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Digital multimodal intervention for cancer-related cognitive impairment in breast-cancer patients: Cog-Stim feasibility study

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Abstract

Background This feasibility study evaluated adherence and effectiveness to a digital multimodal intervention (cognitive and physical training) for cancer-related cognitive impairment (CRCI) in patients with breast cancer.

Methods Breast cancer patients undergoing radiotherapy and with significant cognitive complaints impacting quality of life participated in a 12-week intervention, combining non-simultaneous 20-min cognitive and 30-min physical sessions, twice weekly. Assessments included perceived cognitive impairment (PCI), objective cognition, fatigue, anxiety/depression, sleep and satisfaction. High level of adherence was defined as completing 9/12 weeks of the program. A week was complete when at least 70% of each of the planned sessions was completed. Physical activity intensity was defined by max age-related heart rate.

Results Among 419 radiotherapy-treated patients with breast cancer, 170 had cognitive complaints (41%), 83 were eligible (49%), 29 were not included (35%) due to organizational issue and 20 among eligible contacted patients agreed to participate (37%). The majority of participants (48.3 ± 8 years of age) received chemotherapy (18/20) and 17 had I-II cancer stage. Eleven of twenty participants were highly adherent (higher adherence in physical (95%) than cognitive training (55%)). All expressed satisfaction. Post-intervention, overall objective cognition ($p = 0.016$), PCI ($p = 0.004$), fatigue ($p = 0.011$), and depression ($p = 0.049$) significantly improved. Post-intervention, high adherence was associated with significant improvements in PCI ($p = 0.01$) and fatigue ($p = 0.03$). High-intensity physical training was associated with significant improvements in PCI ($p < 0.05$), fatigue ($p = 0.011$) and depression ($p = 0.037$).

Conclusions This intervention showed to be feasible and potentially efficient for the management of CRCI in patients with breast cancer.

Trial registration NCT04213365, 27/12/2019.

Keywords Digital intervention, Cancer-Related Cognitive Impairment, Cognitive training, Breast cancer, Quality of life, Physical activity

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Background

Approximately 40% to 75% of cancer patients have cognitive complaints [1, 2], particularly related to memory, attention, processing speed, and language abilities [3]. These complaints, which are referred to cancer-related cognitive impairment (CRCI), are associated with several factors that could influence their severity and persistence, such as fatigue, quality of sleep, anxiety, and depression [4, 5]. CRCI can appear before (20–30%) [6], during or after cancer treatments (up to 75%) [2, 7, 8], notably after chemotherapy [2], and persist for years after the end of treatment [4, 9]. In addition, these cognitive complaints significantly impact patients' quality of life [10], social interactions [11], and professional activities or return to work [2, 12, 13].

Patients may actively seek support to alleviate these symptoms [1]. Several studies assessing non-pharmacological approaches like cognitive training and physical activity to manage these difficulties have demonstrated positive outcomes [14]. However, the demand often remains unaddressed. The primary obstacle to meeting this need lies in the inherent challenges associated with implementing interventions within clinical care. To overcome this issue, it is important to identify barriers and facilitators for the clinical adoption of interventions [15].

The conceptual basis of multimodal interventions

Considering the multifactorial nature of CRCI, a multimodal approach seems more appropriate than a monomodal approach, which focuses on only one aspect of CRCI. Notably, the combination of physical and cognitive training has shown considerable promise, as reported in studies in the elderly [16–18]. This kind of intervention seems to facilitate two different paths of neurogenesis, potentially enhancing it [16]. Moreover, the use of multimodal interventions for CRCI is recommended by the latest published guidelines for healthcare professionals [19]. In oncology, only simultaneous cognitive and physical training has been investigated by two small studies [20, 21] that had design limitations and showed poor outcomes, including no improvement in cognition. In both studies, cancer survivors were asked to complete 36 sessions of 30 min (approximately 12 weeks) simultaneously combining physical exercise on a bicycle and cognitive training using NeuroActive cognitive training software. The multimodal intervention was compared to three training modalities: cognitive training, physical training and physical flexibility training (fewer than 10 subjects in each group). Since simultaneous cognitive and physical training proved too demanding for participants in these studies, the authors suggested that a non-simultaneous multimodal intervention might have produced better results. Moreover, the study did not report the rate of acceptance to participate, reasons for non-eligibility, or level of adherence and satisfaction with the training program.

Digitalization of the intervention

One of the main challenges associated with transitioning interventions from research to clinical practice is accommodating patients' schedules, affecting not only those in remote or travel-restricted areas but also leading to lower intervention adherence rates. Additionally, the financial burden of involving several professionals like adapted physical activity (APA) specialists and professionals for cognitive training is a significant barrier for many centers. To address these challenges, the use of digital tools has gained popularity in recent years. Digitalizing interventions enhance engagement by dynamically adjusting difficulty levels based on individual performance and incorporating gamification elements. Both digital cognitive training (also called computerized cognitive training) and physical training have shown positive results [22], but further research is needed to assess their acceptability and feasibility comprehensively.

Objectives

Our feasibility study aimed to fill this gap by assessing the adherence of breast cancer patients who experienced cognitive complaints to a 12-week digital multimodal intervention that combines non-simultaneous cognitive training and APA. Secondary objectives were to evaluate the eligibility, acceptability, and satisfaction of participants with the program. We also assessed the impact on cognition and related factors (fatigue, anxiety/depression, and quality of sleep) at the end of the intervention, taking the level of adherence and the intensity of APA into account.

Methods

Study design and population

The Cog-Stim study was a single-center experimental feasibility interventional study investigating a 12-week non-simultaneous multimodal digital intervention combining cognitive and physical training. This study involved patients with breast cancer undergoing adjuvant radiotherapy who reported cognitive complaints.

The study design and methods have been detailed in a previous publication [23]. The main eligibility criteria were: (1) breast cancer; (2) current adjuvant radiotherapy; (3) cognitive complaints that had a significant impact on patient's quality of life (Functional Assessment of Cancer Therapy, FACT-Cog self-report questionnaire, Quality of Life subscale [24]; (4) no major cognitive dysfunction (based on the Montreal Cognitive Assessment (MoCA) score); (5) no psychiatric or neurological diseases; (6) no

medical contraindication to undertake adapted physical activity (APA).

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local ethics committee (Réf. 2019/102, *Comité de protection des personnes Nord-Ouest III*, France). This trial is registered as ClinicalTrials.gov NCT04213365 (registration date: 2019–12–27). Informed consent was obtained from all individual participants included in the study.

Intervention

The intervention consisted of a 12-week digital multimodal program combining 20-min cognitive sessions and 30-min APA sessions, performed non-simultaneously twice weekly (24 sessions in total for each type of training) at home.

Happy Neuron PRESCO software® was utilized for the cognitive training sessions. Participation was autonomous, without any supervision. The sessions were preset with a randomized selection of exercises targeting the most commonly affected cognitive domains in CRCI with a starting difficulty level of zero that increased based on the patient's performance. Patients received two e-mails per week as a reminder.

For adapted physical activity, participants had access to the online platform Mooven®, where they scheduled two 30-min sessions per week. Each session was supervised by an APA specialist who supervised the session remotely through a video-conference system. The APA sessions were standardized and included a warm-up (5 min), endurance/cardio or muscle-strengthening activities (20 min), and stretching (5 min), following the recommendations of the French National Cancer Institute. The content of the sessions was adapted to participants' constraints and medical contraindications. To monitor the intensity of physical activity, patients' heartbeat was monitored using a wrist heart rate monitor.

Study measures

At baseline, socio-demographic and medical data were collected, including age, functional status (ECOG), previous cancer, comorbidity, analgesic medications, family status, education, cancer stage, estrogen, and progesterone receptor, HER2 status, and anticancer therapies received. Evaluations were performed prior to the start of the intervention (pre-intervention) and at the end of the 12-week intervention (post-intervention). Evaluations included an assessment of self-reported and objective cognitive functioning, using the Functional Assessment of Cancer Therapy–CognitiveFunction (FACT-Cog [24]) and the CNS Vital Signs computerized battery [25], respectively. At both time points, patients were also asked to complete standardized self-report questionnaires to assess fatigue (using the Functional Assessment of Chronic Illness Therapy – Fatigue, FACIT-F [26]), anxiety and depression (using the Hospital Anxiety and Depression Scale, HADS [27]) and quality of sleep (through the Insomnia Severity Index, ISI [28]). At the end of the intervention, their satisfaction with the training program was assessed using a self-report questionnaire developed for this study.

Assessment tools

The FACT-Cog questionnaire is composed of four subscales: Perceived Cognitive Abilities (PCA), Perceived Cognitive Impairment (PCI), Quality of Life (QoL), Comments from Others (OTh). Scores on the PCI subscale of the FACT-Cog, based on normative data (percentiles 10) [29], were used to define significant cognitive complaints.

The following subtests of the Computerized Neurocognitive Assessment Vital Sign (CNS VS) battery were used: Verbal Memory (VBM), Visual Memory (VIM), Finger-Tapping (FTT), Symbol Digit (SDC), Stroop Test (ST), Shifting Attention (SAT), Continuous Performance (CPT), and Neurocognition Index (NCI) for overall objective cognitive performance. Low average, low and very low scores indicate the presence of objective cognitive impairment according to the severity classification grade of the CNS VS.

Fatigue was considered severe when the FACIT-F questionnaire score was below 37 [30]. Scores ≥ 11 on the HADS questionnaire indicated significant anxiety/depression symptoms [31]. A score of 15 or higher on the Insomnia Severity Index (ISI) is considered to indicate clinical insomnia [28].

After the intervention, patient satisfaction was assessed using a self-report questionnaire developed for this study, including 13 items (4-point Likert scale, ranging from "not satisfied at all" to "very satisfied"). The questionnaire gathered feedback on the program, including the overall experience of participants, frequency, difficulty, content, number, and duration of both physical and cognitive sessions and ease of software use.

Statistical analysis

For the socio-demographic and clinical variables, descriptive statistics were performed, including the mean and standard deviation for continuous variables and frequency with corresponding percentage for categorical variables.

The reasons for non-eligibility and the reasons for refusing to participate were described along with corresponding percentages. The rate of acceptability was defined as the proportion of patients who agreed to participate among the eligible patients contacted.

The intensity of physical activity was evaluated using the maximum age-related heart rate for each session: moderate level of intensity when maximum age-related heart rate was between 64–76% and high level of intensity when maximum age-related heart rate was between 77–93% [32].

A session of either cognitive or physical training was considered performed if at least 70% of the session was completed (≥ 14/20 min of cognitive session, and 20/30 min of APA session). For each week of the intervention, adherence was considered to be achieved if all four planned sessions were completed. High adherence to the 12-week multimodal intervention was defined as completing at least 9 weeks of the program.

To explore the effects of the intervention on cognition and related factors, the paired sample Wilcoxon-Mann–Whitney test was performed for quantitative variables and the McNemar test for qualitative variables. Clinical characteristics and baseline cognitive assessment were compared between low adherence participants (completion of fewer than 9 weeks) and high adherence participants (completion of at least 9 weeks) by the chi^2-test or Fisher's exact test for qualitative variables and by the Wilcoxon Mann Whitney test for quantitative variables. Additionally, the effects of the intervention were estimated in each group separately by the paired sample Wilcoxon-Mann–Whitney test. The effects of the intervention on FACT-Cog and FACIT-F subscales were estimated by considering moderate and high intensity physical activity separately by the paired sample Wilcoxon Mann Whitney test. All p-values were considered significant at an alpha level of 5%.

Results

Eligibility and acceptability of the intervention

Between May 2020 and November 2021, 419 breast cancer patients underwent adjuvant radiotherapy: 249 (59%) of them did not report any cognitive complaints that had a significant impact on their quality of life (Fig. 1), and only 46% received chemotherapy. One hundred seventy patients were screened for eligibility, of whom 87 were ineligible, mainly owing to a neurological history (31%), leading to an eligibility rate of 49%.

Among the 83 remaining eligible patients, 29 (35%) could not be included because of organizational issues (with regards to radiotherapy sessions and supportive care incompatible with the study participation over 3 months) and 34 of the eligible contacted patients refused to participate in the study. The main reasons for refusal were not interested in participating in a study (41%), not wanting any intervention for CRCI (26%) and lack of time (21%). Overall, 20 patients agreed to participate, corresponding to an acceptability rate of 37% (Fig. 1).

Patient pre-intervention characteristics

Of the 20 patients included for the analyses (median age: 48.3 ± 8 years) the majority has stage I-II breast cancer ($n = 17$) and a 0–1 performance status (Table 1). All participants had undergone surgery and radiotherapy and the majority received chemotherapy (18/20). Most of the participants had finished grade 12 education or higher ($n = 15$). Cognitive complaints with significant impact on quality of life were of concern for all the 20 patients in accordance with eligibility criteria (QoL FACT-Cog subscale), 15 (75%) patients had significant PCI, 12 (60%) had objective cognitive impairment (NCI), and 10 (50%) reported anxiety symptoms (HADS). Additionally, 18 (90%) reported severe fatigue (FACIT-F) and 13 (65%) clinical insomnia (ISI).

Program follow-up

During the program, two participants dropped out for personal reasons or a medical contraindication. Additionally, one participant was lost to follow-up after the intervention, and the questionnaires of another participant were lost. Thus, the data pertaining to the effects of the intervention on objective cognitive functions were available for 17 patients and 16 patients completed all the questionnaires.

Adherence to the intervention

Overall, participants completed a median of 9 weeks (min–max: 1–12) (cognitive and physical training), and 11 participants were highly adherent to the whole program, completing ≥ 9 weeks of the program.

For cognitive training, participants completed a median of 9 weeks (min–max: 1–12) and 11 participants (55%) were highly adherent.

Concerning physical training, participants completed a median of 12 weeks (min–max: 3–12) and (95%) were highly adherent.

There were no significant differences regarding medical or demographic variables, objective cognitive functioning, anxiety, depression, and insomnia between high and low adherent participants (Table 2).

Nevertheless, participants with high adherence reported more cognitive complaints and fatigue at baseline compared to those with low adherence (Table 2).

Intensity of APA sessions

Participants had on average a heart rate of 140 at the peak intensity of APA training (93–181). Fifteen (75%) participants had a high intensity APA and 5 (25%) a moderate

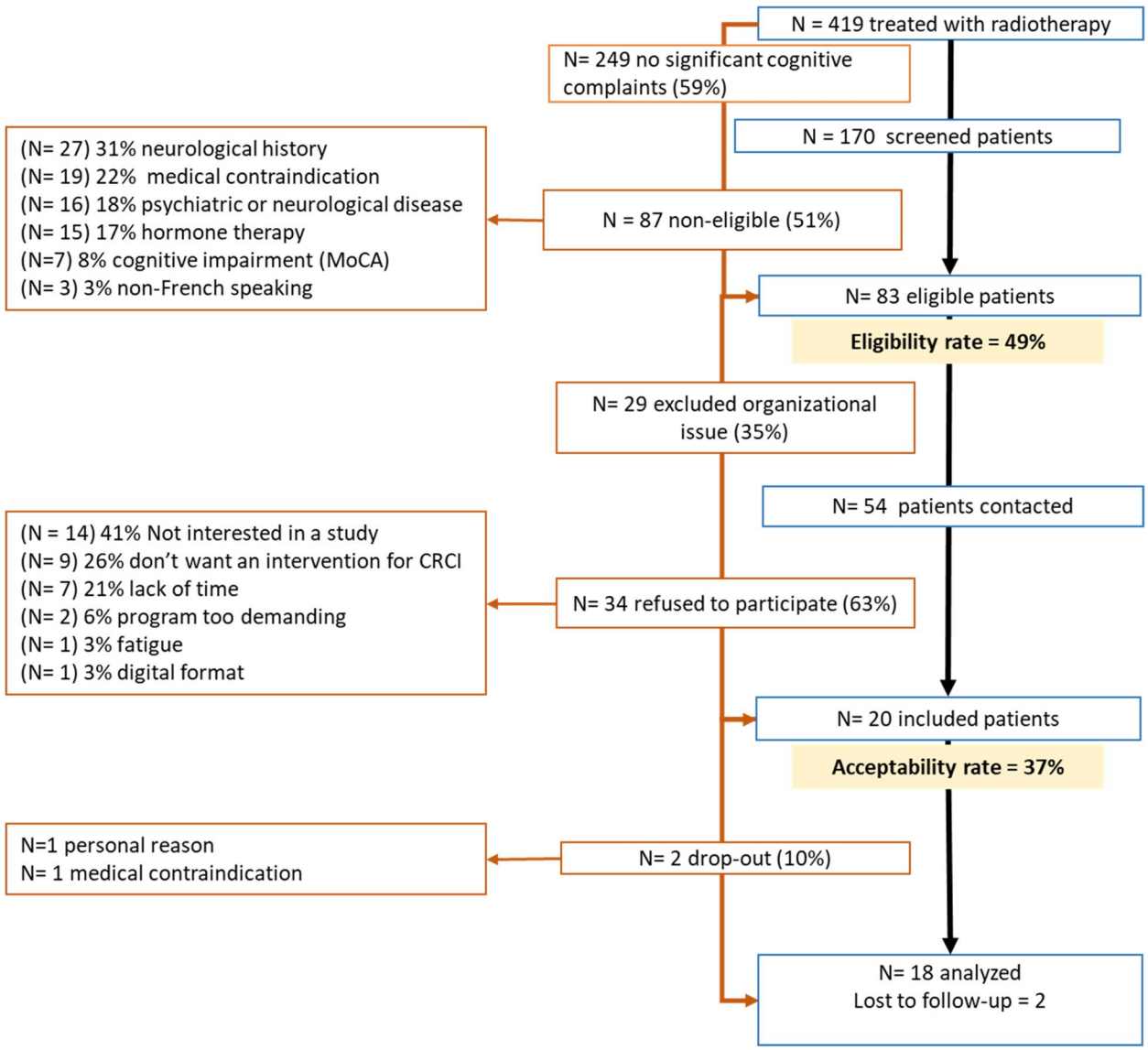

Fig. 1 Flow chart of the study

intensity according to their maximum age-related heart rate.

Outcomes of intervention

Self-reported cognitive functioning (FACT-Cog questionnaire)

Significant improvement in cognitive complaints was observed on the PCI, PCA and Oth subscales post-intervention ($p=0.004$) (Table 3).

Post-intervention, high adherent participants had significantly fewer cognitive complaints (all FACT-Cog subscales, $p<0.05$), while no significant changes were observed for low adherent participants (Table 3).

Similarly, a significant improvement in cognitive complaints on the PCI, PCA and Oth subscales ($p<0.01$) was found for participants engaging in high intensity APA (Fig. 2), while no significant changes were observed among patients engaging in moderate APA intensity.

Objective cognitive functions (CNS-VS)

Post-intervention, there was a significant improvement in overall objective cognition ($p=0.016$) (Table 3) and on the following subscales: psychomotor speed ($p=0.004$), reaction time ($p=0.018$) and motor speed ($p=0.004$) (Table 4). Furthermore, participants who engaged in high intensity APA had a significant increase in overall

Table 1 Demographic and medical characteristics of participants at baseline

Characteristics	*N* = 20	%
Demographic and medical		
Mean age, SD, [range], years	48.3 ± 8 [36-62]	
Education		
Primary school	4	20
Middle school	1	5
High school	9	45
University	6	30
Family Status		
Married/in couple	17	85
Divorced	1	5
Single	2	10
Functional status (ECOG)		
Grade 0	8	40
Grade 1	12	60
Previous cancer		
	2	10
Comorbidity[a]		
	2	10
Analgesic medications[b]		
	4	20
Cancer stage		
I	2	10
II	15	75
III	3	15
Estrogen receptors		
	17	85
Progesterone receptors		
	14	70
HER2		
	7	35
Anticancer therapies		
Surgery	20	100
Chemotherapy		
Neoadjuvant	8	40
Adjuvant	10	50
Radiotherapy	20	100
Cognitive and psychological		
Significant cognitive complaints (FACT-Cog—PCI)		
	15	75
MoCA (mean, SD)		
	26.6 (2.4)	
Overall objective cognition (CNS-VS-NCI)		
Above average	2	10
Average	6	30
Low average	5	25
Low	3	15
Very low	4	20
Objective cognitive impairment	12	60
Anxiety (HADS)		
	10	50
Depression (HADS)		
	3	15
Severe fatigue (FACIT-F)		
	18	90
Clinical insomnia (ISI)		
	13	65

FACT-Cog Functional Assessment of Cancer Therapy, *PCI* Perceived Cognitive Impairment, *MoCA* Montreal Cognitive Assessment, *CNS-VS* Computerized Neurocognitive Assessment Vital Sign, *NCI* Neurocognition Index, *HADS* Hospital Anxiety and Depression Scale, *FACIT-F* Functional Assessment of Chronic Illness Therapy – Fatigue, *ISI* Insomnia Severity Index

[a] Presence of one or more additional medical conditions or diseases (i.e. pulmonary, cardiac etc.…)

[b] Composite score for concurrent use of psychotropic and/or analgesic medications

objective cognitive functioning (NCI, $p = 0.009$) (Fig. 2), psychomotor speed ($p = 0.003$), reaction time ($p = 0.021$) and motor speed ($p = 0.004$) (data not shown).

No significant changes were found in objective cognitive performances according to adherence to the program (data not shown).

Associated factors

A significant improvement in fatigue level was observed post-intervention ($p = 0.011$) (Table 3) and significantly fewer participants reported severe fatigue post-intervention compared to pre-intervention (15/16 patients vs. 8/16; $p = 0.023$) (data not shown). The level of depression decreased significantly between pre- and post-intervention ($p = 0.049$), although no significant changes were observed for anxiety and insomnia (Table 3). High adherent participants had significantly less fatigue ($p < 0.05$) after the intervention (Table 3). Among low adherents, there was no significant change in the associated factors (Table 3). Participants with high intensity APA had a significant improvement in fatigue ($p = 0.01$) and depression ($p = 0.037$) (Fig. 2). Participants with moderate intensity APA did not have significant changes in the associated factors.

Dose–response relationship

A significant relationship was observed between the duration of the intervention (number of sessions) and insomnia. No significant relationships were observed for other associated factors, cognitive complaints and objective cognition (data not shown).

Table 2 Patients' characteristics pre-intervention according to their adherence to the intervention

Characteristic	Low adherence	High adherence	*p*-value
Sociodemographic and clinical			
Age Mean (SD)			
	46.2 (8.8)	49.6 (7.3)	0.361
Education (%)			
Primary school	1 (11)	3 (27)	0.595
Middle school	1 (11)	0 (0)	
High school	5 (56)	4 (36)	
University	2 (22)	4 (36)	
Family status (%)			
Married/in couple	8 (89)	9 (82)	1.000
Divorced	0 (0)	1 (9)	
Single	1 (11)	1 (9)	
Performance Status ECOG (%)			
0	6 (67)	2 (18)	0.065
1	3 (33)	9 (82)	
Chemotherapy(%)			
Neoadjuvant	6 (67)	2 (18)	0.065
Adjuvant	3 (33)	7 (64)	0.370
Cognitive and psychological			
Cognitive complaints (FACT-Cog) mean (SD)			
PCI	46.0 (14.4)	30.0 (12.7)	0.025*
PCA	13.4 (3.2)	10.0 (3.3)	0.016*
Oth	12.8 (3.3)	10.0 (4.4)	0.177
QoL	7.9 (4.9)	5.1 (2.3)	0.249
Overall objective cognition (CNS-VS-NCI) mean (SD)			
NCI	84.6 (15.8)	83.6 (21.6)	0.9
FACIT-F (Fatigue) mean (SD)			
	29.4 (8.9)	20.9 (7.3)	0.033*
HADS (Anxiety) mean (SD)			
	8.9 (3.8)	9.0 (2.7)	0.846
HADS (Depression) mean (SD)			
	5.6 (3.3)	6.4 (4.1)	0.701
ISI (Quality of sleep) mean (SD)			
	15.6 (6.8)	16.7 (4.7)	0.849

FACT-Cog Functional Assessment of Cancer Therapy, *PCI* Perceived Cognitive Impairment, *PCA* Perceived Cognitive Abilities, *Oth* Comments From Others, *QoL* Quality of life, *CNS VS* Computerized Neurocognitive Assessment Vital Sign, *NCI* Neurocognition Index, *HADS* Hospital Anxiety and Depression Scale, *FACIT-F* Functional Assessment of Chronic Illness Therapy – Fatigue, *ISI* Insomnia Severity Index

* For significant results

Participants' satisfaction

The satisfaction questionnaire was completed by 15 patients, who were satisfied overall by the program. They were satisfied with the timing and format of the intervention, including the length and the number of the sessions, the support provided, and the content and difficulty of the exercises. Moreover, 14/15 of patients reported that the intervention improved their quality of life and their cognitive complaints (S*upplementary material,* Fig. 1).

Discussion

This study demonstrates the feasibility and efficacy of a digital multimodal intervention combining non-simultaneous cognitive and physical training in breast cancer patients with cognitive complaints. The intervention showed a high level of adherence and satisfaction. Furthermore, there was a significant improvement in both self-reported and objective cognitive functions, depression, and fatigue of breast cancer patients after the intervention.

Eligibility and acceptability

Among the patients undergoing radiotherapy, 41% had cognitive complaints, which is in line with findings from other studies where complaints were reported in 40% to 75% of cases [1, 2, 33]. Notably, 46% of patients without cognitive complaints did not receive chemotherapy, which is a factor known to be frequently associated with such symptoms [4, 34, 35]. These results underline the importance of future investigations targeting patients who have undergone chemotherapy, a potential inducer of CRCI.

The primary reasons for non-participation were lack of interest in participating in a study (39%), not wanting any intervention for CRCI (26%), and lack of time (21%). These factors could be linked to presenting the study during radiotherapy, i.e. a period when patients prioritize their cancer management and have to contend with fatigue and juggle busy treatment schedules. The demanding nature of their ongoing cancer treatment may have posed challenges for them to commit the necessary time and attention to engage in an additional intervention. In future studies, considering the timing of intervention introduction will be crucial. It might be more beneficial to approach patients for participation in CRCI interventions at a point in their cancer care when they have completed or are near the end of their radiotherapy treatment. At this stage, they may have more emotional and physical resources available to fully engage in and benefit from such interventions, leading to improved interest and participation rates, with a potential enhancement of the efficacy of the intervention. Some patients may also have experienced subtle changes in their cognitive abilities that they did not consider impactful on their quality of life, leading them to believe that they did not need to address them.

As expected, the utilization of the digital format was not perceived as a barrier, as no patients encountered equipment-related limitations when they were approached to participate in the study. Only one of the

Table 3 Cognition and associated factors before and after intervention including adherence

	All patients			Low adherence			High adherence		
	Pre-intervention N = *20*	*Post-intervention* N = *20*	*p- value*	*Pre-intervention* N = *9*	*Post-intervention* N = *9*	*p- value*	*Pre-intervention* N = *11*	*Post-intervention* N = *11*	*p- value*
Cognitive complaints (FACT-Cog) mean (SD)									
PCI	37.3 (15.2)	51.4 (9.8)	0.004*	46.0 (14.4)	56.7 (10.3)	0.141	30.0 (12.7)	48.3(8.5)	0.01*
PCA	11.9 (4.0)	17.0 (5.0)	0.004*	14.0 (3.2)	20.5 (2.9)	0.059	10.0 (3.3)	14.9 (4.9)	0.031*
Oth	11.0 (4.5)	14.3 (1.8)	0.004*	12.8 (3.3)	14.6 (1.9)	0.181	10.0 (4.5)	14.2 (1.9)	0.013*
QoL	6.9 (3.9)	9.0 (5.3)	0.201	7.9 (4.9)	7.83 (5.8)	0.844	5.1 (2.3)	9.7 (5.1)	0.024*
Overall objective cognition (CNS VS) mean (SD)									
NCI	88.2 (18.4)	93.1 (19.7)	0.016*	84.6 (15.8)	98.6 (6.4)	0.125	83.6 (21.6)	90.4 (23.7)	0.092
Associated factors mean (SD)									
FACIT-F Fatigue	23.8 (8.4)	32.3 (8.9)	0.011*	29.4 (8.9)	34.7 (7.5)	0.281	20.9 (7.3)	30.9 (9.7)	0.028*
HADS Anxiety	9.2 (3.3)	7.6 (3.4)	0.162	8.9 (3.8)	8.8 (2.9)	1	9.0 (2.7)	6.9 (3.7)	0.113
HADS Depression	6.3 (4.0)	4.1 (2.8)	0.049*	5.6 (3.2)	3.5 (1.8)	0.089	6.4 (4.1)	4.5 (3.2)	0.172
ISI Quality of sleep	16.9 (4.3)	14.7 (6.1)	0.303	15.6 (6.8)	12.5 (7.0)	0.074	17.0 (4.7)	16.0 (5.5)	0.765

FACT-Cog Functional Assessment of Cancer Therapy, *PCI* Perceived Cognitive Impairment, *PCA* Perceived Cognitive Abilities, *Oth* Comments From Others, *QoL* Quality of life, *CNS VS* Computerized Neurocognitive Assessment Vital Sign, *NCI* Neurocognition Index, *HADS* Hospital Anxiety and Depression Scale, *FACIT-F* Functional Assessment of Chronic Illness Therapy – Fatigue, *ISI* Insomnia Severity Index

* Significant *p* value

54 patients contacted refused to participate specifically owing to the digital format.

Adherence and satisfaction

The criterion of adherence was to have completed at least 9 weeks of the intervention, i.e. 75% of the program. The participants completed a median of 9 weeks, and more than half of them proved to be highly adherent according to our criterion of adherence. These results are akin to those observed in mono-modal digital interventions, where rates of adherence were between 65 and 90%. This suggests that non-simultaneous multimodal interventions with 4 sessions of a maximum 30 min weekly are feasible for breast cancer patients during radiotherapy [22]. However, it must be taken into consideration that the concept and assessment of adherence may change among studies, so caution is required when comparing results in the absence of a consensual definition.

Adherence in this study was higher for physical training, which was supervised, than for cognitive training, which was unsupervised. This underlines the beneficial impact of supervised guidance, consistent with prior studies that emphasized professional oversight [22, 36, 37].

Interestingly, patients with more pronounced cognitive complaints and fatigue at baseline showed higher adherence. Individuals with cognitive complaints might be more motivated to engage in interventions aimed at addressing these issues. Similarly, patients with higher fatigue and a feeling that their condition might improve thanks to APA could have been more motivated to participate in the program.

To our knowledge, this is the first study showing the possible influence of fatigue and cognitive complaints on adherence. These findings underline the importance of considering and evaluating the interplay between cognitive complaints, fatigue, and physical activity in the context of interventions for patients with cancer, both in future studies and in clinical practice.

Overall, the participants reported satisfaction concerning the intervention, including session timing, format, support, exercise content, and difficulty. Most participants reported reduced cognitive difficulties, and all would recommend the program to other patients. This positive perception of the digital format may contribute to program's high level of adherence and satisfaction. These findings are in line with previous research by Von Ah et al. [38], which highlighted digital convenience and flexibility as facilitators in online cognitive interventions. The positive feedback from participants highlights the potential advantages of using digital platforms in future interventions to enhance accessibility and overall satisfaction.

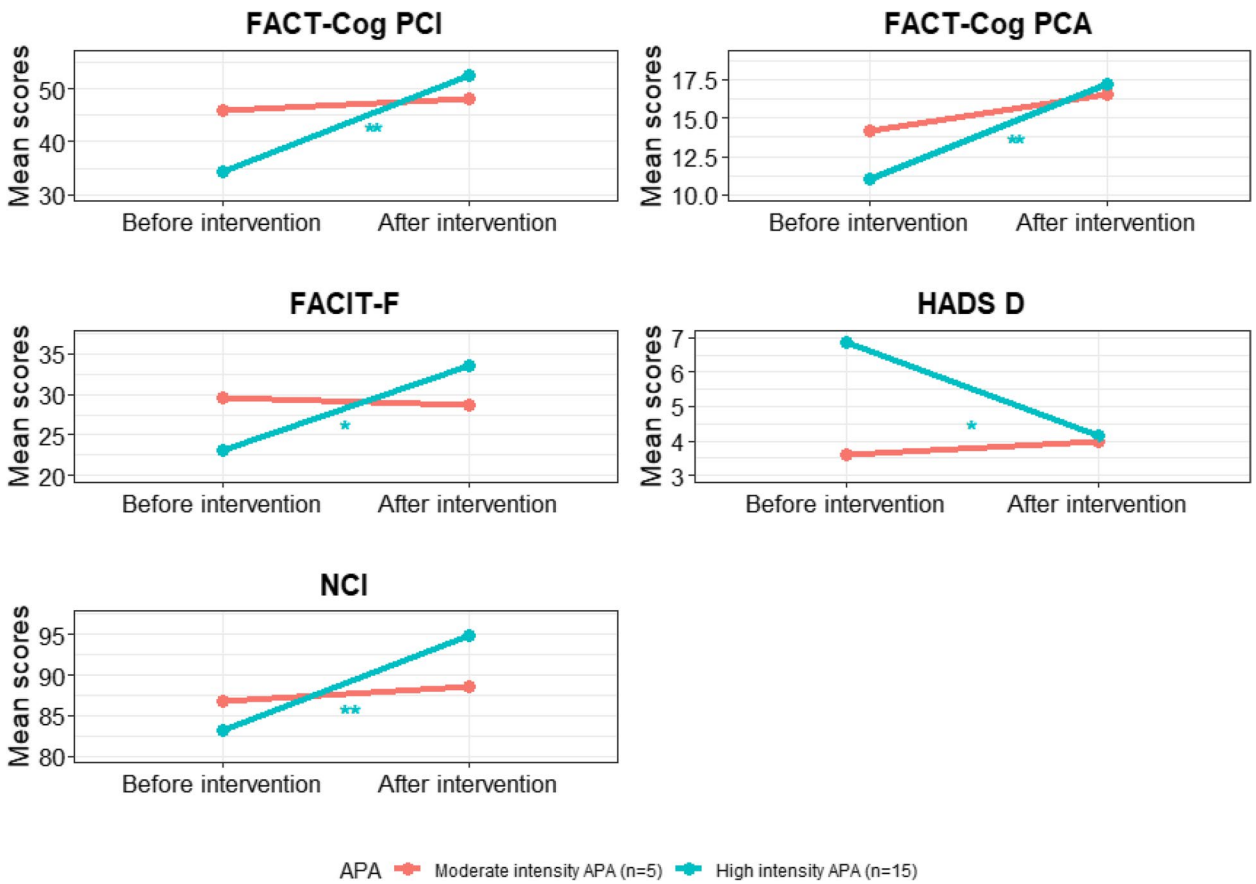

Fig. 2 Cognitive complaints, fatigue, depression and objective cognition according to intensity of the APA sessions. Higher scores in these questionnaires refers to lower complaints (excepted for depression). Stars describe significant difference between before and after intervention in "High intensity APA" group estimated by paired sample Wilcoxon Mann Whitney test. (*: $p < 0.05$, **: $p < 0.01$)

Table 4 Objective cognitive scores before and after intervention

CNS VS subscales Mean (SD)	Evaluation		
	Pre-intervention	Post-intervention	*p*-value
NCI	84.0 (18.7)	93.1 (19.7)	0.016*
Verbal Memory	86.4 (19.6)	94.1 (20.6)	0.162
Visual Memory	96.2 (14.8)	94.8 (13.0)	0.529
Psychomotor Speed	82.8 (22.3)	95.1 (20.8)	0.004*
Reaction Time	79.3 (25.9)	92.5 (20.7)	0.018*
Complex Attention	86.8 (22.9)	96.3 (15.0)	0.344
Cognitive Flexibility	86.3 (21.5)	84.9 (28.3)	0.932
Processing Speed	92.6 (19.3)	96.8 (22.4)	0.191
Executive Functions	87.2 (20.7)	87.5 (24.3)	0.82
Simple Attention	92.0 (19.6)	92.0 (22.3)	0.811
Motor Speed	82.8 (20.2)	95.8 (18.6)	0.004*

* For significant results

Effects of the intervention on cognition and associated factors

This study showed that a digital multimodal intervention combining physical and cognitive training had positive effects on both self-reported and objective cognitive functions and related factors, such as fatigue and depression. Patients had a significant improvement in overall objective cognition, psychomotor speed, motor speed and reaction time. These cognitive domains are relevant in actions such as driving a car and participating in a conversation, for which patients often report difficulties [39]. Usually, monomodal interventions only improve subjective cognition [14]. The results of our study could be explained by the combined action of physical and cognitive training. To confirm this hypothesis, a randomized trial comparing a monomodal intervention with a multimodal intervention is needed.

Furthermore, high adherent participants had better improvement in cognitive complaints and fatigue than low adherent ones, emphasizing the importance of considering adherence levels when interpreting the intervention's outcomes. However, high adherent participants had higher cognitive complaints and fatigue before intervention than other participants, which could induce a greater possibility of improvement. Thus, baseline cognitive function could be considered in the intervention's effect.

Participants who engaged in high-intensity APA had better improvement in objective cognitive functions, cognitive complaints, fatigue, and depression than those with moderate intensity. These results are consistent with previous research that highlighted the beneficial role of physical activity, particularly high-intensity activity, in reducing fatigue [40] and cognitive difficulties [41, 42] in cancer patients. Future physical interventions should thus prioritize the incorporation of high-intensity physical activities when possible, to achieve more favorable outcomes.

Limitations of the study

This study has some limitations. First, the acceptability rate was lower than anticipated, possibly due to the COVID pandemic, so recruitment was challenging. This may have impacted the patients' decision to participate in the program. Second, as a feasibility study, the results regarding the efficacy of the intervention are limited. The sample size was insufficient to achieve the necessary statistical power for a comprehensive investigation of the intervention's effects on cognition and to perform complementary analysis such as the optimal duration of the intervention needed to achieve significant improvements. This limitation may have introduced a bias, especially regarding the objective cognitive outcomes and variations between moderate and high-intensity APA groups. Third, the participants were younger than average breast cancer patients (mean age 62 years [43]), impacting the sample's representativeness. Fourth, there was no control group and/or active control group. Fifth, long-term assessment of the intervention was not possible, yet it is now required to gain a more comprehensive understanding of its efficacy. Finally, other factors need to be explored, such as patients' preferences for mono-modal or multimodal interventions, the appropriate timing for starting an intervention, and associated implementation costs. This would lead to a more comprehensive evaluation of the intervention's feasibility and provide a clearer view of its potential implementation in clinical practice.

Clinical implications

The European survey conducted by the Innovative Partnership for Action Against Cancer (iPAAC) in 2021 drew attention to the gap between research potential and practical applications in clinical settings, and the use of non-validated interventional programs in various centers around Europe [15]. This discrepancy is partially due to limited knowledge about the feasibility and costs of interventions, underlining the pressing need for comprehensive investigations that shed light on the viability of interventions in real-world clinical settings. Moreover, recently published guidelines for healthcare professionals [19] suggest using multimodal interventions to improve cognition in oncological patients. However, although such interventions have shown promising results in mild cognitive impairment, they have not been fully investigated in CRCI [14]. This study is the first to show promising preliminary results concerning the efficacy of non-simultaneous multimodal interventions combining physical and cognitive training, and leading to an improvement in CRCI and associated factors such as fatigue and depression. Moreover, our findings shed light on the barriers and facilitators of the implementation of multimodal interventions for improving CRCI. Three main issues should be considered for future implementations of the intervention: 1) the central role of supervision in increasing adherence; 2) the influence of adherence on the efficacy of the intervention; 3) the influence of the intensity of APA on the efficacy of the intervention. These findings have important implications for the design of forthcoming interventions in clinical settings. While focusing on multimodal interventions, insights from this study can be extended to other cognitive improvement strategies in oncology,

bridging the gap between research and clinical applications. This represents an initial step toward enhanced management of long-term cognitive issues in cancer patients, which is a crucial goal for patients, healthcare providers, and institutions alike [15].

Conclusions

This is the first study proving the feasibility and potential efficacy of a digital multimodal non-simultaneous intervention combining cognitive and physical training. Levels of adherence and satisfaction were high, and the patients experienced a significant improvement in objective cognition, cognitive complaints, fatigue and depression. Moreover, supervision from an expert seems to facilitate adherence, as suggested by the higher level of adherence to the supervised physical training than the autonomous cognitive training.

Abbreviations

APA	Adapted physical activity
CNS VS	Computerized Neurocognitive Assessment Vital Sign
CRCI	Cancer-Related Cognitive Impairment
FACT-Cog	Functional Assessment of Cancer Therapy–Cognitive Function
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
HADS	Hospital Anxiety and Depression Scale
ISI	Insomnia Severity Index
MoCA	Montreal Cognitive Assessment
NCI	Neurocognition Index
Oth	Comments from Others
PCA	Perceived Cognitive Abilities
PCI	Perceived Cognitive Impairment
QoL	Quality of Life

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Authors' contribution

Conceptualization: G.B., F.J., B.C., M.L.; Data analysis: F.C.; Supervision and validation: M.L., B.C., F.J.; Writing: G.B.; Funding acquisition: M.L. Data collection: G.B., M.L. All authors have read and agree to the published version of the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted at the Comprehensive Cancer Center in Caen (France). This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local ethics committee (Réf. 2019/102, Comité de protection des personnes Nord-Ouest III, France). This trial is registered as ClinicalTrials.gov NCT04213365 (registration date: 2019-12-27). Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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