LETTER TO THE EDITOR

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Computerized cognitive remediation of Long COVID in older adults

Key words: aging, cognition, computerized cognitive remediation, depression, executive functions, games for health, Long COVID, neuroplasticity

Some coronavirus disease 2019 (COVID-19) patients display a diverse range of persistent symptoms after the acute phase of SARS-CoV-2 viral infection, collectively referred to as "Long COVID." Post-COVID neurocognitive dysfunction (PCND) is a common characteristic of Long COVID, especially among older adults, potentially occurring in up to 10%–30% of patients who previously contracted the virus (Ceban *et al.*, 2022). Patients with PCND report a range of cognitive symptoms (e.g., "brain fog," poor memory, mental slowing, etc.), though the distinctive feature is impairment in frontoparietal-mediated executive functions (e.g., set-shifting, sustained attention, working memory, inhibitory control) (Becker *et al.*, 2023). PCND is debilitating, costly to society, and may increase the risk for dementia (Li *et al.*, 2022). Older adults are particularly vulnerable to PCND due to pre-morbid age-related cognitive decline, medical comorbidities, weakened immune systems, and susceptibility to more severe acute COVID-19 illness (Cohen *et al.*, 2022).

Morimoto *et al.* developed a neuroplasticity-based computerized cognitive remediation (CCR) program, namely "NeuroFlex," that is well suited to treat PCND in older adults and probe underlying mechanisms (Morimoto *et al.*, 2014). NeuroFlex consists of a series of dynamically adjusted games, administered via computer tablet, designed to repeatedly stimulate the brain's frontoparietal cognitive control network and improve executive functioning. NeuroFlex was developed and optimized for use in late-life major depressive disorder, a condition in which executive deficits are prevalent and predict poor clinical outcomes. In clinical trials, NeuroFlex significantly improved multiple objective measures of executive functioning, reduced everyday functional disability, and improved depressive symptoms in older adults with treatment-resistant depression (Morimoto *et al.*, 2014, 2020). NeuroFlex has also been found to improve mood and cognitive performance in patients after chemotherapy ("chemobrain"), a syndrome with parallels to Long COVID (Vega *et al.*, 2023).

Our group has begun to gather preliminary data on the potential of NeuroFlex to treat PCND in older adults. The study design is a single arm, open-label acceptability and feasibility trial. Participants are prescribed an approximately 45-hour dose of CCR over 6 weeks (~7.5 hours of distributed gameplay per week). The intervention is delivered via computer tablet and can be completed at home.

Formal measures of treatment acceptability, usability, and credibility (see Table 1) are collected in person at baseline (i.e., pretreatment) and posttreatment. Cognitive, emotional, and everyday functioning are also assessed to gather preliminary data on efficacy. We chose the Trail Making Test Part B (Trails B), an objective executive functioning measure of set-shifting, as the primary cognitive outcome due to its strong psychometric properties, reliance on the frontoparietal cognitive control network, and sensitivity to SARS-CoV-2 infection (Douaud *et al.*, 2022).

We report here the results from the first two subjects with PCND who have completed the NeuroFlex treatment regimen. A third subject was offered and initially accepted to undergo treatment, but withdrew due to unexpected personal circumstances. Participants were in their early 60s and met criteria for ongoing PCND, as defined by self-reported cognitive concerns that emerged or worsened following acute COVID-19 infection, have persisted for > 4 weeks, and cannot be explained by alternative diagnoses (Nalbandian *et al.*, 2021). To enhance diagnostic standardization, included participants were required to endorse clinically meaningful cognitive concerns on the FACT-Cog Perceived Cognitive Impairment Scale (score of ≤ 40) at study entry. Exclusionary criteria were a history of dementia or other severe psychiatric, neurodevelopmental, or neurological disorders.

Demographic and outcome measures are presented in Table 1. Importantly, participants found the treatment highly acceptable, credible, and usable, both at baseline (i.e., when the treatment was initially introduced) and at posttreatment. Participants showed good adherence to the treatment regimen, completing on average > 95% of prescribed training exercises. Both participants improved by at least 40 s on Trails *B* at posttreatment compared to baseline. Gains of this magnitude

Table 1. Descriptive statistics and outcome measures ($N = 2$)

	PRE-TX MEAN (RANGE) OR %	POST-TX MEAN (RANGE) OR %	MEAN DIFFERENCE
Age (years)	62.50 (61.00–64.00)	–	–
Sex (% female)	50.00%	–	–
Education (years)	13.50 (13.00–14.00)	–	–
TAAS	60.00 (50.00–70.00)	60.50 (53.00–68.00)	+ 0.50
CEQ	45.10 (42.00–48.20)	43.40 (39.60–47.20)	− 1.70
SUS	87.50 (75.00–100.00)	86.25 (75.00–97.50)	− 1.25
Trail Making Test Part A	40.50 (39.00–42.00)	32.00 (21.00–43.00)	− 8.50
Trail Making Test Part B	137.50 (112.00–163.00)	96.50 (70.00–123.00)	− 41.00
Digit Span Forward	9.00 (8.00–10.00)	8.50 (7.00–10.00)	− 0.50
Digit Span Backward	6.50 (5.00–8.00)	6.50 (5.00–8.00)	+ 0.00
Stroop Color-Word	25.00 (21.00–29.00)	28.00 (26.00–30.00)	+ 3.00
Verbal Fluency	35.50 (35.00–36.00)	38.00 (38.00–38.00)	+ 2.50
Design Fluency	18.00 (12.00–24.00)	25.50 (18.00–33.00)	+ 7.50
CVLT LDFR	7.00 (6.00–8.00)	8.50 (8.00–9.00)	+ 1.50
CVLT LDCR	8.00 (6.00–10.00)	10.50 (10.00–11.00)	+ 2.50
Everyday Cognition Scale	2.16 (1.84–2.47)	1.83 (1.55–2.11)	− 0.33
MADRS	19.50 (16.00–23.00)	9.50 (7.00–12.00)	− 10.00
CESD-R	24.50 (21.00–28.00)	7.50 (6.00–9.00)	− 17.00
Fatigue Assessment Scale	34.00 (30.00–38.00)	25.50 (24.00–27.00)	− 8.50
WHODAS	28.89 (26.91–30.87)	19.88 (18.89–20.87)	− 9.01

Note. Descriptive statistics are displayed as means and ranges (minimum–maximum) or percentages at the pretreatment (Pre-Tx) baseline visit and at the posttreatment (Post-Tx) visit for the first two subjects ($n = 2$) to have completed the NeuroFlex treatment regimen. Mean differences for each outcome measure at posttreatment relative to pretreatment are provided to help guide interpretation of effect sizes. Age, sex, and education are reported only at pretreatment to describe the demographic characteristics of the sample at baseline; no pre- versus posttreatment comparisons are reported for these demographic variables because they were not expected to change meaningfully following this brief (6 week) treatment. TAAS, Treatment Acceptability/Adherence Scale (self-report measure of the extent to which participants find a given treatment acceptable, i.e., fair, reasonable, appropriate, unintrusive, adherable, etc.); CEQ, Credibility/Expectancy Questionnaire (self-report measure of the extent to which participants find a given treatment credible, i.e., believable, convincing, logical, beneficial, etc.); SUS, System Usability Scale (self-report measure of how usable participants perceive a computer-based product or service to be). CVLT LDFR, Long Delay Free Recall on the California Verbal Learning Test (objective measure of episodic memory performance involving free retrieval of previously presented information); CVLT LDCR, Long Delay Cued Recall on the California Verbal Learning Test (objective measure of episodic memory performance involving cued recall of previously presented information); MADRS, Montgomery-Asberg Depression Rating Scale (clinician-rated measure of depressive symptom severity); CESD-R, Center for Epidemiologic Studies Depression Scale-Revised (self-report measure of depressive symptoms); WHODAS, World Health Organization Disability Assessment Schedule (interview-administered measure of everyday functional disability). Higher scores on the TAAS, CEQ, SUS, Digit Span Forward and Backward, Stroop Color-Word, Verbal Fluency, Design Fluency, and CVLT are more favorable / indicate better performance. Lower scores on the Trail Making Test Part A and B, Everyday Cognition Scale, MADRS, CESD-R, Fatigue Assessment Scale, and WHODAS are more favorable / indicate better performance.

on Trails B are clinically meaningful (Borland *et al.*, 2022). Depressive symptoms also showed clinically significant improvements on both a gold-standard clinician-rated scale (Montgomery-Asberg Depression Rating Scale) and a well-validated self-report questionnaire (Center for Epidemiologic Studies Depression Scale-Revised). Reductions in subjective cognitive concerns, fatigue, and functional disability were also observed.

Although additional research is needed, CCR may offer a viable treatment for PCND that is efficient (6-week dose), cost-effective, and can be administered remotely with the potential for wide distribution. NeuroFlex also appears to be a highly acceptable treatment, possibly due to the gamified interface, which may increase treatment engagement and adherence. NeuroFlex is currently available in English and Spanish, and efforts are underway to adapt to other cultures and languages worldwide, thus making international dissemination possible.

Conflict of interest

None.

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