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Combination of transcranial direct current stimulation with online cognitive training improves symptoms of Post-acute Sequelae of COVID-19: A case series

Dear editor,

Given that there is accumulating evidence that one third of patients who develop COVID-19 experience enduring cognitive dysfunction with cumulative symptoms, there is an urgent need to develop treatment alternatives for Post-Acute Sequelae of Sars-Cov2 (PASC) [1]. Cross-sectional studies addressing the incidence of psychiatric and cognitive abnormalities in COVID-19 patients provided initial evidence on the occurrence of delirium, encephalopathy, persisting cognitive impairment, insomnia, psychotic and mood symptoms [2].

In this context, transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation intervention with potential as a PASC treatment as it modulates brain vascular function [3] and enhance ongoing synaptic plasticity [4], which can result in modulation of neural circuits underlying neurological, cognitive, and psychiatric disorders [5].

tDCS has been trialed in non-COVID-19 samples [6] and combined with cognitive tasks to boost neurorehabilitation and improve cognitive performance [7]. Therefore, this combination is a rational candidate for the treatment of PASC neuropsychiatric symptoms.

Here, we investigated the effects of this combined intervention in a case series of four patients with long COVID cognitive symptoms clinically evaluated using the Assessment of PASC inventory (A-PASC, Supplementary Materials Fig. 1) [8]. This is a pilot study that preceded an ongoing, double-blinded, randomized controlled trial comparing the effects of cognitive training combined with sham or active tDCS at University of São Paulo, Brazil.

The intervention consisted of 20 daily 20-min sessions of bilateral prefrontal tDCS (anodal-left/cathodal-right, 2mA; 1 × 1 Mini-CT, Soterix Medical, New York, NY) plus online cognitive training using the BrainHQ platform (Posit Science, San Francisco, Glenn Smith). Several neuropsychological domains were assessed before and after the intervention and their individual data is reported in Table 1.

Although this pilot study was not powered to show efficacy, several trends were observed: 1) An improvement in depression symptoms (QIDS); 2) A decrease of self-reported cognitive and emotional symptoms and functional abilities (A-PASC inventory); 3) An improvement in processing speed (FDT) and self-reported executive functioning (BDEFS); 4) An improvement in delayed and immediate recall (RAVLT).

To conclude, this case series suggest that tDCS combined with cognitive training might improve PASC cognitive symptoms, a condition with no currently available treatments. Notwithstanding, we could not exclude that this improvement occurred due to other factors, such as placebo effects, learning effects, and natural history of disease. Therefore, further randomized, controlled trials are warranted.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **BAC:** No disclosures. **AL:** No disclosures. **KVS:** No disclosures. **LB:** No disclosures. **MB:** The City University of New York holds patents on brain stimulation with MB as inventor. MB has equity in Soterix Medical Inc. MB consults, received grants, assigned inventions, and/or serves on the SAB of SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple. **LC:** No disclosures. **ARB:** Dr. Brunoni received grants for clinical research from the São Paulo Research State (FAPESP 2019/06009-6), Academy of Medical Sciences (NAFR12_1010), SoterixMedical, Flow-Neuroscience and MagVenture. Dr. Brunoni also has small equity in FlowNeuroscience. **KSV:** No disclosures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.09.008.

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Table 1
Sociodemographic characteristics, PASC symptoms and cognitive assessment.

	Sociodemographic characteristics			
	Subj 1	Subj 2	Subj 3	Subj 4
Age	34	67	59	42
Sex	Female	Female	Male	Female
Schooling (years)	16	14	10	16
Long COVID-19 (months)	2	4	3	3

	Symptoms and Cognitive Assessment Baseline				**Endpoint**			
	Subj 1	**Subj 2**	**Subj 3**	**Subj 4**	**Subj 1**	**Subj 2**	**Subj 3**	**Subj 4**
A-PASC inventory								
Physical symptoms	0	24	13	16	5	10	16	2
Cognitive symptoms	13	21	23	14	10	16	6	10
Emotional symptoms	4	9	10	9	3	6	4	5
Functional abilities	3	12	14	15	1	0	6	6
Total	20	66	60	54	29	48	38	33
Mood and anxiety scales								
QIDS	14	5	17	18	11	5	5	10
PANAS +	30	35	22	29	36	40	27	26
PANAS -	16	26	26	28	23	20	17	15
STAI – State	38	41	39	45	43	48	38	41
STAI – Trait	35	46	41	57	17	23	15	23

	Neuropsychological tests							
	Baseline				***Endpoint***			
	Subj 1	**Subj 2**	**Subj 3**	**Subj 4**	**Subj 1**	**Subj 2**	**Subj 3**	**Subj 4**
Cognitive screening								
MoCA	30	23	25	30	30	24	27	28
Premorbid intelligence								
WAT-Br	38	37	37	40	38	33	37	40
Verbal episodic memory								
RAVLT – Learning over trials	27	23	9	25	19	27	24	11
RAVLT – Total	67	53	49	65	64	47	59	71
RAVLT – Immediate recall	12	10	11	15	15	13	14	15
RAVLT – Delayed recall	12	13	9	13	15	13	13	14
RAVLT – Recognition	15	9	13	15	15	6	15	15
Visual memory								
Rey-Osterrieth Complex Figure – Recall	27	6	26.5	30	26	15.5	26	34
Attention								
TEADI – Divided Attention Test	171	122	117	178	169	147	123	180
TEACO – Sustained Attention Test	140	137	115	180	135	139	105	178
Language								
TENON – Immediate correct answers	81	68	83	75	85	80	89	86
TENON – Late correct answers	5	8	3	6	4	4	3	1
Semantic verbal fluency (animals)	23	19	16	21	21	17	17	26
FAS – Phonemic verbal fluency	53	41	54	65	54	31	60	64

Table 1 (*continued*)

	Sociodemographic characteristics							
	Subj 1		Subj 2		Subj 3		Subj 4	
Executive Functioning (self-report)								
BDEFS – Self-Management Time	42	32	62	52	38	25	42	25
BDEFS – Self-Organization/Problem Solving	34	43	62	41	41	31	45	27
BDEFS – Self-Restraint	24	29	26	30	28	22	24	26
BDEFS – Self-Motivation	15	15	24	12	17	12	20	12
BDEFS – Self-Regulation of Emotion	19	24	24	34	23	21	25	37
Executive Function and Speed (tasks)								
FDT – Reading	18	23	35	19	15	20	27	15
FDT – Counting	19	23	31	22	17	23	31	20
FDT – Choosing	26	44	45	34	23	37	40	31
FDT – Shifting	32	67	69	35	30	57	52	31
FDT – Inhibition	8	21	10	15	8	16	13	16
FDT – Flexibility	14	44	34	16	15	37	25	16
Letter-number Sequencing	11	10	9	5	13	5	9	14

Note. A-PASC=Assessment for Post-Acute Sequelae of Sars-CoV-2; QIDS = Quick Inventory of Depressive Symptomatology; PANAS=Positive (+) and Negative (−) Affect Scale; BDEFS=Barkley Deficits in Executive Functioning Scale; WAT-Br=Word Accentuation Test–Brazilian version; STAI=The State-Trait Anxiety Inventory; MoCA=Montreal Cognitive Assessment; RAVLT = Rey Auditory Verbal Learning Test; TENON = Brazilian version of the Bachy-Languedock oral naming test; FDT=Five Digit Test. Scores on tasks and scales are reported as raw scores on tasks and scales. Higher score indicates better performance for MoCA, WAT-Br, RAVLT, TEADI, TEACO, TENON (immediate correct answers), Semantic verbal fluency (animals), FAS and Letter-number sequencing. FDT is measured in seconds, with less time indicating better performance. Lower scores on A-PASC inventory, BDFES, mood, and anxiety scales indicates less impairment. All participants completed all the sessions. The intervention was well tolerated, and no side effects were reported. The improvement criterion used was that of at least 3 patients performing better on a given task after the intervention. Despite having subjective complaints of cognitive decline assessed by the A-PASC inventory, patients' performance on neuropsychological tests at baseline did not show cognitive impairments when compared with available normative data.

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