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Neuromodulation through brain stimulation-assisted cognitive training in patients with post-COVID-19 cognitive impairment (Neuromod-COV): study protocol for a PROBE phase IIb trial

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ABSTRACT

Introduction A substantial number of patients diagnosed with COVID-19 experience long-term persistent symptoms. First evidence suggests that long-term symptoms develop largely independently of disease severity and include, among others, cognitive impairment. For these symptoms, there are currently no validated therapeutic approaches available. Cognitive training interventions are a promising approach to counteract cognitive impairment. Combining training with concurrent transcranial direct current stimulation (tDCS) may further increase and sustain behavioural training effects. Here, we aim to examine the effects of cognitive training alone or in combination with tDCS on cognitive performance, quality of life and mental health in patients with post-COVID-19 subjective or objective cognitive impairments.

Methods and analysis This study protocol describes a prospective randomised open endpoint-blinded trial. Patients with post-COVID-19 cognitive impairment will either participate in a 3-week cognitive training or in a defined muscle relaxation training (open-label interventions). Irrespective of their primary intervention, half of the cognitive training group will additionally receive anodal tDCS, all other patients will receive sham tDCS (double-blinded, secondary intervention). The primary outcome will be improvement of working memory performance, operationalised by an n-back task, at the postintervention assessment. Secondary outcomes will include performance on trained and untrained tasks and measures of health-related quality of life at postassessment and follow-up assessments (1 month after the end of the trainings).

Ethics and dissemination Ethical approval was granted by the Ethics Committee of the University Medicine Greifswald (number: BB 066/21). Results will be available through publications in peer-reviewed journals and presentations at national and international conferences.

Trial registration number NCT04944147.

Strengths and limitations of this study

- This is the first randomised controlled trial to investigate the effects of cognitive training and transcranial direct current stimulation on cognitive outcomes and quality of life in patients with post-COVID-19 cognitive impairment.
- The Neuromod-COV trial will assess a behavioural intervention alone, and a combined behavioural and brain stimulation intervention.
- Multifaceted outcomes will allow for evaluation of interventional effects, transfer effects and effects on patient-centred measures such as quality of life.
- Monocentric trial design may increase risk of bias.

BACKGROUND

After roughly 1 year of the COVID-19 pandemic in Europe, a large number of patients with COVID-19 who have recovered from acute symptoms are still suffering from the long-term sequelae of the disease.[1–5] In hospitalised patients with COVID-19, first studies assessed the occurrence of self-reported cognitive impairment and found that 17%–38% of the patients experienced chronic memory loss.[2 3] So far, much less is known about cognitive sequelae of patients who were treated in primary care. However, first reports indicate that even without the need for assisted ventilation or even hospital admission, more than half of the patients suffer from persistent postviral fatigue, indicating the existence of severe long-lasting symptoms that outlast the acute illness.[6] Cognitive deficits following COVID-19 infection have been reported in various domains such as memory, executive functions or attention.[3 7] The

most prominent cognitive symptoms seem to concern the executive domain.[8] These deficits might be due to a number of different factors, including systemic inflammatory damage to the brain, viral encephalitis, cerebrovascular changes and dysfunction of peripheral organs, or a combination of these factors.[9–11] Cognitive impairment puts serious strains on abilities of daily living, quality of life and, especially in younger patients, on working capacity. Thus, it is of high clinical, patient-oriented and socioeconomic relevance to develop treatments for post-COVID-19 cognitive symptoms.[12 13] So far, evidence-based treatment approaches for post-COVID-19 cognitive symptoms are not available.

Previous evidence suggests that cognitive training may be beneficial to ameliorate cognitive deficits due to a number of different aetiologies, including mild cognitive impairment or dementia due to Alzheimer's disease (AD), stroke or age-related cognitive decline.[14–17] Several different training approaches have been suggested, including training of episodic memory and of working memory (WM).[18 19]

However, these programmes require a large amount of practice over many sessions, and transfer to untrained domains is limited.[20] Recently, it has been suggested that transcranial direct current stimulation (tDCS) can boost the effect of behavioural training, enhance consolidation of training effects and enable transfer to other domains.[21–23] In particular, excitatory ('anodal') tDCS over task-relevant brain regions is thought to facilitate cortical excitability by changing the resting membrane potential towards depolarisation.[24 25] Studies that applied anodal tDCS over frontal brain regions during WM practice have shown beneficial effects on trained and untrained memory functions and tasks relevant for everyday life.[26–28] Our own group has employed WM training with concurrent tDCS in several previous clinical studies in patients with subjective cognitive decline or mild cognitive impairment due to AD,[29] participants with age-related cognitive decline[30] and patients with postchemotherapy cognitive impairment (ClinicalTrials.gov identifier: NCT04817566).

However, effects of cognitive training alone or in combination with tDCS on cognitive performance, quality of life and mental health have not yet been evaluated in patients with post-COVID-19 subjective or objective cognitive impairments.

In the Neuromod-COV study, we will assess in a prospective randomised open blinded end-point (PROBE)[31] phase II clinical trial the effects of cognitive training in patients with post-COVID-19 subjective or objective cognitive impairment (open-label primary endpoint).[32] The secondary intervention (concurrent tDCS) will be assessed in a double-blinded, sham-controlled manner.

All patients will participate in a 3-week intervention consisting of three sessions per week. Patients will be randomly allocated to one of three study arms: (1) patients will train WM-updating ability while receiving anodal focalised tDCS over the left dorsolateral prefrontal cortex (DLPFC); (2) patients will train WM-updating ability while receiving sham tDCS; (3) a control group will be enrolled in defined muscle relaxation training (progressive muscle relaxation, PMR),[33] combined with sham tDCS for a total of nine sessions. Our primary hypothesis is that cognitive training with sham or active tDCS will result in more pronounced WM improvement on an untrained task (n-back) compared with the control group (PMR). We also hypothesise (secondary hypothesis) that training combined with anodal tDCS will lead to higher performance on an untrained task compared with training combined with sham tDCS. Additionally, we will determine the effects on measures of health-related quality of life (HRQoL), trained cognitive functions and untrained cognitive functions, immediately after the intervention as well as their maintenance 1 month later. This protocol describes the design and methods of the Neuromod-COV trial and was prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[34 35]

METHODS

Participants, intervention and outcomes

Design and setting

This is a monocentric, prospective randomised open endpoint-blinded (PROBE) trial evaluating the effectiveness of a 3-week cognitive training intervention versus control intervention (PMR). At secondary endpoint, the effectiveness of training with concurrent tDCS will be assessed in a double-blinded, sham-controlled manner. The cognitive training regimen will be similar to our current trials in healthy older adults and adults with subjective cognitive decline or mild cognitive impairment due to AD.[29 30] Patients with persistent subjective or objective cognitive impairment after PCR-positive (ie, laboratory-confirmed) COVID-19 will adhere to nine interventional visits and two preintervention and postintervention visits, taking place in the Department of Neurology at the University Medicine Greifswald. A follow-up visit will assess the maintenance of potential beneficial effects 1 month after the end of the intervention. Estimated study start date (as registered at ClinicalTrials.gov) was in August 2021. Primary endpoint completion is estimated to be in July 2023 and estimated study completion will be in September 2023. A flow chart of the study is shown in figure 1.

Eligibility criteria

Before randomisation, participants eligible for the study must meet all the following criteria:

- History of COVID-19 condition at least 6 weeks prior to study inclusion.
- Self-reported concerns regarding cognitive functioning (in accordance with the concept of subjective cognitive decline, cf ref 36 37).
- Age: 18–60 years (an upper age limit was chosen to exclude participants with possible age-associated

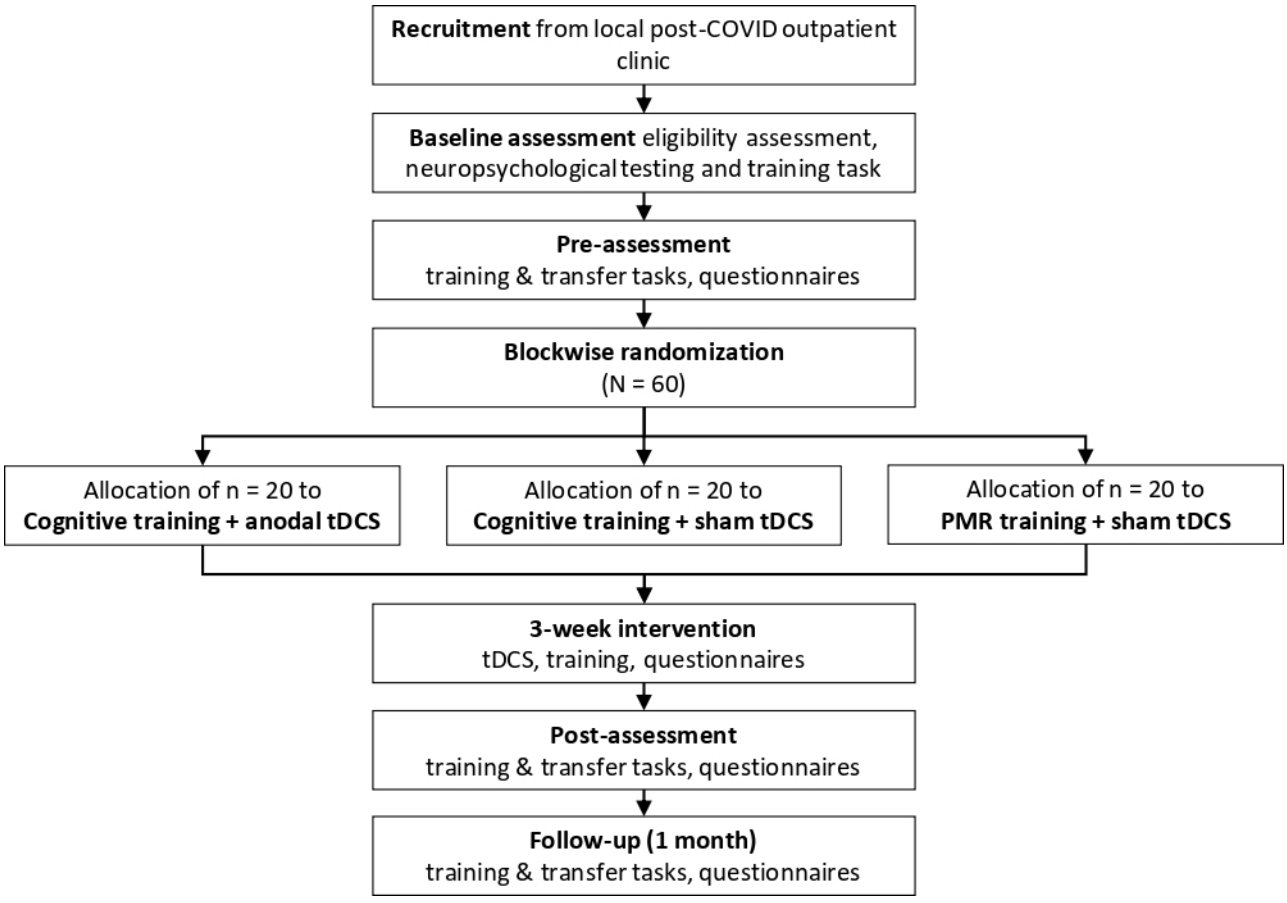

Figure 1 Neuromod-COV study flow chart. PMR, progressive muscle relaxation; tDCS, transcranial direct current stimulation.

cognitive impairment and to minimise risk of incipient neurodegenerative disease).
- Normal or corrected to normal vision.

In case one or more of the following criteria are present at randomisation, potential participants will be excluded:
- Acute COVID-19 illness.
- History of dementia before COVID-19.
- Other neurodegenerative neurological disorders; epilepsy or history of seizures.
- Severe and untreated medical conditions that preclude participation in the training, as determined by responsible physician.
- History of severe alcoholism or use of drugs.
- Severe psychiatric disorders such as severe depression (if not in remission) or psychosis.
- Contraindication to tDCS application.[38]

Eligible participants will provide written informed consent prior to study inclusion.

Intervention

Patients will be invited to nine training sessions in 3 weeks (three sessions per week). Each session will, depending on the study group, follow the same procedure: administration of anodal or sham tDCS concurrent to the letter updating training task (for active and sham tDCS groups, respectively); administration of PMR training with concurrent sham tDCS (for PMR group).

For the cognitive training groups, an established letter updating task[39] will be presented on a tablet computer to train the updating of information stored in WM. Lists of letters A–D (with lengths of 5, 7, 9, 11, 13 or 15 letters; six times each; total of 36 lists) will be presented in random order, one letter at a time (presentation duration: 2000 ms, interstimulus interval: 500 ms). After each list, patients will be asked to recall the last four letters that were presented.

For the PMR group, PMR[33] will be administered for approximately 20 min per session, matching the duration of the cognitive training task. While PMR has been shown to reduce anxiety, fatigue or negative emotions,[40] to date there is no specific evidence of PMR with regard to cognitive impairment. We thus chose PMR as a non-specific control intervention for tailored training of WM performance. Trained study personnel will read out standardised PMR instructions which involve sequential tension and relaxation of different muscle groups along the whole body combined with controlled breathing exercise. As the cognitive training group will receive concurrent tDCS (either anodal or sham), we decided to perform PMR training under sham tDCS as well. This will make the circumstances during PMR training as comparable to the cognitive training as possible, and we will thus avoid possible bias through the tDCS set-up (eg, bias due

to more contact with study staff during set-up or due to placebo effects).

tDCS will be administered in a double-blinded fashion via a battery-operated stimulator (Neuroelectrics Starstim 8, Barcelona, Spain) and a multielectrode set-up that allow for focal delivery of electric current.[41 42] Electrodes (NG Pistim, 1 cm diameter) will be placed in a 32-channel cap and filled with highly conductive saline gel (Signagel). The anode will be placed over the left DLPFC, as determined by position F3 from the 10-20 *electroencephalogram* system. Four return electrodes will be arranged in a circle around the anode to constrain the current flow to the target region. Stimulation will be administered with 2 mA and a local anaesthetic (EMLA cream) will be applied prior to stimulation to ensure participant blinding in both stimulation conditions. Stimulation will consist of 20 min of continuous stimulation with 20 additional seconds of gradually ramping the current up and down at the beginning and end of stimulation, respectively. In the sham tDCS group, the same electrode montage and ramp time will be used, but current will only be applied for 30 s to assure blinding of participants regarding the stimulation condition.[41 43] Stimulation will be started simultaneously with the training. Participants will be instructed to avoid excessive alcohol consumption or smoking on the day of the study, to adhere to their usual sleep duration and to avoid drinking caffeine 90 min prior to the training visits. Perception of adverse events (AE) related to the stimulation will be assessed every third interventional visit using a standardised questionnaire.[38]

Outcome measures

Outcome measure for the training task will be acquired at each visit. Additionally, outcomes for possible untrained domains will be acquired at preassessment, postassessment and follow-up assessment. All assessment time points and respective acquired measures are displayed in table 1. Analyses for each measure will compare potential differences between cognitive training (with or without anodal tDCS) and PMR groups as well as differences between cognitive training with anodal tDCS compared with cognitive training with sham tDCS.

Primary outcomes

The primary outcome measure will be WM performance at postassessment, operationalised by per cent change of correct responses in the n-back task compared with the pretraining assessment.

Secondary outcomes

Secondary outcome measure will be WM performance at 1-month follow-up assessment, operationalised by per cent change of correct responses in the n-back task compared with the pretraining assessment; additionally, performance in the training task assessing WM updating, operationalised by number of correctly recalled lists in the letter updating task, and performance in an untrained task assessing visuospatial memory, operationalised by number of correctly recalled items in a virtual reality (VR) task[44] at the postvisit and follow-up visit. Further, secondary outcomes assessed at previsit, postvisit and follow-up visit will comprise the sensitivity measure d-prime for performance on the n-back task (adjusted according to ref 45), Patient-Reported Outcome Measurement Information System (PROMIS)[46] scores for HRQoL (PROMIS-Preference score, including scores of subscales; eg, cognitive function), scores on the Post-COVID Functional Scale (PCFS)[47] and general activity measures (habitual bedtimes and wake times), monitored using an actigraphy device (GT3X, ActiGraph, Pensacola, Florida, USA).

Participant timeline

Patients will adhere to 13 visits (four assessments, nine intervention sessions) taking place at the University Medicine Greifswald. After completion of a baseline assessment (V0), eligible patients will successively be invited to start the training sessions (V2–V10), which will be scheduled across three consecutive weeks for 3 days/week. Three days before and after the intervention, preassessment (V1) and postassessment (V11) will be conducted. During the weeks prior to and after the intervention, general activity will be monitored using an actigraphy device. Four weeks after postassessment, the follow-up visit (V12) will take place.

Baseline measures

During the baseline visit (V0), written informed consent of the patients will be obtained. Subsequently, the medical history with regard to COVID-19 will be assessed and the Diagnostic Interview for Psychiatric Disorders (DIPS)[48] will be conducted to exclude possible psychiatric disorders. Baseline neuropsychological testing and questionnaires will also be administered, if not already assessed in the post-COVID-19 outpatient clinic within the last 6 months (table 1). Furthermore, the training task will be performed as described above, except that at baseline, the letter updating task starts with one practice trial with four lists. The baseline visit will take approximately 3 hours.

Preassessment, postassessment and follow-up assessment

At previsit, postvisit and follow-up visit (V1, V11, V12), the investigator will perform a semistructured interview on the self-reported well-being of the participant, quality and duration of sleep and potential stressors 2 hours prior to the visit. Then, PROMIS, sleeping behaviour and post-COVID-19 function questionnaires will be administered and the training task (letter updating) and untrained tasks (n-back and VR tasks) will be performed. During the weeks prior to and after the intervention, patient's general activity will be recorded with an actigraphy device (table 1).

Sample size

Power calculation is based on recent studies using multisession application of cognitive training compared with a control training on immediate performance in the

Table 1 Neuromod-COV outcome measures

			Baseline	Pre	T1–T9 (3 weeks)	Post (3 days)	FU (1 month)
			~3 hours	~3 hours	~1 hour	~3 hours	~3 hours
Time point	**Measurement**	**Mode**	**V0**	**V1**	**V2–V10**	**V11**	**V12**
Enrolment							
Informed consent		Paper	x				
Eligibility screening	Medical history	Paper	x				
	DIPS	Paper	x				
Neuropsychological screening	VLMT, ROCF, DS, TMT, Stroop test, VF, MoCA	Paper	x				
Questionnaires	MCRS, ITQ, IQCODE, CTS, FAS, VR12, PSQI	Paper	x				
Intervention					⟷		
Training tasks	Letter updating	Tablet PC	x	x	x*	x	x
	PMR	Instructed			x†		
Brain stimulation	tDCS (anodal vs sham)	Device			x		
Questionnaires	Initial state questionnaire	Paper	x	x	x	x	x
	PANAS	Paper			x		
Additional assessments							
Untrained tasks	n-back	Computer		x		x	x
	Virtual reality task	Computer		x		x	x
Questionnaires	PROMIS	Paper		x		x	x
	Sleeping behaviour	Paper		x		x	x
	Post-COVID Functional Scale	Paper		x		x	x
	Adverse events questionnaire	Paper			x‡		
General activity	Actigraphy	Device		x		x	

*Only for cognitive training groups.
†Only for PMR group.
‡Assessed only at the end of each training week (V4, V7 and V10).
CTS, Childhood Trauma Screener; DIPS, Diagnostic Interview for Psychiatric Disorders; DS, Digit Span Test; FAS, Fatigue Assessment Scale; FU, follow-up assessment; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; ITQ, International Trauma Questionnaire; MCRS, Median COVID Recovery Score; MoCA, Montreal Cognitive Assessment; PANAS, Positive and Negative Affect Schedule; PMR, progressive muscle relaxation; PROMIS, Patient-Reported Outcome Measurement Information System; PSQI, Pittsburgh Sleep Quality Index; ROCF, Rey-Osterrieth Complex Figure Test; tDCS, transcranial direct current stimulation; TMT, Trail Making Test; T1–T9, trainings 1–9; VF, (semantic) verbal fluency; VLMT, verbaler Lern-und Merkfähigkeitstest (German version of the auditory verbal learning test); VR12, Veterans RAND Health Survey 12; V0–V12, visits 0–12.

trained task (primary outcome).[49–51] Based on these data, we estimated an effect size of 0.8 (Cohen's d). To demonstrate an effect in the primary outcome between cognitive training groups and control (% correct in the n-back task for training groups vs PMR group) with an independent t-test using a two-sided significance level of α=0.05 and a power of at least 80%, 60 participants (40 for cognitive training groups (for secondary comparison of training plus anodal vs sham tDCS groups), 20 for PMR group) need to be included. This conservative approach using a t-test was chosen, even though we intend to analyse the primary outcome conducting analysis of covariance models.[52] This monocentric clinical trial will serve to calculate the sample size for a subsequent multicentre clinical trial. Sample size estimation was conducted using R software (http://www.R-project.org) and the pwr package (https://cran.r-project.org/package=pwr).

Recruitment

Patients from the local post-COVID-19 outpatient clinic will be informed about the possibility to participate in the study, receiving both oral and written information.

Assignment of interventions

Allocation to the training and anodal tDCS, training and sham tDCS and PMR and sham tDCS groups will be performed using stratified block randomisation with variable block length. Participants will be randomly allocated by a researcher not involved in assessments. Allocation to the three experimental groups will be performed with a 1:1:1 ratio with performance in the n-back task at preassessment (two performance strata; ≤87% correct and >87% correct in the n-back task) as strata. Randomisation blocks with varying block sizes will be generated for each of the two randomisation groups using R software (http://www.R-project.org) and the blockrand package (https://CRAN.R-project.org/package=blockrand). Participants will then be allocated to the anodal tDCS, sham tDCS or PMR groups, based on the generated randomisation sequences within each block and stratum.

Blinding

Endpoint assessors, who will conduct data analyses, will be blinded to the study conditions, as all data will be entered with blinded record of group allocation. Spreadsheets containing allocation information will be stored separately and will only be available to personnel responsible for the randomisation procedure.

For cognitive training groups, double blinding of study personnel and patients will be feasible. This will be ensured by using preconfigured tDCS and sham stimulation protocols. Study personnel will be unaware of which stimulation protocol runs anodal stimulation and which sham. The 'blinded mode' of the stimulation software will prevent study assessors into the ongoing stimulation protocol (ie, active or sham). Participants in all three groups will be blind to the stimulation condition. To blind participants, in the sham tDCS groups (ie, one cognitive training group and PMR group), current will be applied for 30 s, as previous research showed that sham tDCS is a safe and valid method of blinding study participants.[41 43] After the last training visit, participants will be asked to state whether they believed they received anodal or sham tDCS.

Data collection, management and analysis

Data collection methods

Neuropsychological and behavioural data will be collected from each participant. Study assessors will be thoroughly trained in administering the assessments. In table 1, time points of data collection are shown.

Neuropsychological and behavioural assessment

At baseline visit (V0), unstandardised and semistructured interviews will be performed to assess patients' medical history and screen for psychiatric disorders (DIPS[48]). Neuropsychological testing, if not assessed as part of the post-COVID-19 outpatient consultation, or conducted more than 6 months prior, comprises cognitive screening with the Montreal Cognitive Assessment[53] and assessment of verbal memory (verbaler Lern-und Merkfähigkeitstest),[54] visuospatial memory with the Rey-Osterrieth Complex Figure Test,[55] WM with the digit span,[56] and Trail Making Test and executive functions with the Stroop[57] and semantic verbal fluency tests. Furthermore, the following paper-pencil questionnaires to quantify quality of life, self-reported cognitive and emotional functioning, well-being and sleep quality will be conducted at the local post-COVID-19 outpatient clinic and transferred to the case report forms if patients consent: Median COVID Recovery Score (contains Generalized Anxiety Disorder Scale-7,[58] Patient Health Questionnaire 9[59] and International Trauma Questionnaire (ITQ Part 1),[60] Informant Questionnaire on Cognitive Decline in the Elderly,[61] Childhood Trauma Screener,[62] Fatigue Assessment Scale,[63] Veterans RAND Health Survey 12,[64] Pittsburgh Sleep Quality Index).[65] The letter updating training task will be performed at every visit and is described in detail in the Intervention section.

Computer-based assessments of the two untrained tasks and paper-pencil questionnaires will be administered at previsit, postvisit and follow-up visit (V1, V11–13): first, patients will perform a numeric n-back task (1-back and 2-back) to assess WM, followed by a VR maze task[44] assessing visuospatial memory. PROMIS,[46] Epworth Sleepiness Scale,[66] Morningness-Eveningness Questionnaire[67] and PCFS[47] will be administered as well.

Retention and adherence

Patients will be provided with information about their appointments via telephone and detailed study information and a printout of all the sessions will be handed out to ensure retention throughout the study. Time and date of the next visit will be discussed at each visit. In case of not being able to attend a visit or wanting to reschedule, participants will be encouraged to leave a message on the study site's 24/7 answering machine and will then be contacted by the study team. All study participants will receive a reasonable financial reimbursement (approximately €10 per hour). If complete adherence to the protocol is not possible, any effort to collect as much data as feasible will be made.

Data management and monitoring

To ensure data security, patients' data will be pseudonymised and any record containing patient IDs or personal data will be secured with a password, solely accessible for study staff. Digital data, that is, output files from computer-based tasks, will be stored on a secure file server directly after acquisition. Non-digitally acquired data will be manually digitalised by a member of the research staff and double-checked by another member. Progress of data entry and checking procedures will be documented. Files containing subject records will be stored securely. Sensitive data, such as names and medical records, will be stored separately in a lockable cabinet. All digitally acquired data, for example, output files from computer-based tasks, will be stored on a secure file server. Following

good scientific practice, data will be stored for at least 10 years.

Patient and public involvement

Patients were involved in selection of secondary endpoints including assessments of quality of life and social support. We will conduct a brief semistructured interview at the last visit (V13) to assess the patients' satisfaction with the trial and answer any upcoming questions. All patients will be informed about the study details (eg, the experimental group they participated in) on completion of the study.

AE monitoring

Cognitive training may lead to frustration and lack of motivation, particularly when patients perceive the training tasks as very difficult. During both multisession cognitive training and PMR, some patients might experience boredom due to the repetitive character of the respective training programmes. To prevent patients' frustration, study personnel will be instructed to keep the patients motivated by providing feedback on training progress and mitigating unrealistic expectations regarding training effects.

Using the parameters and procedures outlined above, tDCS permits painless modulation of cortical activity and excitability through the intact skull and current evidence indicates that tDCS is a well-tolerated technique, resulting only in minimal side effects.[38] For standard tDCS parameters (maximum intensity 2 mA), reported side effects were mild, short lived, well tolerated and restricted to itching, tingling, headache, burning sensation and discomfort.[68 69] Similar mild AEs have been reported for focalised tDCS protocols.[70–72] Patients will be informed about all possible risks and about their right to withdraw consent at any time without providing cause. An AE questionnaire[38] will be implemented at the end of every third stimulation visit (V4, V7, V10), to monitor possible AEs at a reasonable frequency, without drawing the participant's attention too much to stimulation-induced sensations, and cause distractions from the tasks. Further, study assessors will monitor and document possible incidence of AEs and serious AEs (SAEs, as defined by the Guideline for Good Clinical Practice of the International Conference of Harmonisation[73]). In case an SAE occurs, the study physician will first make an assessment as to whether a causal relationship with the intervention is considered possible. If more than three of the enrolled participants suffer from SAEs that are likely to be associated with the intervention (as assessed by the study physician), the trial will be discontinued.

Statistical analysis

The primary outcome, per cent change of correct responses in the n-back task compared with the pretraining assessment, will be analysed using linear mixed models with change of correct n-back as dependent variable, group allocation (cognitive training (n=20+20) vs PMR (n=20)) as factor and preassessment n-back performance as covariate. Similar linear mixed models will be conducted for secondary outcomes with experimental group as between-subjects factor. All models will be corrected for age and performance at preassessment on the task included in the respective model. We will use random intercept models that account for the clustering of measures within individuals. In case of violation of requirements for parametric methods, data will be transformed before analysis or appropriate non-parametric tests will be conducted. Analyses of primary and secondary outcomes will be reported in detail in the statistical analysis plan to be written and registered before unblinding of investigators performing the analyses. Confirmatory analysis of treatment effects will be conducted within an intention-to-treat framework with multiple imputed data sets in case of missing data (under the assumption of missing completely at random or missing at random). Further as sensitivity analyses, we will perform 'per protocol' analyses, including only those participants who finished postassessment. Data analysis will be conducted using IBM SPSS Statistics for Windows Version 25 (IBM), MATLAB (MathWorks, 2016) and R software (https://www.R-project.org).

ETHICS AND DISSEMINATION

The study was approved by the Ethics Committee of the University Medicine Greifswald and will be conducted in accordance with the Helsinki Declaration. All data collected will be pseudonymised. Any substantial amendments to the study protocol will be submitted to the institutional ethics committee for review and approval and will be included in publications reporting the results of this trial. Study results will be disseminated through peer-reviewed journal articles and contributions to national and international scientific conferences. Furthermore, the scientific and lay public can access the study results on the ClinicalTrials.gov website.

DISCUSSION

With this trial, we will for the first time investigate the immediate and long-term effects of a cognitive training intervention and a combined training and brain stimulation intervention on trained (WM) performance and transfer to other domains in patients with post-COVID-19 cognitive impairment. The study results will contribute to the development of urgently needed therapies for a new clinical condition.

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Contributors FT, DA and AF conceptualised and designed this trial. AF is supervising its implementation. SS, AS, MM and RF provided resources and expertise for assessment of quality of life and COVID-specific measures. FT, DA and E-LB will be implementing the trial and supervise its conduct. FT will perform recruitment and assessments. FT drafted the study protocol. UG will be performing statistical analyses. FT, DA, RF, MM, UG, SS, E-LB, AS and AF will be contributing to interpretation of the data. All authors read and revised the original draft and consecutive versions of the manuscript. All authors read and approved the final version of the study protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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