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Use of focused computerized cognitive training (Neuroflex) to improve symptoms in women with persistent chemotherapy-related cognitive impairment

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Abstract

Purpose: Chemotherapy-related cognitive impairment (CRCI) is a distressing and increasingly recognized long-term sequela reported by breast cancer patients following cancer treatment. There is an urgent but unmet clinical need for treatments that improve CRCI. In this context, we proposed the use of a novel cognitive enhancement strategy called Neuroflex to target CRCI experienced by breast cancer survivors.

Methods: The primary aim of this pilot study was to evaluate the feasibility and acceptability of Neuroflex, a novel digital cognitive enhancement strategy, in breast and gynecologic cancer survivors with CRCI. Secondary analyses focused on whether improvements in performance on Neuroflex were associated with improvement in subjective cognitive complaints and objective cognitive performance measures.

Results: Participants ($N = 21$) completed an average of 7.42 hours of Neuroflex training per week, an average of 44.5 (± 1.01) hours total, and had a 100% completion rate. Participants exhibited significant improvement in self-reported cognitive function as well as significant improvement on tasks of verbal learning and memory and auditory working memory. Participants also exhibited improvement in mood, as well as improvement on a disability assessment.

Conclusions: Results demonstrate feasibility and that breast cancer survivors are capable of completing a lengthy and challenging cognitive training program. Secondly, Neuroflex may confer specific cognitive benefits to both self-reported and objective performance. Results strongly support further investigation of Neuroflex in a larger controlled trial to establish efficacy for CRCI symptoms. Further studies may also result in optimization of this digital intervention for women with CRCI.

Keywords

Chemotherapy-related cognitive impairment, digital cognitive interventions, Neuroflex, neuroplasticity-based cognitive remediation, breast cancer, survivorship, cognitive impairment, clinical trial, digital medicine

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Background

Advances in breast cancer treatment are resulting in a growing number of cancer survivors, which has broadened the scope of care from treating acute cancer to managing long-term effects of cancer treatment on multiple organ systems, including the brain.[1] A distressing and increasingly recognized long-term sequela reported by breast cancer patients and survivors[2] is chemotherapy-related cognitive impairment, sometimes referred to as cancer-related cognitive impairment (CRCI).[3] To date, there is limited research into the day-to-day impact of CRCI.[4] Although the symptoms of "chemobrain" or "chemofog" have been well recognized among patients for decades and have been widely publicized in the popular press, patient reports suggest that these symptoms have generally not been a focus of assessment or treatment by clinicians.[5] Historically, the reluctance to acknowledge CRCI has been primarily based on the belief that many chemotherapy drugs do not cross the blood–brain barrier (BBB); therefore, symptoms described by patients have often been attributed to the stress of cancer diagnosis and treatment.[6] The lack of validation and understanding from healthcare professionals, friends, and family has led to reports from survivors of disempowerment, resulting in survivors receiving minimal levels of emotional and professional support.[7,8] There are currently more than 3 million breast cancer survivors in the US.[9] As the number of cancer survivors who will have to cope with cognitive dysfunction associated with CRCI is likely to increase, there is an urgent and unmet clinical need for treatments that improve CRCI.

The prevalence of CRCI varies across studies, but longitudinal studies estimate that 35–60% of survivors exhibit decrements in cognitive performance after chemotherapy.[2] However, the number of cancer survivors with cognitive complaints and deficits not measured by standard tests is likely greater than 35–60%. Although some chemotherapy regimens such as methotrexate and 5-fluorouracil[10] are clearly associated with neurotoxicity, CRCI is not limited to those agents. Research suggests that the causes of CRCI are likely multifactorial, and several biological mechanisms have been suggested to play a role in the development of CRCI. Briefly, proposed mechanisms include BBB damage, neurotoxic cytokines, neuroinflammation, changes in hormones, DNA damage, oxidative stress, reduced synaptic plasticity, altered growth factor levels, and impaired hippocampal neurogenesis.[11–13] Further mechanisms may include psychological factors such as styles of coping with stress, fatigue, and depression.[5,11–13]

Among the most common cognitive difficulties reported among breast cancer survivors include executive functions.[14] Executive dysfunction is linked to disability in a wide range of neuropsychological disorders and results in symptoms including difficulty with planning, problem-solving,[2] sustained attention, organization, impaired concentration, and time management skills, all of which are crucial to maintaining activities of daily living, workplace performance, and quality of life (QOL).[15] Neuroimaging studies in patients with CRCI have consistently and repeatedly demonstrated altered structure and function of the prefrontal cortex, a specialized brain area that contributes to intact executive function.[12] Survivors experiencing CRCI typically report that greater mental effort is required for everyday tasks.[16] These struggles become particularly noticeable when returning to work and may result in lost work/productivity.[8] Although the severity of CRCI is typically described as "mild to moderate in nature" and would not qualify for a diagnosis of mild cognitive impairment (MCI) or dementia,[17,18] it is important to note that even subtle impairments in cognitive functioning can have significant impact on QOL.[19] Moreover, this subtlety, together with the reliance on tests designed to detect more severe, localized deficits such as traumatic brain injuries, strokes, and Alzheimer's disease, means that the cognitive changes that cancer survivors experience are often undetected and underestimated by clinicians.[20]

There is currently no established standard of care for managing CRCI in cancer survivors.[9] There is some evidence that suggests that nonpharmacological interventions may be beneficial for patients with CRCI.[12] Studies in CRCI demonstrate that cognitive training interventions improved memory and attention in breast cancer patients.[21,22] In a wait-list randomized controlled trial by Kesler et al.[23] of an online cognitive training program in 41 patients with breast cancer, an average of 6 years after treatment suggested efficacy of cognitive training with improvement in cognitive flexibility, verbal fluency, and processing speed. Participants receiving the active treatment reported improvements in planning, organization, and task monitoring.[23] Bray et al. conducted a randomized controlled trial in breast cancer survivors, evaluated an online cognitive rehabilitation program, and compared it with standard care in cancer survivors.[24] These studies suggest that online cognitive interventions show promise for remediating cognitive changes following breast cancer treatment. Importantly, the application of nonpharmacological intervention may be promising and particularly appealing to cancer survivors who are not interested in taking medication. In this context, we proposed to use a novel cognitive enhancement strategy to target the executive function cognitive deficits experienced by breast cancer survivors.

The field of plasticity enhancement has developed extensively in the past two decades, and there is compelling evidence to believe that targeted enhancements can be made to neural circuit dysfunction if training is done in a way that takes neurobiology, cognitive symptoms, and circuit characteristics into account.[25–29] Neuroflex[29] is a digital cognitive intervention based on the hypothesis that specific changes in brain function can be facilitated through the induction of neuroplasticity, subsequently improving

cognitive performance.[27,28] Neuroplasticity is an umbrella term that refers to the brain's ability to modify, change, and adapt both structure and function throughout life in response to experiences. One approach to induce neuroplasticity is through focused cognitive training,[27] as neuroplasticity requires intensive practice coupled with the heightened neurotransmission associated with reward as modulated by dopamine and norepinephrine.[30] Neuroflex, as opposed to other interventions, is theoretically founded in animal models of induction of neuroplasticity in the aging brain.[25] Neuroflex training paradigms rely on what is known about the organization of neural function of the targeted circuit/s and utilize cognitive neuroscience paradigms as the bases for training stimuli and tasks.[25] Use of Neuroflex has improved executive functioning in a patient population with similar cognitive deficits (major depressive disorder) that survivors with CRCI endorse and may represent an inexpensive, innovative, nonpharmaceutical treatment that is easily disseminated to patients with CRCI.[25]

The primary aim of this pilot study was to evaluate the feasibility and acceptability of Neuroflex in cancer survivors with CRCI by measuring completion rates and attendance. Exploratory analyses focused on whether improvements in performance on Neuroflex tasks were associated with improvement in subjective cognitive complaints and objective cognitive performance measures.

Methods

Study design

Initially, the study was designed to have participants receive all Neuroflex training sessions in-person; however, the delivery of the training was altered to operate during the current COVID-19 pandemic. Neuroflex training was moved to remote delivery via videoconference or phone (further described below and in supplement), and other research visits were structured in a manner that reduced the amount of time participants were onsite. Onsite visits were conducted within the Center for Cognitive Medicine at Vanderbilt University Medical Center (VUMC). This study has a single-arm, open-label design using pre–postassessment. Participants underwent a baseline assessment and were then assessed again following completion of the Neuroflex intervention (Figure 1(a)).

Participants and enrollment criteria

Recruitment began in February 2020 and ended in June 2021. Participants were recruited through VUMC-affiliated clinics and the greater Nashville, TN, area. The cancer types included in the study (breast cancer, ovarian cancer, and endometrial cancer) were chosen with the aid of an oncologist, given that individuals diagnosed with these types of cancer receive similar cytotoxic regimens. Inclusion criteria included (a) ages of 35–80 years; (b) previous diagnosis of invasive breast cancer, endometrial cancer, or ovarian cancer; (c) systemic chemotherapy treatment within the last 1–8 years; (d) endorsement of persistent CRCI subjective complaints (as defined below); and (e) fluency in English. The rationale for requiring participants to be 1–8 years post-chemotherapy is that we were interested in helping people with persistent CRCI. Up to 75% of patients experience cognitive decline during cancer treatment.[19] As mentioned above, longitudinal studies estimate that 35–60% of survivors continue to exhibit decrements in cognitive performance after completing chemotherapy.[2] Given that there is a portion of patients whose cognitive functioning will improve with time and without intervention after completing cancer treatment, we wanted to target the subset of patients whose cognitive dysfunction persists for at least a year following completion of chemotherapy. While cognitive declines have been observed to persist for 10–20 years following treatment,[31–33] we required participants to be no more than 8 years post-treatment, because we wanted participants to feel confident that their changes in cognition were directly attributable to their cancer treatment and not to aging.

Following initial pre-screening, a review of medical records was conducted to ensure good general health and to confirm that CRCI participants met the criteria for cancer diagnosis and had received systemic chemotherapy. Participants were excluded for (a) any *active* neurologic disease or history of significant head trauma followed by persistent neurologic deficits, or known structural brain abnormalities; (b) any active untreated *current* major depression or another major DSM5 psychiatric disorder (use of psychotropic medications (e.g. antidepressants) for past depression was permitted, provided dosing had been stable for at least 3 months); (c) history of alcohol or substance abuse or dependence within the past 2 years; (d) any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol; (e) use of any investigational drugs within 30 days or 5 half-lives; and (f) red–green color blindness.

Study procedures

Screening assessment. All participants were screened to exclude individuals with evidence of clinically significant cognitive impairment or dementia.[34,35] Participants were evaluated using the Wechsler Abbreviated Scale of Intelligence (WASI), mini-mental state exam,[36] or Montreal Cognitive Assessment (MMSE FULL score $\geq$ 26), Brief Cognitive Rating Scale[37] (score $\leq$ 2), and the Mattis Dementia Rating Scale[38] (score $\geq$ 125) to establish a Global Deterioration Scale (GDS; score $\leq$ 2) score[39] which rates the degree of cognitive impairment. To rule out the presence of active or inadequately treated mood disorders, all participants were psychiatrically assessed using an abbreviated

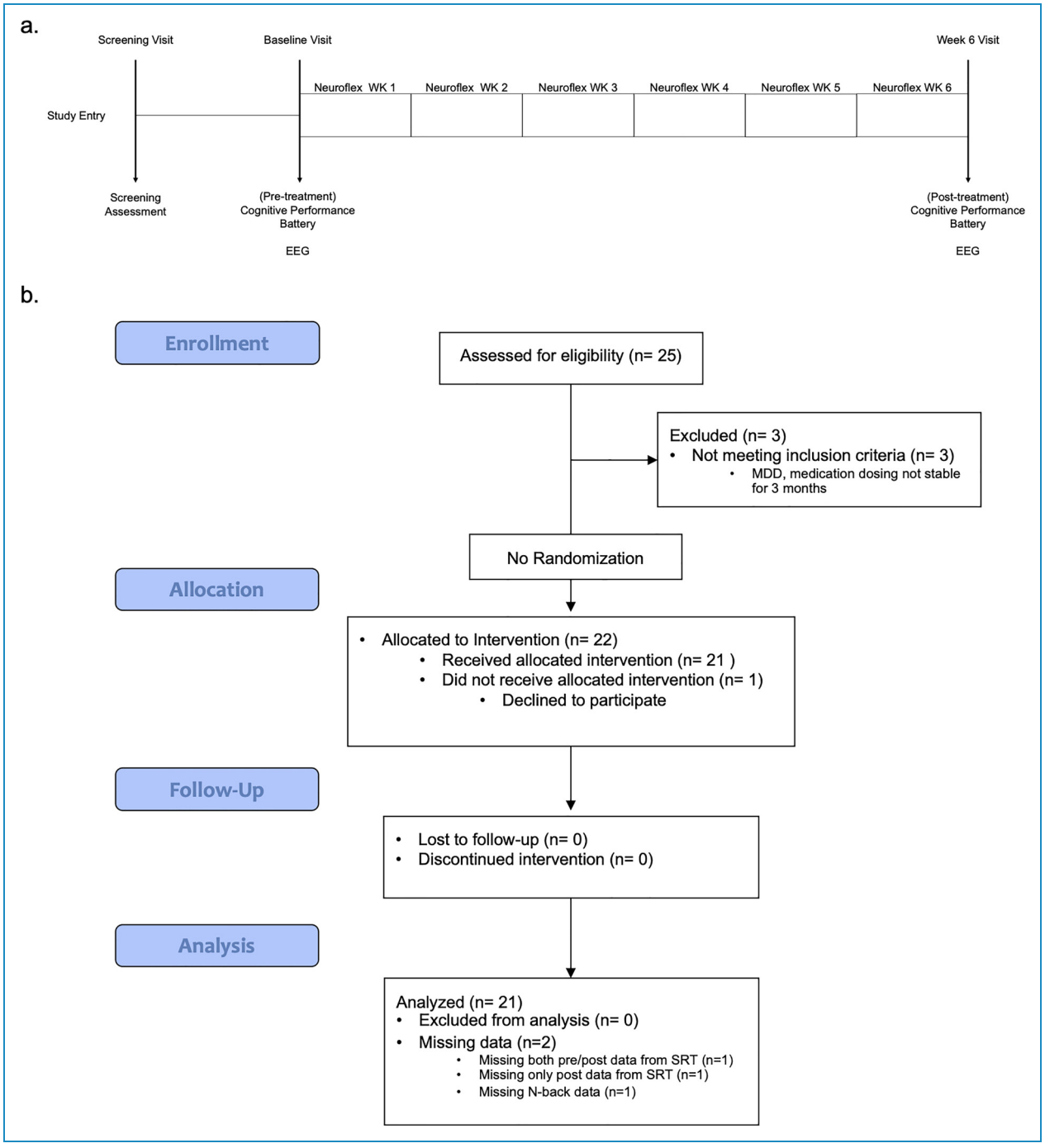

Figure 1. Study design and consort diagram. (a) Overall study design. This study was a single-arm, open-label design using pre-postassessment. Participants underwent a baseline assessment, completed 6 weeks of Neuroflex training, and were then assessed again following the completion of the Neuroflex intervention. (b) Participant enrollment. Twenty-five participants were screened, with three excluded due to not meeting inclusion criteria (MDD medication); one participant was eligible but withdrew at baseline prior to starting the Neuroflex treatment.

Structured Clinical Interview[40] for DSM disorders and diagnoses (SCID-IV) and the Montgomery–Åsberg depression rating scale (MADRS; score ≤ 19),[41] which is a 10-item clinician-rated interview used to assess depression severity over the previous 2 weeks. Once participants completed the screening visit, eligibility was determined by the PIs (JNV, PN, SSM) for the study. Any questions regarding the eligibility of participants were discussed and agreed upon by all PIs. The study staff were trained to administer all behavioral and neuropsychological tests and to administer the intervention.

For the purpose of the current study, CRCI was defined as (a) self-report of cognitive changes directly linked to chemotherapy treatment received in the last 1–8 years, (b) evidence of subjective cognitive impairment on the cognitive complaint index[42] (CCI, see below), and (c) subjective complaints not better accounted for by the presence of depression and/or another psychiatric or neurologic condition. See Supplemental material for additional information on screening assessment and the full cognitive and behavioral battery (Supplemental Table 1). The CCI was chosen as the screening measure because previous research has shown that the CCI score correlates with underlying neurodegenerative changes even when unaccompanied by deficits on formal testing,[42] and it has been used in previous studies by our group examining cognitive complaints in post-menopausal women[43,44] and cancer survivors.[34,35,45] A CCI score is calculated based on the percentage of all items endorsed. To be considered as having chemotherapy-related subjective complaints to be eligible for the current study, participants must endorse at least 20% of the items.[42]

Feasibility outcomes

Completion rates were calculated by dividing the number of participants who completed all 6 weeks of Neuroflex training by the number of participants who received the intervention. The weekly goal for participant training was 8 hours per week for a total of 45 training hours over 6 weeks. All training sessions were monitored remotely by study coaches. A tracking dashboard in REDCap allowed coaches to track participant training hours.

Subjective cognition measures and behavioral questionnaires

The primary measure used to assess subjective cognitive performance was the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) scale,[46] which consists of four subscales: perceived cognitive impairment (PCI), perceived cognitive abilities (PCA), QOL, and comments from others (CFO)). At baseline and post-treatment visits, participants rated on a five-point Likert scale how they assessed various aspects of their cognitive functioning over the last 7 days. Higher scores indicate better ratings of cognitive functioning. See Supplemental material for additional information. The profile of mood states (POMS)[47] was used to monitor changes in mood post-treatment (see Supplemental material for additional information). The 65 items form six subscales resulting in five negative mood dimensions (tension/anxiety, depression, anger/hostility, fatigue, and confusion) and one positive mood dimension (vigor/activity). A total score of mood disturbance (TMD) score can also be calculated by summing the scores of the five subscales for the negative mood states and subtracting from it the score for the positive subscale. For tension/anxiety, depression, anger/hostility, fatigue, confusion, and TMD, higher scores indicate greater mood disturbance. Conversely, for the vigor subscale, higher scores indicate greater levels of enthusiasm and optimism. Raw scores were used for all measures.

Objective cognitive performance measures

The selective reminding task (SRT)[48] was used to assess immediate and delayed memory recall. Participants are read a list of 16 words and must immediately recall the list across eight trials. Upon completing the immediate recall portion of the SRT, and after a 20-minute delay, participants are asked to complete a single delayed recall trial. SRT total immediate recall was analyzed using the number of correctly recalled words across trials 1–8 (total recall), and total delayed recall was analyzed using the number of words correctly recalled after a 20-minute delay (delayed recall).

A visually presented *N*-back sequential letter task was used to assess working memory performance.[49] Four conditions were presented: 0-back, 1-back, 2-back, and 3-back. The 0-, 1-, 2-, and 3-back conditions were performed in two blocks of 27 trials each for a total of 216 trials. The main outcome variables of the *n*-back task were the median response time; the sensitivity (d'), calculated as Z (hit) $-$ Z (false alarms); or the bias (C), calculated as: $-[Z\ (\text{hit}) + Z\ (\text{false alarms})]/2$. Response bias measures the amount of information required by the participant before they make a selection.[50,51] More positive values represent a more conservative bias in responding, in which participants require more information before they make reach a decision criterion. Negative values indicate a more liberal bias, in which participants respond with less information. A score of zero represents a neutral bias. More conservative response biases have been observed in depressed participants.[52] Sensitivity and bias were assessed for each of the four conditions. Additional objective cognitive measures are described further in the Supplemental material.

Neuroflex treatment

Neuroflex personalizes training with adaptive algorithms that increase difficulty on a trial-by-trial basis, based on three parameters: accuracy, learning curve (plateau criteria), and norm-based percentile achievement (graduation criteria). Participants are dynamically moved through program levels, keeping performance between 75 and 85% correct to maximize learning and avoid habituation. Neuroflex programs are designed to "layer" executive functions gradually and individually increase challenges. At advanced levels, algorithms unique to Neuroflex can hold all other executive functions constant while varying difficulty levels (speed, response interval, and *n*-back) of one function producing a highly personalized intervention for executive dysfunction.

Neuroflex behavioral training paradigms were designed to engage targeted cerebral networks with sensory, motor, and cognitive tasks that are (a) increasingly challenging, (b) individually adaptive, (c) attention demanding, and (d) immediately rewarding.[27] Each session was administered and supervised via videoconference by trained coaches who scheduled, monitored, aided participants with technical issues, and guided participants throughout the entirety of each session. Once it was clear that participants could use the programs and understood the Neuroflex rules, an action plan/training schedule was created to support regular weekly "game play." Coaches had access to a tracking dashboard (REDCap), which they used to track each participant's weekly hours. Coaches were present (via videoconference) for every training session for the duration of the entire session. The weekly training goal for participants was 8 hours per week and 45 hours total over 6 weeks. Participants scheduled training sessions that were convenient for their schedule and typically met 3–4 times per week to complete the weekly training goal.

Neuroflex's training exercises[29] include three programs that give immediate, multisensory rewards (visual and auditory feedback) for correct responses[21,53] and employ dynamic difficulty adjustments to minimize frustration from incorrect responses[54] and maintain performance levels in the desired range: (a) *Memory Ball Recall* was designed to provide individually titrated training in visual attention, inhibition of prepotent responses, working memory, cognitive flexibility, and dual-task performance; (b) *Ultimate Word Master* (*UWM*) was designed to enhance semantic strategy. UWM trains participants to reorganize verbal material; and (c) *Neurogrow* was designed to provide individually titrated training in the inhibition of prepotent responses, working memory, cognitive flexibility, and dual-task performance.

Statistical methods

Analyses were performed using IBM SPSS Statistics for Mac, version 28 (IBM Corp., Armonk, NY, USA). For feasibility outcomes, such as completion rates and participant attendance, basic descriptive statistics were calculated. Paired samples t-tests were used to evaluate pre–post-differences in behavioral and cognitive performance measures. Correlations between behavioral and cognitive measures were performed using the Pearson product–moment correlation.

Results

Feasibility outcomes

Twenty-five female participants were screened. Three participants were not eligible and withdrawn (Figure 1(b)). One participant was eligible but withdrew (declined to participate) at the baseline prior to starting Neuroflex. Of the remaining participants ($N = 21$), most were breast cancer survivors ($n = 17$), followed by ovarian cancer ($n = 3$), and one endometrial cancer survivor ($n = 1$; Table 1). The mean age was 56.45 ± 11.03 years. Participants were on average 3.51 ± 1.78 years post-chemotherapy. The weekly goal for participant training was 8 hours per week, and the goal for total training hours was 45 hours. Participants completed an average of 7.42 hours of Neuroflex training per week and an average of 44.5 (± 1.01) hours total. Twenty-one ($N = 21$) participants were enrolled, and all

Table 1. Demographics.

		$n = 21$
Age in years (mean ± SD)		56.19 ± 10.55
Years since chemotherapy (mean ± SD)		3.54 ± 1.69
Neuroflex weekly training hours (mean ± SD)		7.41 ± 0.17
Neuroflex total training hours (mean ± SD)		44.5 ± 1.01
Mean screening CCI score		51.49 ± 11.64
Mean screening MADRS score		5.81 ± 5.36
Mean screening MMSE score		29.38 ± 0.97
Cancer type	Breast	17
	Ovarian	3
	Endometrial	1
Cancer Stage	I	7
	II	9
	III	4
	IV	1
Cancer treatment	Chemotherapy	21
	Surgery	21
	Radiation	13
Current endocrine therapy	Yes	12
	No	9
Received targeted therapy	Yes	6
	No	15

CCI: cognitive complaint index; MADRS: Montgomery–Åsberg depression rating scale; MMSE: mini-mental state exam.

completed the intervention. No participants dropped out or failed to complete training.

Subjective cognition measures and behavioral outcomes

Participants exhibited statistically significant improvement in self-reported cognitive function on all four subscales on the FACT-Cog: FACT-Cog PCI, FACT-Cog PCA, FACT-Cog CFO, and FACT-Cog QOL subscales, as well as the total score (Table 2). The mean improvement in the FACT-Cog PCI score was 12 points, which is considered a clinically meaningful improvement.[55] Participants also exhibited improvement in mood as measured by the POMS: POMS-confusion, POMS-vigor, and POMS total mood disturbance. In addition, participants exhibited improvement on the WHODAS total score (Table 2). The following measures were not statistically significant: POMS-tension, POMS-depression, POMS-anger, and POMS-fatigue.

Objective cognitive performance outcomes

Participants exhibited statistically significant improvement on tasks of verbal learning and memory (SRT immediate recall, SRT delayed recall) and auditory working memory (digit backwards) (Table 3). The following measures were not statistically different following treatment: digit span forward, brief test of attention (BTA), and trail-making task. The results of the *N*-back task are displayed in Supplemental Table 2. Analysis of the median RT showed that participants responded faster on the easier conditions compared to the harder conditions ($F\,(3, 51) = 33.9$, $p < 0.001$, $\eta^2_p = 0.67$). There was no effect of time; however, there was an interaction between time and condition, in which participants responded faster on three-back trials pre-Neuroflex and faster on two-back trials post-Neuroflex ($F\,(3, 51) = 3.8$, $p = 0.015$, $\eta^2_p = 0.18$). There was no overall difference in responding across the intervention period ($F < 1$). Analysis of the sensitivity scores (d') on the *N*-back task showed a significant effect of condition, with worse performance on the more difficult blocks ($F\,(3, 51) = 78.7$, $p < 0.001$, $\eta^2_p = 0.82$); however, there was no change in sensitivity across the intervention or an interaction between time and conditions (both $p > 0.3$). Analysis of the bias showed similar effect of condition ($F\,(3, 51) = 3.5$, $p < 0.022$, $\eta^2_p = 0.17$), but also a main effect of time, with response bias decreasing for post-Neuroflex compared to pre-Neuroflex ($F\,(1, 17) = 5.8$, $p < 0.028$, $\eta^2_p = 0.25$). This decrease in response bias showed that participants were responding less conservatively following Neuroflex; that is, they required less information before making a decision about whether the target was a match or mismatch. There was no interaction between time and condition for response bias ($F < 1$).

Discussion

The 6-week Neuroflex intervention, delivered remotely, demonstrated excellent acceptance and feasibility confirmed by the high rates of adherence and engagement. Analyses of secondary outcomes also showed that participants exhibited significant improvement in self-reported cognitive function on the total FACT-Cog score, and all four subscales on the FACT-Cog that measured PCI, PCA, QOL, and CFO. The mean increase in the FACT-Cog PCI score from baseline was 12 points, which is a clinically meaningful improvement[55] in self-reported PCI.[46] Participants also reported improvement in mood on POMS subscales measuring confusion and activity/vigor, as well as improvement in total mood disturbance. In addition, participants reported a significant reduction in overall disability. After 6 weeks of treatment, participants demonstrated significant improvement over baseline performance on tasks of working memory, verbal learning, and episodic memory and working memory. Moreover, these improvements in working memory were associated with a reduction in confusion reported by participants across the treatment period.

The findings of this study clearly support feasibility and acceptability of Neuroflex in cancer survivors with CRCI, and in addition, improvements in our secondary objective measures of executive functioning were observed. Although the primary goal of this study was to determine feasibility, positive improvements in subjective and objective measures of cognition were observed. On the N-back task, changes in response bias in which participants responded less conservatively compared to baseline were observed following Neuroflex. This improvement in cognitive performance was also associated with improved subjective mood, with the reduction of response bias on the 2-back task being associated with improved self-reported levels of confusion across the treatment period. The associations between the MADRS and the change in POMS subscales (see Supplemental material) over the treatment period indicated that the participants who were endorsing the greatest numbers of mood symptoms also showed the greatest improvement in mood following the 6 weeks of Neuroflex. In future studies, this intervention could serve as a neurobiological probe of CRCI mechanisms and suggest potential future targets for plasticity-based cognitive interventions. We suggest that our data is the first essential step to identifying cognitive functions of interest that may be enhanced with targeted cognitive remediation to improve CRCI.

One study has evaluated the use of a remote online cognitive rehabilitation program in breast cancer survivors; however, participants were unsupervised while performing

Table 2. Subjective cognition measures and behavioral outcomes.

		Mean	*N*	Std. deviation	Effect size (Cohen's *d*)	*t*-statistic
FACT-Cog	Pre-treatment PCI score	42.76	21	14.363	11.73	$t(20) = -4.69$; $p < 0.001$***
	Post-treatment PCI score	54.76		12.066		
	Pre-treatment CFO score	13.52	21	2.695	2.4	$t(20) = -2.91$; $p < 0.01$**
	Post-treatment CFO score	15.05		2.598		
	Pre-treatment PCA score	13.43	21	4.249	6.91	$t(20) = -2.62$, $p < 0.05$*
	Post-treatment PCA score	17.38		8.182		
	Pre-treatment QOL score	11.52	21	2.857	2.501	$t(20) = -4.45$; $p < 0.001$***
	Post-treatment QOL score	13.95		1.91		
	Pre-treatment total score	81.24	21	20.731	17.125	$t(20) = -5.51$; $p < 0.001$***
	Post-treatment total score	101.81		19.015		
POMS	Pre-treatment POMS-T score	4.33	21	3.396	4.784	$t(20) = 0.87$; $p > 0.05$
	Post-treatment POMS-T score	3.43		3.802		
	Pre-treatment POMS-D score	1.71	21	1.953	2.517	$t(20) = 0.61$; $p > 0.05$
	Post-treatment POMS-D score	1.38		1.431		
	Pre-treatment POMS-A score	2.14	21	2.613	3.665	$t(20) = 1.07$; $p > 0.05$
	Post-treatment POMS-A score	1.29		2.101		
	Pre-treatment POMS-F score	7.71	21	5.841	6.266	$t(20) = 1.81$; $p > 0.05$
	Post-treatment POMS-F score	5.24		3.687		
	Pre-treatment POMS-C score	6	21	2.933	2.606	$t(20) = 3.94$; $p < 0.001$***
	Post-treatment POMS-C score	3.76		1.998		
	Pre-treatment POMS-V score	14.48	21	7.174	7.204	$t(20) = -2.61$; $p < 0.05$*
	Post-treatment POMS-V score	18.57		5.537		
	Pre-treatment POMS TMD score	7.43	21	17.699	19.649	$t(20) = 2.54$; $p < 0.05$*
	Post-treatment POMS TMD score	-3.48		11.007		
WHODAS	Pre-treatment WHODAS total score	54.62	21	14.972	11.192	$t(20) = 2.54$; $p < 0.05$*
	Post-treatment WHODAS total score	48.43		9.584		

FACT-Cog: function assessment of cancer therapy–cognitive function; PCI: perceived cognitive impairment; PCA: perceived cognitive abilities; QOL: impact on quality of life; CFO: comments from others; POMS: profile of mood states; T: tension/anxiety; D: depression; A: anger/hostility; F: fatigue; C: confusion; V: vigor/activity; TMD: total mood disturbance; WHODAS: World Health Organization Disability Assessment Schedule 2.0.

*Significance at $p < 0.5$.

**Significance at $p < 0.01$.

***Significance at $p < 0.001$.

Table 3. Objective cognitive performance outcomes.

		Mean	N	Std. deviation	Effect size (Cohen's *d*)	*t*-statistic
SRT	Pre-treatment SRT immediate total recall	75.05	20	18.84	14.34	$t(19) = -5.85$, $p < 0.001$**
	Post-treatment SRT immediate total recall	93.8		16.04		
	Pre-treatment SRT delayed total recall	9.63	19	3.29	3.17	$t(18) = -2.82$, $p < 0.05$*
	Post-treatment SRT delayed total recall	11.68		3.35		
Digit span	Pre-treatment digit forward total	10.95	21	2.01	1.29	$t(20) = -0.68$, $p > 0.05$
	Post-treatment digit forward total	11.14		2.24		
	Pre-treatment digit backward total	9.43	21	1.89	1.83	$t(20) = -2.62$, $p < 0.05$*
	Post-treatment digit backward total	10.48		2.56		
BTA	Pre-treatment BTA	17.29	21	3.04	4.34	$t(20) = 0$, $p > 0.05$
	Post-treatment BTA	17.29		4.59		
TMT	Pre-treatment trail-making task	29.33	21	17.83	18.72	$t(20) = -0.36$, $p > 0.05$
	Post-treatment trail-making task	30.81		20.98		

SRT: selective reminding task; BTA: brief test of attention; TMT: trail-making test.
*Significance at $p < 0.5$.
**Significance at $p < 0.001$.

the intervention and completing assessments.[24] This had a significant impact on completion rates and had implications for the median training time. While that study met its primary endpoint with an average training time of 25 hours, participants did not reach the recommended 40-hour training period. Recruitment for our current study began in February 2020, coinciding with the start of the current COVID-19 pandemic. As a result, we quickly transitioned to supervised, fully remote Neuroflex training. This switch to remote training had numerous benefits. The supervised nature of the visits had the benefit of providing in-person technology support in the event that participants experienced any technical difficulties. The remote nature of the training sessions also may have led to significantly higher retention rates as participants could complete training from the comfort of their own homes and provided more flexibility in terms of scheduling and completing training sessions. This also allowed a wider recruitment area because participants did not have to commute to the research site multiple times per week. Having remote training sessions also may have led to better study adherence. The weekly goal for participant training was 8 hours per week, and the goal for total training hours was 45 hours, which is very close to the completed averages of 7.42 hours of Neuroflex training per week and an average of 44.5 hours of total Neuroflex training hours that participants completed. This suggests that, if proven to be effective at improving subjective and objective cognitive symptoms in this population in a larger study, this intervention could be clinically applied through remote use.

While the etiology of CRCI remains unclear, research suggests that neuroinflammation plays a role in the neurobiology of CRCI.[56,57] There is also an extensive body of research showing that systemic inflammation and immune activation have also been implicated in depression.[58] There is an overlap between the type of cognitive impairment cancer survivors and people with late-life depression (LLD) experience, and we have demonstrated (preliminarily) that Neuroflex is beneficial in both populations. Interestingly, the syndrome of cognitive symptoms that COVID-19 survivors frequently experience closely resembles CRCI. Preliminary research has demonstrated that neuroinflammation may also be central to the pathophysiology of the development of cognitive dysfunction following COVID-19.[57] While speculative, strategies that restore neural plasticity and rescue cognition, such as Neuroflex, may also be beneficial in restoring healthy cognitive function following COVID-19.[57]

It is important to note that this intervention was not specifically designed or optimized for this population. This

intervention has been previously used to successfully treat cognitive impairment in older adults with LLD.[29] While patients with LLD may share difficulties with executive function as is seen in CRCI, patients with depression may exhibit differences in the broader profile of observed cognitive difficulties compared to CRCI patients. Our group has developed neuroplasticity-based digital cognitive interventions (e.g. Neuroflex) based on the relationship between frontal systems abnormalities and executive dysfunction and between executive dysfunction and remission from depression.[25] These interventions have demonstrated NIMH-defined "target engagement"; that is, improving executive functions improves depression in treatment-resistant older adults with LLD.[27,28] This work we present here is the first step in our iterative, digital design process: Defining our target, where data produced by each participant's interaction with Neuroflex are paired with analysis of objective and subjective cognitive gains, identifies underlying neurocognitive deficits related to our outcomes of interest. Our next step will be to optimize Neuroflex to maximize learning, engagement, and usability of NeuroFlex-C: a bespoke intervention for CRCI.

Study limitations

An important limitation to consider is that this study only included women as participants, which limits the generalizability of these results to men with persistent CRCI.[35] Our study is not unique by including exclusively women as the vast majority of CRCI research has occurred primarily in breast cancer survivors[2]; however, more research is needed to determine if the results of the current study would generalize men and other cancer types.[35]

Additionally, there was no comparison or inactive treatment group. A potentially informative comparison group would be cancer survivors with persistent CRCI that were randomly assigned to a 45-hour non-therapeutic digital intervention. It is possible that simply performing a computerized intervention with an expectation of benefit may improve self-reported cognitive impairment. Further, since this study was designed to be a feasibility study and was not adequately powered due to the small sample sizes of this study, many of the reported effects should be considered preliminary. Therefore, future iterations of this investigation will include larger samples randomized either to Neuroflex or a concurrently studied, computer-presented control condition.

Clinical implications

To date, there has been a large and unmet need for effective treatment options for cancer survivors experiencing cognitive symptoms after chemotherapy treatment. Neuroflex may confer specific cognitive benefits to both self-reported and objective performance. Results strongly support further investigation of Neuroflex in a larger controlled trial to establish efficacy for CRCI symptoms. Further studies should also focus on optimization of this digital intervention for women with CRCI. Mitigating CRCI is becoming a critical part of long-term cancer care. The availability of an inexpensive, well-tolerated, digital intervention that can be easily disseminated would be highly innovative for patients with persistent CRCI and would encourage early treatment to improve subjective cognitive complaints and cognitive performance and have significant potential to improve QOL for large numbers of breast cancer survivors. This intervention has the potential to provide a new treatment option for patients with cancer with cognitive symptoms, where previously none existed.

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