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Applied Psychophysiology and Biofeedback
https://doi.org/10.1007/s10484-022-09560-4

Effects of SMR Neurofeedback on Cognitive Functions in an Adult Population with Sleep Problems: A Tele-neurofeedback Study

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Accepted: 7 September 2022

Abstract
A good night's sleep is vital for normal human cognitive performance. We earlier reported that a home-based tele-neurofeedback program effectively reduced sleep problems (Krepel et al. in Appl Psychophysiol Biofeedback, https://doi.org/10.1007/s10484-021-09525-z, 2021). The present article presents a follow-up on this earlier study and investigates improvements in cognitive functions after sensory-motor rhythm (SMR) neurofeedback. Thirty-seven participants reporting sleep problems received SMR neurofeedback. Cognitive measures were assessed pre- and post-treatment. Measurements included a continuous performance/working memory (CPT/WM) task, Stroop task, and Trailmaking A and B test (from the IntegNeuro cognitive test battery). For neurofeedback-Learners relative to non-Learners significantly improved CPT/WM response time ($d=0.50$), omission errors ($d=0.67$), and Stroop incongruent performance ($d=0.72$) were found. A significant time effect for both groups were found for the Stroop, the Trailmaking test part B ($d=0.52$), and the Stroop interference score ($d=0.55$). No significant correlations between changes in sleep and changes in cognition ($p>0.05$) were found for the sample. SMR neurofeedback specifically improved measures of attention (response time and omission errors in a CPT/WM test) and working memory (Stroop incongruent) for SMR Learners compared to non-Learners with medium effect sizes. Furthermore, overall improvements for the whole sample were found on measures of executive function and visual attention, possibly reflecting non-specific or practice effects. Future better powered randomized control trials are needed to investigate if cognitive improvements are a direct effect of SMR neurofeedback or mediated by sleep improvements.

Keywords Sleep · SMR neurofeedback · URGOnight · Neuropsychological · Cognition

Introduction

Too little sleep leads to cognitive deficits such as impairments of sustained attention, impaired executive functioning, and attentional problems (Astill et al., 2012; Axelsson et al., 2008; Belenky et al., 2003; Fallone et al., 2001; Lim & Dinges, 2010; Van Dongen et al., 2003). Chronic sleep restriction is a significant predictor of lower grades in adolescents and decreased study concentration, even after controlling for covariates (van der Heijden et al., 2018). As an important side note Van Dongen et al. (2003) showed that a sleep restriction to 6 h for 14 days had the same effects as two nights of full sleep deprivation on measures of sustained attention, without the participants being aware of their cognitive deficits. This suggests that chronic sleep deprivation leads to cognitive deficits that people are unaware off. Besides the cognitive impairments being unnoticed, the impairments (inattention in particular) take more days of normal sleep to recover than the actual nights of exposure to restricted sleep. A more recent meta-analysis by Alfonsi et al. (2020) highlighted the harmful effects of sleep loss once more, including worsening of executive functioning, attention, and memory.

Sensory-Motor Rhythm Neurofeedback

SMR neurofeedback has been shown to be able to improve sleep problems by training the reticulo-thalamocortical-cortical circuit, involved in generating sleep-spindles (for review:

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Published online: 17 September 2022

Arns & Kenemans, 2014; Arns & Sterman, 2019). The SMR rhythm is an EEG rhythm between 12 and 15 Hz (low beta, or SMR rhythm), located over the sensorimotor cortex. Training the reticulo-thalamocortical-cortical network, which results in long-term potentiation (LTP) of the network, increases the synaptic strength within this network and therefore the likelihood the network will be activated in the future (Arns et al., 2014). Learning to control this SMR rhythm, for example by up-regulation, increases sleep spindle-density along with changes in sleep parameters. Furthermore, studies have also reported SMR neurofeedback to improve attention deficit hyperactivity disorder (ADHD) symptoms of inattention and impulsivity (Arns et al., 2020; Krepel et al., 2020).

Here we follow-up on earlier work where we investigated a tele-neurofeedback based program employing SMR neurofeedback in adults with a primary sleep disorder (Krepel et al., 2021), where we found significantly increased sleep duration and improved sleep quality [Pittsburgh Sleep Quality Index (PSQI)] with medium to large effect sizes, that were sustained after an average of 5.3 months follow-up. Subjects classified as 'SMR-Learner' (Participants that showed a positive slope of regression of SMR power across sessions) specifically demonstrated a 1.0 h. longer sleep duration, with no such effect for non-Learners,. Given SMR neurofeedback has been demonstrated to improve ADHD symptoms of inattention and impulsivity (Arns et al., 2020; Krepel et al., 2020) we here further analyzed changes in cognitive tests before and after SMR neurofeedback. Since sleep duration improved most in the Learner group, we expect to see the same Learner vs. non-Learner contrast when investigating the cognitive outcomes. Sustained attention and working memory (assessed using a continuous performance test/working memory test, CPT/WM) were deemed the primary outcome measure since these are most prone to be affected by sleep restriction and are also the primary affected cognitive domains in ADHD. We specifically analyzed reaction time (RT) and omission errors as they reflect inattention (Weafer et al., 2013). To further measure working memory and selective attention we use Trail making and Stroop tests. Based on the well-established link between sleep and cognitive functioning (Astill et al., 2012; Axelsson et al., 2008; Belenky et al., 2003; Fallone et al., 2001; Lim & Dinges, 2010; Van Dongen et al., 2003), prior neurofeedback studies in ADHD (Arns et al., 2013, 2014), and the outcomes of the first URGOnight study (Krepel et al., 2021), we hypothesize that SMR neurofeedback will not only improve sleep parameters but also enhance cognitive functioning.

Methods and Materials

This study is an open-label feasibility trial. Only patients that had a primary sleep problem and no primary psychiatric comorbidities that potentially explained the sleep problems were included. Patients between 18 and 70 years of age with a primary sleep problem expressed as a sleep onset problem [latency (SOL) ≥ 30 min], sleep maintenance problem (wake after sleep onset (WASO) ≥ 30 min), or sleep duration problem (sleeping ≤ 6 h. per night) were included. Sleep complaints had to occur at least three times a week, and the duration of complaints should be at least 6 months as quantified on the PSQI. Medication usage was allowed but had to remain stable during the treatment. Exclusion criteria were: comorbid medical or psychiatric complaints [as assessed using the Mini International Neuropsychiatric Interview (M.I.NI.)]; recent parenthood; night shifts; students; pregnancy; excessive alcohol and caffeine usage; diagnosis of a primary sleep disorder other than primary insomnia.

URGOnight was used in the main study (for further details see Krepel et al., 2021) as a tele- neurofeedback device for improving sleep quality and by providing sleep hygiene support. In short, the study entailed 37 participants undergoing SMR neurofeedback to treat sleep problems. Participants that were able to control their SMR rhythm, were classified as Learners (for a detailed description regarding the Learning definition and calculation, see: Krepel et al., 2021). Of the 37 participants, 11 were classified as Learners and 21 as non-Learners. Learners demonstrated a significantly larger gain in sleep duration ($d = 0.86$ pre-post) compared to non-Learners. In addition, significant improvements in PSQI Total ($d = 0.78$), PSQI Sleep Duration ($d = 0.52$), Holland Sleep Disorders Questionnaire (HSDQI) Total ($d = 0.80$), and HSDQ Insomnia ($d = -0.79$) scores, indicating improved sleep quality, were reported.

In addition to the above-mentioned sleep data, cognitive measures were assessed both pre-treatment as well as post-treatment using the full IntegNeuro cognitive test battery. High scores on the cognitive measures reflect inattention and problems in working memory (Gerrits et al., 2019; Wearfer et al., 2013).

As primary outcome measures, the cognitive domains of inattention and working memory, defined as reaction time and omission errors during the CPT/WM were defined. The CPT/WM test is an n-back test where a series of letters is presented on the screen one at a time. The subject is required to press a response button only when the same letter appears twice in a row. This task reflects updating of working memory and omission errors are a reflection of inattention (Gerrits et al., 2019).

As secondary outcome measures, the Stroop and Trail-making A and B test were investigated, both assessing working memory. In the Stroop test the subject is presented with four colored words, one at a time. Each word is drawn from a set of four colors. Below each colored word is a response pad with the four possible names of the colors displayed in black and in fixed format. In part 1, the subject is required to identify the name of each colored word as quickly as possible

and in part 2, the subject is required to identify the correct color of the ink in which the word is printed, as quickly as possible. Each of the two parts lasts for 1 min. Responses are made on the screen by pressing on the appropriate word on the bottom screen.

In the Trailmaking test part A, the subject is presented with a display of 25 numbers and asked to connect the numbers in ascending numerical sequence (1, 2, 3...). The screen will not allow a wrong connection and resets to the last correct number. In Part B, the subjects are presented with a pattern of 13 numbers (1–13) and 12 letters (A-L) on the screen. They are required to press on the number-letters in alternating and ascending order (1-A-2-B and so on). An erroneous attempt to join, say, 1-B, is met with a "wrong" signal appearing briefly on the screen. This eliminates the problem with the paper and pencil version where the tester has to intervene, introducing a variable that is hard to standardize. Tertiary outcomes included the digit span test in which participants are required to recall digits either forward or backward. In the tapping test participants are required to tap the touchscreen with their index finger as fast as possible, and finally in the Corsi blocks the participant has to mimic the tapping sequence of the researcher.

Treatment: URGOnight

The URGOnight tele-neurofeedback platform was used in the main study (see Krepel et al., 2021) for improving sleep quality and by providing sleep hygiene support. It consists of a portable EEG headband connected to a mobile application via Bluetooth technology. The URGOnight headband includes two dry measuring electrodes (UrgoTech, Paris) over the sensorimotor cortex in positions C3 and C4 of the international 10–20 system. Reference and ground are positioned on the left and right mastoids, respectively. The EEG data measured by the headband is transferred to the mobile application in real-time to allow the user to perform neurofeedback training autonomously. In addition to the neurofeedback program, the URGOnight mobile application provides daily advice to improve sleep and sleep hygiene, an assessment of sleep quality and sleep hygiene levels using questionnaires, and a sleep diary.

Recording was set to a sampling frequency of 100 Hz. At home, participants trained four times per week, where every fifth session was done in the clinic supervised by a trained neurofeedback specialist. All instructions during sessions were provided by the mobile application and additional questions were answered by the therapists during weekly visits at the clinic. Neurofeedback sessions lasted approximately 20 min, including 1 min of baseline measurement. This consisted of a 30-s period where participants were instructed to relax and keep their eyes closed, followed by a 30-s period with their eyes open. Then, five 3-min neurofeedback runs were performed. Participants were free to take a 1-min break between runs or to go straight to the next run.

During neurofeedback runs, participants were presented with a bar corresponding to their real-time SMR power (12–15 Hz) associated with a threshold level (1, 2, 3, 4, or 5) and an animated wallpaper. An additional character (portrayed as a robot) appeared on the screen when the EMG band power exceeded 70 µV on one of the sensors. If this was the case, the participant was asked to relax. No rewards were given when the EMG band power value exceeded the threshold.

The sound and visual environment of the training could be customized by the participants before training; however, feedback screens were designed to reflect 'discrete' feedback aimed at a reinforcement rate of 25–30% in line with earlier recommendations (Sherlin et al., 2011). They received audio and visual rewards each time their SMR band power value exceeded the threshold for 400 ms. When participants managed to keep their SMR power above the threshold for two seconds, the threshold was increased, and they received a visual cue to indicate that the level had increased. When SMR band power was below the threshold for seven seconds, the level was decreased to the preceding one and they received a visual cue to indicate that it had been lowered.

When subjects succeeded in increasing their own SMR power between the first run and the fifth run (Kober et al., 2013; Reichert et al., 2015; Zoefel et al., 2011) (assessed by plotting the regression slope of normalized relative SMR power averaged across all sessions performed and for each run of training for every participant), a positive slope of regression was expected and they were classified as Learners. Participants with a negative slope of regression were classified as non-Learners. The computation process is described in detail in Krepel et al. (2021). Subjects underwent 40 sessions or 60 sessions. however, no differences between the 40 and 60 session groups were found (for detailed outcomes and calculations, see Krepel et al., 2021), hence all data were collated over groups. On average participants received 49 sessions.

Statistics

To investigate whether SMR neurofeedback impacted the primary outcomes, repeated measures ANOVAs were performed with factor Time (pre-treatment and post-treatment) as within-subject factor and the ability to learn to control the sensory motor rhythm (Learner vs. non-Learner) as between-subject factor. To investigate the correlations of changes in sleep and changes in cognition, a subsequent bivariate correlation was performed between difference scores on sleep parameters and the difference scores on the cognitive measures. Statistical analysis was

performed using IBM SPSS Statistics, Version 25. p values < 0.05 were considered to be statistically significant.

Results

The study was conducted at Research Institute Brainclinics, Nijmegen from April 2019 to December 2020. A total of 37 participants were included (9 male; average 48.2 years), 32 of which were classifiable as Learner or non-Learner (for the remaining five participants, no Learner classification could be made due to missing session data or data recovery issues), and 30 had complete neuropsychological data. Of 37 participants, 10 were unmedicated, 13 used sleep medication (mostly benzodiazepines), and three used other psychoactive drugs. Demographics and Baseline sleep parameters of the Learners and non-Learners are represented in Table 1, and no differences between groups were found.

Table 1 Demographics and Baseline sleep parameters of the Learner and non-Learner groups

Demographics	Learner	Non-Learners
Female/male	9/2	15/4
Age (years)	48.7	46.2
Baseline sleep parameters		
PSQI baseline	13.5	12.3
HSDQ total	2.3	2.2
HSDQ insomnia	3.9	3.8

There were no significant differences between any of these variables between groups (all p > 0.326)

Primary Outcome: WM/CPT Test

For RT a Time X Learner interaction was found (p = 0.018; DF = 1,24; F = 6.497) and no Time effect (p = 0.261). Repeating the analysis separately yielded a significant decreased RT for Learners (p = 0.018; DF = 1,9; F = 8.398; d = 0.50) and no effect for non-Learners (p = 0.321).

Groups did not differ on RT pre-treatment (p = 0.466), but post-treatment a trend for a difference was found (p = 0.107; DF = 1,24; F = 2.807; d = 0.67).

For WM inattention errors, no effects were found for commission errors Time: p = 0.973; Time X Learner p = 0.240). For omission errors there was a significant Time X Learner interaction (p = 0.013; DF = 1,25; F = 7.08), where Learners showed a downward trend on numerical errors (p = 0.145; DF = 1,9; F = 2.548; d = 0.67) and non-Learners increased on number of errors (p = 0.049; DF = 1,16; F = 4.533; d = 0.70). Omission and commission errors were no different between groups at baseline (all p > 0.191), whereas after treatment groups differed significantly on omission errors (p = 0.030; DF = 1,25; F = 5.310; d = 0.97).

Primary outcome results were synthesized in Fig. 1 below.

Secondary Outcomes: Trailmaking Test (SWOA) and Stroop

For Trailmaking Part A (connecting digits) no significant main effects nor interactions were found involving Time. For Trailmaking Part B there was a significant Time effects for the average response time (p = 0.018; DF = 1,25; F = 6.473; d = 0.52), presented in Fig. 2, but no significant interactions.

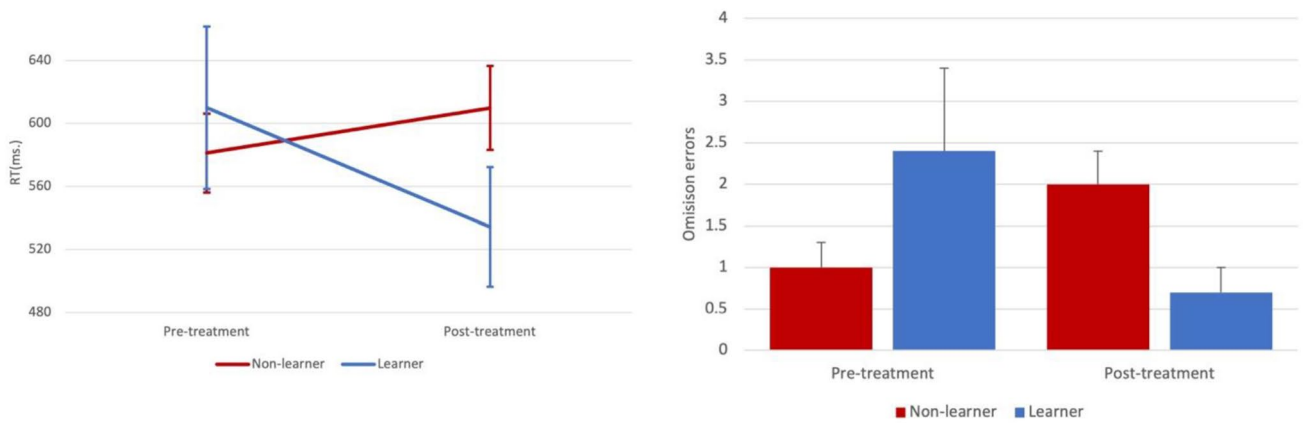

Fig. 1 Visualization of the significant Time effects for the Learner group only on WM/CPT demonstrating faster reaction times (left) and fewer inattention errors (right) post-treatment. Error bars represent standard error of the mean (SEM)

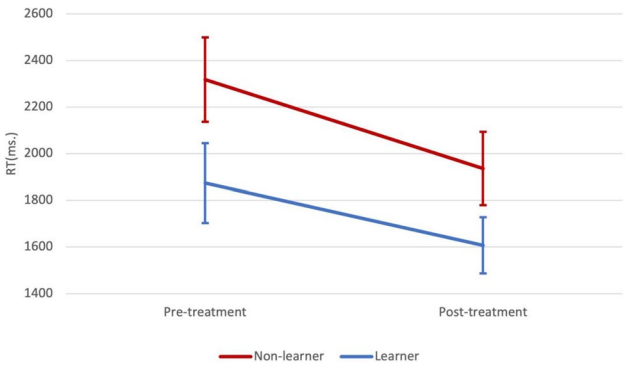

Fig. 2 The significant effect on the Trailmaking Part B average response time, note that for the Trailmaking Part A (the control condition) no differences were found, suggesting only an effect for the task component including a working memory component. Error bars represent SEM

Stroop Test

There were no main effects nor interactions involving time for the total score in the congruent condition ($p > 0.124$), however, for the Stroop incongruent condition a significant effect of Time ($p = 0.013$; $DF = 1,25$; $F = 7.195$) and a significant effect for Time X Learner ($p = 0.029$). Repeating analysis for Learners and non-Learners separately yielded an effect of Time for Learners ($p = 0.011$; $DF = 1,10$; $F = 9.8$; $d = 0.72$) of no effect for non-Learners ($p = 0.771$; $d = 0.06$) (Fig. 3). For the Stroop interference score an effect of Time was found ($p = 0.003$; $DF = 1,25$; $F = 11.045$; $d = 0.55$) and no Time X Learner interaction ($p = 0.430$) (Fig. 3), suggesting that both groups improved, and for the Learner mostly driven by a large improvement mainly in the non-congruent condition.

Tertiary Outcomes

No effects were found for the various verbal memory metrics (e.g., short term, intermediate and long-term recall; all $p > 0.248$) and memory recognition ($p > 0.147$); forward and reverse digit span ($p > 0.200$), Corsi-blocks ($p > 0.359$) and Tapping test ($p > 0.199$).

Association of Sleep and Cognition

No significant correlations were found between improvements in sleep and improvements in the cognitive outcomes.

Discussion

After on average 49 sessions of SMR tele-neurofeedback, participants were able to improve their cognitive functioning, most specifically for those that achieved control of their SMR (Learners). Eleven participants were classified as Learners, of the remaining participants no classification could be made as a result of missing data. Participants that were able to control their own SMR activity (Learners) decreased their response time on CPT/WM tasks ($d = 0.50$) and likewise decreased the number of omission errors ($d = 0.67$) relative to non-Learners. When trailmaking tests involved a working memory component, these Learners again decreased their response time ($d = 0.7$) suggesting a direct effect of neurofeedback on cognitive functions. A significant time effect was found in both groups for the Trailmaking test ($d = 0.52$), and the Stroop Interference test ($d = 0.55$), with no difference between Learners vs. non Learners, therefore these effects are likely non-specific or reflective of test–retest improvements. In the initial study by Krepel et al. (2021), SMR neurofeedback using URGOnight had already shown to significantly reduce sleep problems based on self-reported PSQI scores and HSDQ scores.

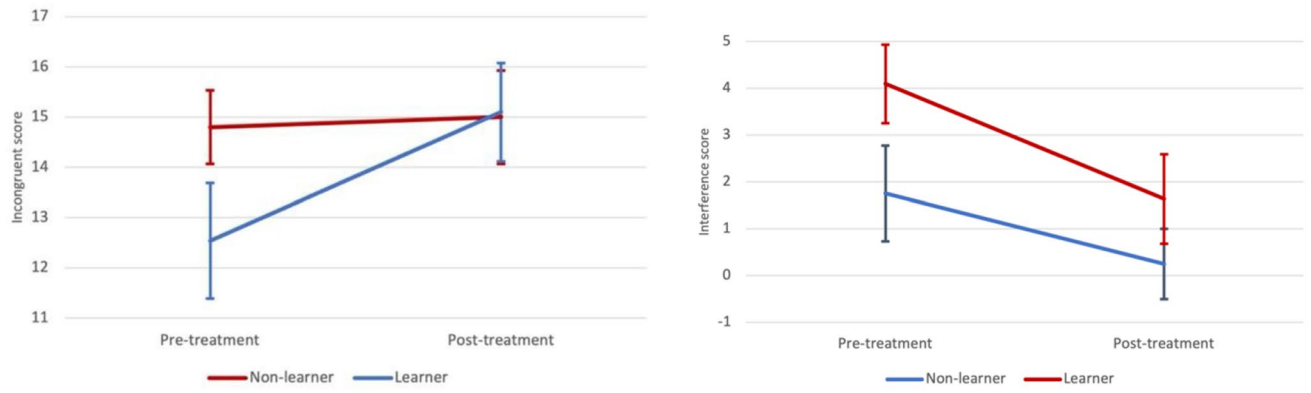

Fig. 3 Visualization of the results from the Stroop test. The Stroop Incongruent score (left) for Learners and non-Learners and the Stroop interference score on the right. Error bars represent SEM

These gains in sleep paramaters due to SMR neurofeedback including sleep duration seemed most strongly present in the Learner group. The current study extends these findings and shows that not only sleep paramaters, but also cognitive functioning, improve after SMR neurofeedback, most pronounced in the Learner group. Interestingly the specific cognitive improvements found were for attention (response time and omission errors in a CPT/WM test) and working memory (Stroop incongruent) with medium to large effect sizes, which are also the primary cognitive domains affected in ADHD (Arns & Kenemans, 2014), despite this pertaining a group of sleep disordered patients. Tertiary analyses yielded no cognitive improvements in verbal memory, memory recognition and motor tapping, confirming SMR neurofeedback has potential to improve the specific cognitive domains of (sustained) attention and working memory, in a transdiagnostic manner.

SMR neurofeedback is hypothesized to act via the reticulo-thalamocortical-cortical sleep-spindle network. By strengthening these networks, SMR neurofeedback is thought to remediate sleep problems, expressed as a reduced SOL and increased sleep duration. Since we know how closely sleep is associated with cognitive functioning, the effects of this SMR neurofeedback not only improved sleep onset- or duration-related measures, but also improved cognitive functions such as working memory and attention. In this study however, we found no significant associations between the improvements in sleep and the improvement in cognitive variables, whereby we cannot rule out, nor confirm that the cognitive improvements are mediated via sleep improvements or are a direct effect of the SMR neurofeedback. This could be attributable to the small sample size, especially in the Learner group ($N = 11$). Therefore, future research should include larger samples sizes and more controlled designs to further investigate if effects of SMR on cognition are mediated by sleep improvement or are direct effects of SMR neurofeedback. As our neurofeedback treatment approach was quite intensive, further research should take motivation during the treatment into account. To further elucidate the exact working mechanism, future studies should complement this by using he gold-standard polysomnography to more accurately quantify sleep and to track changes in sleep-spindle density as a mediator of treatment effect, using sufficient neurofeedback sessions. Also, classifying participants in Learner vs non-Learner is rather arbitrary as recent studies (Veilahtri et al., 2021) have shown non-linear neurofeedback learning pathways, which makes it unsuited for identifying late Learners.

Acknowledgements We would like to thank Vera Kruiver, Myrthe Olde Bijvank-van Eerdt, Joris van Neijenhof, Eva de Valcke, and Helena Voetterl for the data collection. We would also like to acknowledge Hanneke van Dijk, Rosalinde van Ruth, Iris van Oostrom, Monique Verhallen, and Esther Kloet for their supportive roles and contribution to this study, and Barry Sterman for his important contributions to, and valuable insights into SMR neurofeedback. We would also like to thank Beatrice Spiluttini for initiating the collaboration and Emma Touré Cuq for pursuing this project and for his contribution to the learning analysis.

Funding This study was funded by UrgoTech (Paris).

Declarations

Conflict of interest PB is an employee of UrgoTech. MA is unpaid chairman of the Brainclinics Foundation, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications related to EEG, neuromodulation and psychophysiology, but receives no royalties related to these patents; Research Institute Brainclinics received research funding from UrgoTech (France), Brainify.ai (US) and neuroCare Group (Munich, Germany), and equipment support from Deymed.

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