Statistical Analysis Plan (SAP)

"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" Acronym: **Neuromod-COV**

Version 1
Date: 25.11.2024

Intervention therapy: Nine-session cognitive training over three weeks, with either anodal or sham tDCS applied over the left dorsolateral prefrontal cortex (DLPFC).
Control therapy: Nine-session Progressive Muscle Relaxation (PMR) over three weeks, with sham tDCS.
Study population: Post-COVID patients with subjective or objective cognitive impairment
Clinical phase: Mono-centric prospective randomized open endpoint-blinded trial.
Clinicaltrials.gov Identifier: NCT04944147
Study protocol: Thams, F., Antonenko, D., Fleischmann, R., Meinzer, M., Grittner, U., Schmidt, S., Brakemeier, E. L., Steinmetz, A., & Flöel, A. (2022). 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. BMJ open, 12(4), e055038. https://doi.org/10.1136/bmjopen-2021-055038

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1. Study objective

A significant proportion of COVID patients experience persistent long-term symptoms (1–4), including cognitive deficits in attention, executive functions and memory (3,5,6). These cognitive impairments can impact daily living abilities, quality of life, and working capacity. Currently, there are no evidence-based treatment approaches for cognitive symptoms following post-COVID. Cognitive training interventions are a promising approach to counteract cognitive impairment (7–10). Moreover, transcranial direct current stimulation (tDCS) may enhance the effects of behavioral training, improve the consolidation of training outcomes, and facilitate transfer to other cognitive domains (11–13). However, the efficacy of cognitive training alone or in combination with tDCS on cognitive performance, quality of life, and mental health has not been evaluated in post-COVID patients with subjective or objective cognitive decline. The Neuromod-COV trial (14) aims to fill this gap by assessing the immediate and delayed effects of cognitive training, with or without concurrent tDCS, on cognitive performance, quality of life and mental health in patients experiencing post-COVID subjective or objective cognitive impairments.

The analyses described in this Statistical Analysis Plan will evaluate the efficacy of a three-week cognitive training intervention with or without concurrent tDCS in patients with post-COVID cognitive impairments. This SAP has been prepared following the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (15). The trial will be reported following the Consolidated Standards of Reporting Trials [CONSORT (16)].

1.1. Study design

This study is a monocentric, prospective, randomized, open-blinded endpoint (PROBE) (17) phase II clinical trial designed to evaluate the effectiveness of a cognitive training intervention compared to a control intervention [Progressive Muscle Relaxation; PMR (18)] in patients with post-COVID subjective or objective cognitive impairment (primary endpoint).

Patients with post-COVID cognitive impairment participate in a three-week intervention program consisting of nine sessions (three per week) of either cognitive training or PMR (18) (open-label interventions). In the cognitive training group, participants are further divided into two subgroups: half receive anodal tDCS while the other half receive sham tDCS in a double-blinded, sham-controlled manner (secondary endpoint). Thus, participants are randomly allocated to one of three study arms: (1) cognitive training with anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC); (2) cognitive training with sham tDCS over the left DLPFC; or (3) PMR with sham tDCS.

Random allocation to these three groups is done through a stratified block randomization method with variable block length, using a 1:1:1 ratio. The stratification is based on participants' performance in the n-back task during pre-assessment, with two strata: those scoring ≤87% correct and those scoring >87% correct. The randomization sequences are generated using the R software's *blockrand* package (https://CRAN.R-project.org/package=block- rand; http://www.R-project.org). Following a telephone screening and baseline assessment, eligible participants who provide written informed consent are randomly assigned to a study arm according to the generated randomization sequence within each block and performance stratum.

Secondary hypotheses related to the comparison of the two cognitive training arms with active or sham tDCS, will be evaluated in a double-blinded, sham-controlled manner.

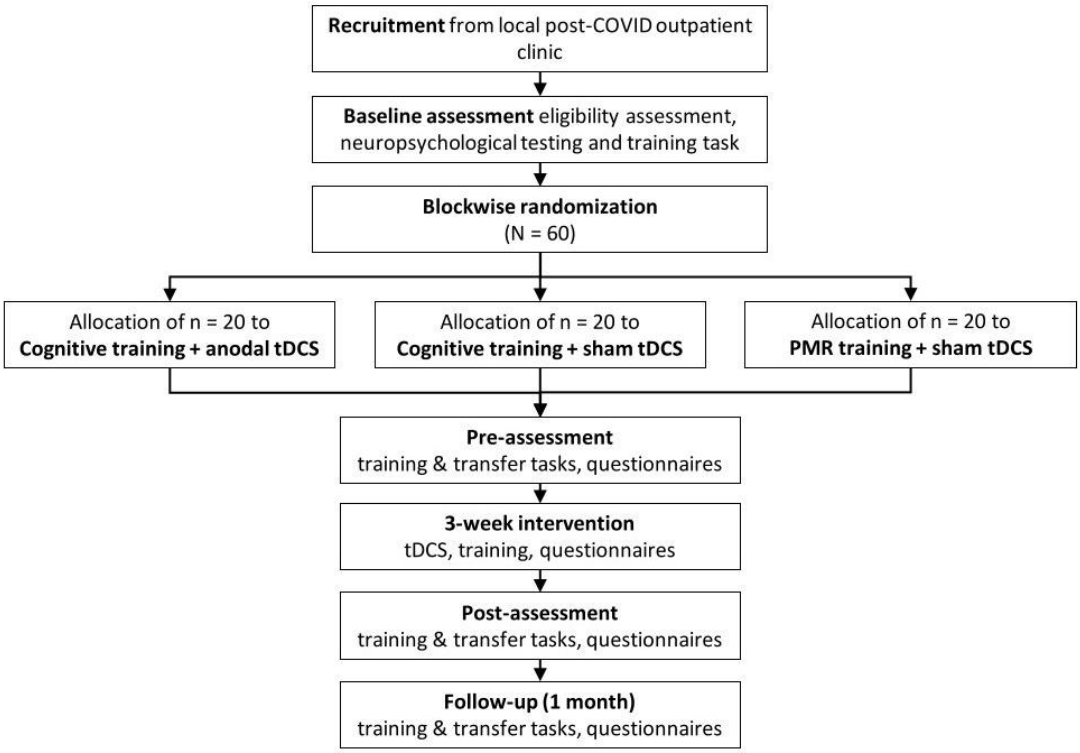

Figure 1. Neuromod-COV study flowchart. tDCS: transcranial direct current stimulation; PMR: Progressive Muscle Relaxation. Obtained from Neuromod-COV study protocol (14).

1.2. Primary hypothesis

- Cognitive training, combined with either active or sham tDCS, will result in greater improvement in untrained working memory performance at post-assessment compared to the control group receiving PMR in post-COVID patients. This outcome is operationalized by the percentage of correct responses on the n-back task at post-assessment.

1.3. Secondary hypotheses

- **Cognitive training with either active or sham tDCS will result in greater improvements at post- and follow-up assessments compared to the control group (PMR) in post-COVID patients** across multiple domains: (a) untrained working memory, measured by the percentage of correct responses on the n-back task (transfer task); (b) trained working memory, measured by the number of correctly recalled lists on the letter updating task; (c) visuospatial memory, measured by the number of goals reached on the virtual reality task; (d) working memory discrimination, measured by the d-prime scores on the n-back task; (e) health-related quality of life, measured by the preference-based scores (PROPr scores) on the Patient Reported-Outcomes Measurement Information System (PROMIS®) 29-Profile v2.1; (f) subjective cognitive functioning, measured by the T-scores on the PROMIS®

Cognitive Function Scale (short form 8a - v2.0); (g) post-COVID functional status, measured by the total raw scores on the Post-COVID Functional Scale (PCFS); and (h) sleep efficiency levels, measured as the percentage of time spent asleep relative to total time in bed, as recorded by an actigraphy device.

These outcomes will be assessed at post- and follow-up assessments, except for (a) untrained working memory, which will be evaluated only at the follow-up assessment, and (g) sleep efficiency levels, which will only be measured at the post-assessment.

- **Cognitive training with active tDCS will result in greater improvements at post and follow-up assessments compared to cognitive training with sham tDCS in post-COVID patients** across multiple domains: (a) untrained working memory, measured by the percentage of correct responses on the n-back task (transfer task); (b) trained working memory, measured by the number of correctly recalled lists on the letter updating task; (c) visuospatial memory, measured by the number of goals reached on the virtual reality task; (d) working memory discrimination, measured by the d-prime scores on the n-back task; (e) health-related quality of life, measured by the PROPr scores on the PROMIS® 29-Profile v2.1; (f) subjective cognitive functioning, measured by the T-scores on the PROMIS® Cognitive Function Scale (short form 8a - v2.0); (g) post-COVID functional status, measured by the total raw scores on the PCFS; and (h) sleep efficiency levels, measured as the percentage of time spent asleep relative to total time in bed, as recorded by an actigraphy device.

  These outcomes will be assessed at both post and follow-up assessments, except for the (g) sleep efficiency levels, which will only be measured at post-assessment.

1.4. Sample size calculation

The power calculation is based on recent studies using multi-session cognitive training interventions compared to control training (19–21), focusing on immediate performance in the trained task. Based on these findings, we estimated an effect size of Cohen's $d = 0.8$. To detect an effect in the primary outcome (percentage of correct responses on the n-back task between the cognitive training and control PMR groups) using an independent t-test with a two-sided significance level of $\alpha = 0.05$ and a power of at least 80%, 60 participants are required. This includes 40 participants for the cognitive training groups (for secondary comparisons of training combined with anodal vs. sham tDCS) and 20 participants for the PMR group. Even though we intend to analyze the primary outcome using covariance models, a conservative t-test approach was chosen for the power calculation. The sample size was estimated using the R software's *pwr* package (https://cran.r-project.org/package=pwr, http://www.R-project.org). This monocentric clinical trial will enable us to calculate the sample size for a subsequent multicenter clinical trial applying tDCS-accompanied cognitive training.

2. Analysis sets

2.1. Definitions

The **full analysis set** will consist of all randomized participants who received at least one day of intervention. If participants withdraw informed consent after baseline assessment, they will be considered screening failures and, therefore, will not be included in the full analysis set. The

per-protocol analysis set comprises all subjects who received the full three weeks of intervention or control intervention and completed all visits in the treatment groups they were allocated to. Safety outcomes [see Safety outcomes section (22)] are assessed during tDCS intervention, and all participants who received at least one intervention will be included in the safety analysis set according to their actual treatment. Since no participant received other treatment as intended or switched treatment groups during the study, and no information on safety measures is available for participants who missed intervention or follow-up visits or dropped out, the safety analysis set is the same as the per protocol analysis set in this study.

2.2. Application

The primary efficacy analysis will be done using the full analysis set, including estimated values from multiple imputations for missing values (Intention to treat). A sensitivity analysis of the primary outcome in the per-protocol analysis set will be conducted. The safety analysis will be done in the safety analysis set, which is the same as the per-protocol analysis set.

3. Trial centers

Participant recruitment takes place at one center: *Universitätsmedizin* Greifswald.

3.1. Recruitment

Patients are recruited from the post-COVID-19 outpatient clinic at the *Universitätsmedizin* Greifswald. We also search for participants by distributing flyers to local post-COVID support groups and placing announcements in the local newspaper. Interested participants are provided with detailed information about the study, both orally and in writing. All potential participants undergo a telephone screening, where study details are also explained. Those who meet the eligibility criteria are invited to attend a baseline assessment. The recruitment process is shown in the CONSORT flow diagram (Figure 1).

4. Analysis variables

All measures are detailed below in Table 1.

4.1. Primary outcome

Untrained working memory performance at post-assessment, measured by the percentage of correct responses on the n-back task (23).

4.2. Secondary outcomes

Secondary outcomes will be assessed at both post-assessment and follow-up with specific exceptions indicated by an asterisk (*). These include:

- Untrained working memory performance, measured by the percentage of correct responses on the n-back task [(23) *at follow-up assessment].
- Trained working memory performance, measured by the number of correctly recalled lists on the letter updating task (24).

- Untrained visuospatial memory performance, measured by the number of reached goals on the virtual reality task (25).
- Working memory discrimination, measured by the d-prime scores on the n-back task (23,26).
- Health-related quality of life, measured by the PROPr scores (27) on the PROMIS® 29-Profile v2.1 (28).
- Subjective cognitive functioning, measured by the T-scores on the PROMIS® Cognitive Function Scale [short form 8a - v2.0; (28)].
- Post-COVID functional status, measured by the total raw scores on the PCFS (29).
- Sleep efficiency levels, measured as the percentage of time spent asleep relative to total time in bed, as recorded by an actigraphy device (*at post-assessment).

4.3. Safety outcomes

Safety is assessed through an adapted (22) self-report questionnaire administered every third training day (V4, V7 and V10). This questionnaire asks participants to rate the intensity of various sensations, including itching, pain, burning, warmth/heat, metallic or iron taste, fatigue, decreased alertness, and others.

Table 1. Neuromod-COV outcome measures. Adapted from Neuromod-COV study protocol (14).

			Baseline	**Pre (3 days before T1)**	**T1-T9 (9 sessions for 3 weeks)**	**Post (3 days after T9)**	**FU (1 month after Post)**
			~ 3h	**~ 3h**	**~ 1h**	**~ 3h**	**~ 3h**
Time point	**Measurement**	**Mode**	**V0**	**V1**	**V2-V10**	**V11**	**V12**
Enrollment							
Informed consent		Paper	x				
Eligibility screening	Medical history	Paper	x				
	Mini-DIPS (30)	Paper	x				
Questionnaires	Demographics	Paper	x				
Neuropsychological screening	VLMT (23) ROCF (31) DS (32) TMT(23) Stroop (33) PF (23) SF (23)	Paper	x				
Intervention					⟷		
Training tasks	Letter updating task (24)	Tablet-PC	x	x	x [a]	x	x
	PMR (18)	Instructed			x [b]		
Brain stimulation	tDCS (anodal vs. sham)	Device			x		

Questionnaires	Initial state questionnaire	Paper	x	x	x	x	x
	PANAS (34)	Paper			x		
	Adverse events questionnaire [c] (22)	Paper			x		
Additional assessments							
Untrained tasks	n-back task (23)	Computer		x		**X**[d]	x
	Virtual reality task (25)	Computer		x		x	x
Questionnaires	PROMIS® (29-Profile v2.1 & Cognitve functioning SF 8a v2.0; 28)	Paper		x		x	x
	Sleeping behavior: PSQI (35) ESS (36) MEQ (37)	Paper		x		x	x
	PCFS (29)	Paper		x		x	x
General activity	Actigraphy	Device		x		x	

T1-T9: trainings 1-9; FU: follow-up assessment; V0-V12: visits 0-12; Mini-DIPS: Brief Diagnostic Interview for Psychiatric Disorders; VLMT: German version of the auditory verbal learning test; ROCF: Rey-Osterrieth Complex Figure Test; DS: Digit Span Test; TMT: Trail Making Test. Stroop: Stroop Test; PF: Phonological fluency; SF: Semantic fluency; PMR: Progressive Muscle Relaxation; tDCS: transcranial Direct Current Stimulation.
PANAS: Positive and Negative Affect Schedule; PROMIS®: Patient-reported Outcome Measurement Information System; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; MEQ: Morningness-Eveningness Questionnaire; PCFS: Post-COVID Functional Scale.
[a] Only for cognitive training groups.
[b] Only for the PMR group.
[c] Assessed every third training day (V4, V7 and V10).
[d] Primary outcome

5. Handling of missing values

In cases of missing data and assuming the data are missing at random (MAR) or completely at random (MCAR), multiple imputation will be used to estimate the missing values with 30 imputed datasets.

6. Statistical analyses

For all outcomes and time points, we will present appropriate descriptive statistics (mean, standard deviation, median, interquartile range, and absolute and relative frequencies) depending on the scale and distribution of each outcome variable in total (only at pre-assessment) and by group. The statistical analyses will evaluate the immediate treatment effects at post-assessment (V11) and the sustained treatment effects at the one-month follow-up

assessment (V12). In the secondary analyses, we will compare the cognitive training and groups, as well as the cognitive training groups receiving active versus sham tDCS.

6.1. Primary analysis

- Treatment effects on the transfer task (n-back task) at post-assessment will be analyzed using a linear mixed-effects model. This model will include the n-back performance at post- and follow-up assessments (percentage of correct responses) as the dependent variable. Fixed effects will include group (cognitive training vs. PMR), measurement time point (post vs. follow-up) and task difficulty (1-back vs. 2-back). Control covariates will include the n-back performance at pre-assessment (percentage of correct responses), age, and sex. A random intercept for subjects will also be included. The primary outcome (immediate transfer effects at post-assessment) will be estimated via marginal means (95% CI) from this model.

6.2. Secondary analyses

Effects of cognitive training vs. PMR

- Treatment effects on the transfer task (n-back task) at follow-up assessment will be examined by estimating marginal means (and 95% CI) from the model above.

- Treatment effects on the training task (letter updating task) at post- and follow-up assessments will be analyzed using a linear mixed-effects model. This model will include the letter updating performance at post- and follow-up assessments (number of correctly recalled lists) as the dependent variable. Fixed effects will include group (cognitive training vs. PMR) and measurement time point (post vs. follow-up). Control covariates will include the letter updating performance at pre-assessment (number of correctly recalled lists), age, and sex. A random intercept for subjects will also be included. Immediate and sustained training effects at post- and follow-up assessments will be estimated via marginal means (95% CI) from this model.

- Treatment effects on the visuospatial memory task (virtual reality task) at post- and follow-up assessments will be analyzed using a linear mixed-effects model. This model will include the virtual reality task performance at post- and follow-up assessments (number of goals reached) as the dependent variable. Fixed effects will include group (cognitive training vs. PMR) and measurement time point (post vs. follow-up). Control covariates will include the virtual reality task performance at pre-assessment (number of goals reached), age, and sex. A random intercept for subjects will also be included. Immediate and sustained effects on visuospatial memory performance at post- and follow-up assessments will be estimated via marginal means (95% CI) from this model.

- Treatment effects on working memory discrimination (n-back task d'prime scores) at post- and follow-up assessment will be analyzed using a linear mixed-effects model. This model will include the n-back d'prime scores at post-and follow-up assessments as the dependent variable. Fixed effects will include group (cognitive training vs. PMR), measurement time point (post vs. follow-up) and task difficulty (1-back vs. 2-back). Control covariates will include the n-back d'prime scores at pre-assessment, age, and sex. A random intercept for subjects will also be included. Immediate and sustained effects on working memory discrimination at post- and follow-up assessments will be estimated via marginal means

(95% CI) from this model.

- Treatment effects on health-related quality of life (PROMIS® PROPr scores) at post- and follow-up assessment will be analyzed using a linear mixed-effects model. This model will include the PROMIS® PROPr scores at post-and follow-up assessments as the dependent variable. Fixed effects will include group (cognitive training vs. PMR) and measurement time point (post vs. follow-up). Control covariates will include the PROMIS® PROPr scores at pre-assessment, age, and sex. A random intercept for subjects will also be included. Immediate and sustained effects on health-related quality of life at post- and follow-up assessments will be estimated via marginal means (95% CI) from this model.

- Treatment effects on subjective cognitive functioning (PROMIS® T-scores) at post- and follow-up assessment will be analyzed using a linear mixed-effects model. This model will include the PROMIS® cognitive functioning T-scores at post-and follow-up assessments as the dependent variable. Fixed effects will include group (cognitive training vs. PMR) and measurement time point (post vs. follow-up). Control covariates will include the PROMIS® cognitive functioning T-scores at pre-assessment, age, and sex. A random intercept for subjects will also be included. Immediate and sustained effects on subjective cognitive functioning at post- and follow-up assessments will be estimated via marginal means (95% CI) from this model.

- Treatment effects on the post-COVID functional status (PCFS total raw scores) at post- and follow-up assessment will be analyzed using a linear mixed-effects model. This model will include the PCFS total raw scores at post-and follow-up assessments as the dependent variable. Fixed effects will include group (cognitive training vs. PMR) and measurement time point (post vs. follow-up). Control covariates will include the PCFS total raw scores at pre-assessment, age, and sex. A random intercept for subjects will also be included. Immediate and sustained effects on post-COVID functional status at post- and follow-up assessments will be estimated via marginal means (95% CI) from this model.

- Treatment effects on the sleep efficiency levels (sleep efficiency percentage) at post-assessment will be analyzed using a linear mixed-effects model. This model will include the sleep efficiency percentage at post-assessment as the dependent variable. Fixed effects will include group (cognitive training vs. PMR). Control covariates will include the sleep efficiency percentage at pre-assessment, age, and sex. A random intercept for subjects will also be included.

Effects of cognitive training with active vs. sham tDCS

We will use the same analytical approach to assess the effects of active versus sham tDCS on all outcomes, replacing the group effect (cognitive training vs. PMR) with the stimulation group variable (active vs. sham tDCS). The only exception will be the analysis of treatment effects on the training task (letter updating task), which will be examined using the following two linear mixed-effects models:

- The first model will assess the treatment effects on the training task (letter updating task) at training- and post- assessments. This model will include the letter updating performance across all training and post-assessments (number of correctly recalled lists in sessions from V2 to V11) as the dependent variable. Fixed effects will include the stimulation group (active vs. sham tDCS) and measurement time point (V2 to V11). Control covariates will include

the letter updating performance at pre-assessment (number of correctly recalled lists), age, and sex, along with a random intercept for subjects. Training and immediate post-assessment effects will be estimated through marginal means (95% CI) from this model.

- The second model will evaluate the treatment effects on the training task (letter updating task) at follow-up assessment. This model will include the letter updating performance at post- and follow-up assessments (number of correctly recalled lists) as the dependent variable. Fixed effects will include group (active vs. sham tDCS) and measurement time point (post vs. follow-up). Control covariates will include the letter updating performance at pre-assessment (number of correctly recalled lists), age, and sex. A random intercept for subjects will also be included. Sustained training effects at follow-up assessment will be estimated via marginal means (95% CI) from this model.

The choice of link function (logistic, linear, or ordinal) for all analyses will depend on the scale of the dependent variable. For skewed continuous data, we will apply appropriate transformations before analysis. In case of missing values, all secondary analyses will be done using the full analysis set with multiple imputed data. Per-protocol analyses will be conducted as sensitivity analyses. All secondary analyses will be conducted within an exploratory framework.

6.3. Safety analysis

Safety outcomes will be reported as incidence (n & rates with 95% CI) both overall and by intervention groups, based on the safety analysis set. Incidence rates and corresponding 95% CIs will be estimated using Poisson regression models, which account for different observation periods across participants. Group comparisons will be conducted using incidence rate ratios and their 95% CIs. The safety analysis results will be interpreted and discussed comprehensively, including minor differences between groups.

6.4. Example table of baseline characteristics

Table 2. Baseline characteristics of the study sample.

	All (*n* =)	**Cognitive training** (*n* =)	**PMR** (*n* =)	**Cognitive training + active tDCS** (*n* =)	**Cognitive training + sham tDCS** (*n* =)
Demographics					
Age (years)					
Sex (F: M)					
Education (years)					
Cognitive data					
Auditory verbal learning					
Learning					
Immediate recall					
Delayed recall					
Recognition					
ROCF					

Figure copy	
Figure retrieval	
Digit-span	
Forward	
Backward	
TMT	
Part A (sec)	
Part B (sec)	
Stroop test interference (sec)	
Phonological fluency	
Semantic fluency	

Data are shown as mean (SD) or n (%). PMR: Progressive Muscle Relaxation; ROCF: Rey–Osterrieth Complex Figure *Test;* TMT: Trail Making Test

7. References

1. Leite VF, Rampim DB, Jorge VC, de Lima M do CC, Cezarino LG, da Rocha CN, et al. Persistent Symptoms and Disability After COVID-19 Hospitalization: Data From a Comprehensive Telerehabilitation Program. Archives of Physical Medicine and Rehabilitation. 2021 Jul;102(7):1308–16.

2. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. Journal of Infection. 2020 Dec;81(6):e4–6.

3. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 2021 Feb;93(2):1013–22.

4. Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. 2021 Apr;76(4):396–8.

5. Almeria M, Cejudo JC, Sotoca J, Deus J, Krupinski J. Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. Brain Behav Immun Health. 2020 Dec;9:100163.

6. Hampshire A, Trender W, Chamberlain SR, Jolly AE, Grant JE, Patrick F, et al. Cognitive deficits in people who have recovered from COVID-19. EClinicalMedicine. 2021 Sep;39:101044.

7. Chung CS, Pollock A, Campbell T, Durward BR, Hagen S. Cognitive rehabilitation for executive dysfunction in adults with stroke or other adult non-progressive acquired brain damage. Cochrane Stroke Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2013 Apr 30 [cited 2021 Sep 14]; Available from: https://doi.wiley.com/10.1002/14651858.CD008391.pub2

8. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. The Lancet. 2011 May;377(9778):1693–702.

9. Bahar-Fuchs A, Martyr A, Goh AM, Sabates J, Clare L. Cognitive training for people with mild to moderate dementia. Cochrane Dementia and Cognitive Improvement Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2019 Mar 25 [cited 2021 Sep 14]; Available from: https://doi.wiley.com/10.1002/14651858.CD013069.pub2

10. Leung IHK, Walton CC, Hallock H, Lewis SJG, Valenzuela M, Lampit A. Cognitive training in Parkinson disease: A systematic review and meta-analysis. Neurology. 2015 Nov 24;85(21):1843–51.

11. Elmasry J, Loo C, Martin D. A systematic review of transcranial electrical stimulation combined with cognitive training. RNN. 2015 Jun 17;33(3):263–78.

12. Passow S, Thurm F, Li SC. Activating Developmental Reserve Capacity Via Cognitive Training or Non-invasive Brain Stimulation: Potentials for Promoting Fronto-Parietal and Hippocampal-Striatal Network Functions in Old Age. Front Aging Neurosci [Internet].

2017 Feb 23 [cited 2021 Sep 14];9. Available from: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00033/full

13. Perceval G, Flöel A, Meinzer M. Can transcranial direct current stimulation counteract age-associated functional impairment? Neurosci Biobehav Rev. 2016 Jun;65:157–72.

14. Thams F, Antonenko D, Fleischmann R, Meinzer M, Grittner U, Schmidt S, et al. 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. BMJ Open. 2022 Apr 11;12(4):e055038.

15. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017 Dec 19;318(23):2337–43.

16. Butcher NJ, Monsour A, Mew EJ, Chan AW, Moher D, Mayo-Wilson E, et al. Guidelines for Reporting Outcomes in Trial Reports: The CONSORT-Outcomes 2022 Extension. JAMA. 2022 Dec 13;328(22):2252–64.

17. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press. 1992 Aug;1(2):113–9.

18. Jacobson E. Progressive relaxation; a physiological and clinical investigation of muscular states and their significance in psychology and medical practice. Chicago: Univ. of Chicago Press; 1938.

19. Carretti B, Borella E, Zavagnin M, de Beni R. Gains in language comprehension relating to working memory training in healthy older adults. Int J Geriatr Psychiatry. 2013 May;28(5):539–46.

20. Cantarella A, Borella E, Carretti B, Kliegel M, de Beni R. Benefits in tasks related to everyday life competences after a working memory training in older adults. Int J Geriatr Psychiatry. 2017 Jan;32(1):86–93.

21. Xin Z, Lai ZR, Li Fu, Maes JHR. Near- and Far-Transfer Effects of Working Memory Updating Training in Elderly Adults: Updating training promote cognitive ability. Appl Cognit Psychol. 2014 May;28(3):403–8.

22. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017 Sep;128(9):1774–809.

23. Lezak MD, editor. Neuropsychological assessment. 5th ed. Oxford ; New York: Oxford University Press; 2012. 1161 p.

24. Dahlin E, Nyberg L, Bäckman L, Neely AS. Plasticity of executive functioning in young and older adults: immediate training gains, transfer, and long-term maintenance. Psychol Aging. 2008 Dec;23(4):720–30.

25. Hartley T, Maguire EA, Spiers HJ, Burgess N. The well-worn route and the path less traveled: distinct neural bases of route following and wayfinding in humans. Neuron. 2003

Mar 6;37(5):877–88.

26. Hautus MJ. Corrections for extreme proportions and their biasing effects on estimated values ofd′. Behavior Research Methods, Instruments, & Computers. 1995 Mar 1;27(1):46–51.

27. Dewitt B, Jalal H, Hanmer J. Computing PROPr Utility Scores for PROMIS® Profile Instruments. Value Health. 2020 Mar;23(3):370–8.

28. Cella D, Choi SW, Condon DM, Schalet B, Hays RD, Rothrock NE, et al. PROMIS® Adult Health Profiles: Efficient Short-Form Measures of Seven Health Domains. Value Health. 2019 May;22(5):537–44.

29. Klok FA, Boon GJAM, Barco S, Endres M, Geelhoed JJM, Knauss S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. Eur Respir J. 2020 Jul 2;56(1):2001494.

30. Margraf J, Cwik JC. Mini-DIPS Open Access: Diagnostisches Kurzinterview bei psychischen Störungen. 2017 [cited 2024 Oct 8]; Available from: https://omp.ub.rub.de/index.php/RUB/catalog/book/102

31. Shin MS, Park SY, Park SR, Seol SH, Kwon JS. Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. Nat Protoc. 2006;1(2):892–9.

32. Wechsler D. Wechsler Adult Intelligence Scale--Fourth Edition [Internet]. 2012 [cited 2024 Oct 8]. Available from: https://doi.apa.org/doi/10.1037/t15169-000

33. Stroop JR. Studies of interference in serial verbal reactions. Journal of Experimental Psychology. 1935;18(6):643–62.

34. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. Journal of Personality and Social Psychology. 1988;54(6):1063–70.

35. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193–213.

36. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540–5.

37. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 1976;4(2):97–110.