (longer-term) follow-up measurements are necessary to investigate the NF training effects on cognitive functions in MS in more detail.

Summing up, we found positive effects of a repeated EEG-based NF training on diverse cognitive functions in patients with MS, who were able to regulate their own sensorimotor rhythm in the EEG. Our results indicate the potential value of EEG-based NF training as cognitive rehabilitation tool in MS, enabling cost-effective, user-friendly, home-based training and should be corroborated and extended by further studies.

Author contributions

S.E.K., D.P., S.F., C.E., C.N., and G.W. designed the research; S.E.K. and D.P. performed research; S.E.K., D.P., H.D., C.N., C.E., and G.W. contributed new reagents/analytic tools; S.E.K., D.P., A.D., C.E., and G.W. analyzed data; and S.E.K., D.P., C.E., and G.W. wrote the paper. All authors reviewed and approved the manuscript.

Statistical analysis

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Data availability

Data that support the findings of this study are available on request from the corresponding author (S.E.K.) after contacting the Ethics Committee of the Medical University of Graz (ethikkommission@medunigraz.at) for researchers who meet the criteria for access to confidential data. These ethical restrictions prohibit the authors from making the data set publicly available.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.08.025.

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