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1 Review article Neuroscience & Biobehavioral Reviews

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3 **How to assess and manage cognitive impairment induced by**
4 **treatments of non-central nervous system cancer**

5

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1 **Abstract**

2

3 A number of neurotoxicity associated with oncological treatments has been reported in non-
4 central nervous system cancers.

5 An expert group presents the state of the art and a guide to help the choice of appropriated
6 tools to assess patient cognition in studies on oncology and neurobehavior in animal models.

7 In addition, current cognitive rehabilitation programs currently under evaluation are also
8 discussed.

9 Cognitive assessments in oncology depend on the research question, study design, cognitive
10 domains, patients' characteristics, psychometric properties of the tests, and whether the tests
11 are supervised or not by a neuropsychologist. Batteries of electronic tests can be proposed, but
12 several of them are characterized by weak psychometric developments. In order to improve
13 the comprehension on the impact of cancer treatments on cognition, new animal models are in
14 development, and would in the future include non-human primate models.

15 By bringing together the skills and practices of oncologists, neurologists, neuropsychologists,
16 neuroscientists, we propose a series of specific tools and tests that accompany the cognitive
17 management of non-CNS cancer patients.

18

19

20 **Keywords:** Cognition; cancer treatments; cancer patients; electronic cognitive tests; animal
21 model; behavior; management of cognitive impairment

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1 **Highlights**

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- Cognitive assessments in oncology studies depend on various methodological issues

4

- Some batteries of electronic tests are weak in terms of psychometric development

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- Preclinical models have showed the impact of cancer treatments on cognition

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- Cognitive rehabilitation appears the most promising method of cognition management

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8

1 **1. Background**

2 Neurotoxicities associated with oncological treatments are frequently observed even in non-
3 central nervous system (CNS) cancers. Chemotherapy, hormonal therapies and targeted
4 therapies can induce cognitive impairment in some populations of cancer patients. These
5 alterations, subtle or moderate in most cases, mainly concern memory, executive functions,
6 attention and information processing speed and can have a negative impact on patient's
7 quality of life (Joly et al., 2015). This phenomenon, also named cancer-related or
8 chemotherapy-related cognitive impairment (CRCI), has been mainly studied in breast cancer
9 patients treated with adjuvant chemotherapy (Ahles, Root, & Ryan, 2012) and some clinical
10 guidelines for survivorship including cognitive difficulties care have been recently proposed
11 (Runowicz et al., 2016).

12 In cancer patients, cognitive functioning can be assessed subjectively with self-report
13 questionnaires and objectively with neuropsychological tests. In most clinical trials, objective
14 cognition has been evaluated with pencil-and-paper cognitive tests and in 2011, the
15 International Cognition and Cancer Task Force (ICCTF) published guidelines on minimal
16 battery of pencil-and-paper tests usable in standard clinical protocols (Wefel, Vardy, Ahles, &
17 Schagen, 2011). These standardized tests, requiring the presence of a neuropsychologist, have
18 been shown sometimes to be replaced by electronic tests whose some can be performed by the
19 patient himself. Nevertheless, some of these electronic batteries do not show currently robust
20 psychometric properties. It appears important to developed their use and assess their
21 robustness, notably by comparing them with traditional pencil-and-paper tests, by a
22 neuropsychologist who remains the validated way to get a diagnosis.

23 Due to the potential impact on social, professional and/or quality of life (Boykoff, Moieni, &
24 Subramanian, 2009), the management of these disorders is essential. Among existing
25 approaches, the non-pharmacological one, mainly cognitive rehabilitation, appears the most

1 promising method (Chan, McCarthy, Devenish, Sullivan, & Chan, 2015) among various
2 cognitive programs which have not yet been compared with each other's.
3 Experimental works performed in animal models are complementary to clinical studies and
4 especially useful to assess the direct impact of anticancer agents on cognition regardless of the
5 cancer itself, the surgery, anxiety/depression and/or additional co-morbidities. It should help
6 investigating underlying neurobiological mechanisms and the influence of some parameters
7 such as stress, mood and aging on potential therapy-induced cognitive dysfunctions (Dubois
8 et al., 2014; Winocur, Johnston, & Castel, 2018; Seigers & Fardell, 2011).
9 In this context, an expert group of neuropsychologists, oncologists, geriatrics, neurologists,
10 neuroscientists and biostatisticians, from the International Cancer and Cognition Platform, the
11 Reflection Group on Cognitive Evaluations in Oncology (GREC-ONCO) and/or the French
12 speaking association of Neuro-oncologists (ANOCEF), present the CRCI state of the art and a
13 guide to help the choice of appropriated tools to assess objective cognition in oncology
14 studies in patients and animal models. Cognitive rehabilitation programs were discussed and
15 the main propositions of the expert groups are presented hereafter.

16

17 **2. Cognitive assessment in cancer patients**

18 Cognitive assessment and interpretation of results in oncology are challenging due to various
19 factors and co-morbidities that may impact cognitive functioning, such as anxiety/depression
20 and fatigue (Lange et al., 2014).

21 The choice of the tests and its' modalities depends on the presence of a neuropsychologist, the
22 research question, the study design (control group or normative data; study design
23 longitudinal or not ± alternate test forms...) (Wefel et al., 2011), the assessed cognitive
24 domains (e.g. visuospatial abilities with androgenic deprivation therapy), the patients'

1 characteristics (e.g. lack of familiarization of elderly patient with electronic tools), but also
2 the psychometric test properties such as reliability and validity.

3

4 **2.1. Standard pencil-and-paper tests**

5 Cognitive assessment in oncology studies needs the use of standardized tests, available and
6 validated for each language and including normative data among the age group of the
7 population studied. In complement and based on the ICCTF recommendations (Wefel et al.,
8 2011), the GREC-ONCO proposed, according to normative data, to use a more extensive
9 battery composed by a core battery of cognitive tests and optional tests (Taillia et al., 2015)
10 (Table 1). Additional tests or tests varying from those proposed by the ICCTF are presented
11 below.

12 The National Adult Reading test adapted for instance in French (fNART) (Mackinnon, 2005),
13 the Wide Range Achievement Test also adapted (WRAT) (Wilkinson & Robertson, 2006),
14 which is a marker of the pre-morbid cognitive level and a proxy of cognitive reserve, can be
15 used at study enrollment. The global cognitive functioning test Montreal Cognitive
16 Assessment (MoCA) is also advocated (Nasreddine et al., 2005).

17 To assess verbal memory, two tests can be used depending on the patients' age, the follow-up,
18 and/or the time available for cognitive assessment, e.g. the RL/RI-16 items (Grober, Buschke,
19 Crystal, Bang, & Dresner, 1988) or the Hopkins Verbal Learning test (HVL) (Brandt, 1991).

20 The last one, recommended by the ICCTF, has few normative data in French as in other
21 languages. The Rey's figure delayed recall can be used to assess visual memory (Rey, 1959).

22 Concerning attention and executive tests, the Computerized Speed Cognitive Test (CSCT)
23 (Ruet, Deloire, Charre-Morin, Hamel, & Brochet, 2013) is recommended. The paper version
24 (Digit Symbol) can also be used (Wechsler, 2008). The GREC-ONCO proposed two verbal
25 fluency tasks (animals and letter P) (Godefroy & and the Reflection Group on the Evaluation

1 of Executive Functions (GREFEX), 2008) instead of the Controlled Oral Word Association
2 (COWA) - rarely used in France for lexical reasons - questioning the necessity of adaptation
3 depending on the country.

4 The ICCTF also recommends assessing working memory. In this situation, the GREC-ONCO
5 proposes to use digit and spatial spans (Wechsler, 2008; Wechsler, 2009).

6

7 **2.2. Electronic cognitive tests**

8 **2.2.1. Electronic cognitive tests used in oncology**

9 Among electronic batteries of cognitive tests used in oncology studies with adult patients
10 excluding CNS cancer (Table 2), the most frequently used are CogTrack, the Cambridge
11 Neuropsychological Test Automated Battery (CANTAB), CNS Vital Signs, CogState and
12 BrainBaseline. They assess various cognitive domains pertinent in oncology such as attention,
13 processing speed and memory. For each of them, patient can perform the assessment without
14 professional assistance.

15 The Cognitive Drug Research System (CDR), or **CogTrack**, was developed to assess
16 cognition in clinical trials. The normative data are based on a large sample size (Wesnes,
17 McNamara, & Annas, 2016). Psychometric properties have recently been described (Wesnes
18 et al., 2017) and this battery showed a beneficial effect of modafinil on memory speed,
19 episodic memory and attention in breast cancer survivors (Kohli et al., 2009).

20 **CANTAB** was used in neuroscience research in multiple neurological patient populations.
21 Moderate correlations with paper-pencil tests and low test-retest reliability were found (Lowe
22 & Rabbitt, 1998). Some authors concluded that there is an adequate assessment of an
23 underlying “general” cognitive factor, but that measurement of specific constructs, such as
24 memory, must be approached with caution (Smith, Need, Cirulli, Chiba-Falek, & Attix,

1 2013). A weak association was observed between global deficit score (pencil-and-paper tests)
2 and CANTAB in colorectal cancer patients treated by chemotherapy (Vardy et al., 2014).

3 **CNS Vital Signs** includes familiar cognitive tests. Test-retest reliability, concurrent validity
4 with traditional tests and discriminating validity were assessed and showed similar
5 characteristics than the traditional neuropsychological tests (Gualtieri & Johnson, 2006).
6 Nevertheless, compared with other electronic batteries including CogState, the proportion of
7 scores that met at least adequate reliability seems to be lower (Cole et al., 2013). CNS Vital
8 Signs should not replace the comprehensiveness of traditional neuropsychological tests but it
9 can play a role in screening or serial assessment (Gualtieri & Johnson, 2008). This battery has
10 been used in breast cancer patients and in lymphoma survivors, showing cognitive functioning
11 worsening over the course of chemotherapy (Collins, Mackenzie, Tasca, Scherling, & Smith,
12 2013) and impaired attention, respectively (Krolak, Collins, Weiss, Harris, & Van der Jagt,
13 2017).

14 **CogState** was used in phase I to phase IV trials. High test–retest reliability was found when
15 participants were assessed over 3 months (Lim et al., 2013; Fredrickson et al., 2010).
16 Compared with 3 other electronic batteries, Cog-State had the highest proportion of scores
17 that met adequate reliability (Cole et al., 2013). In breast cancer survivors a trend towards
18 significance for validity criterion related to working memory among 4 assessed domains was
19 found (Patel et al., 2017). No statistical significance correlation was observed with traditional
20 tests (Patel et al., 2017). These results could be partly explained by the few cognitive
21 impairment found and the small sample size (n=26). In breast cancer, during the 5th year of
22 treatment, the overall cognitive scores of patients receiving tamoxifen had worsened
23 compared with those treated with aromatase inhibitors (Phillips et al., 2010). A second study
24 showed no significant impact of ovarian function suppression on breast cancer patients’

1 cognition while a third one assessed the effect of cognitive rehabilitation program and showed
2 no difference between groups (Bray et al., 2017; Phillips et al., 2016).

3 **BrainBaseline** is difficult to evaluate the usefulness of this tool due to little information
4 available on website. Nonetheless, a study in breast cancer survivors showed an association
5 between physical activity and executive and working memory functioning (Ehlers et al.,
6 2017).

7

8 **2.2.2. Electronic cognitive tests used in other pathologies**

9 Other cognitive tests or batteries are frequently used notably in clinical context in various
10 patient populations. Often presented as electronic versions of traditional pencil-and-paper
11 tests they require professional assistance (Table 3, non-exhaustive list).

12 Several Wechsler batteries, such as the Wechsler Adult Intelligence Scale-IV (**WAIS-IV**
13 (Wechsler, 2008)) and the Wechsler Memory Scale (**WMS-IV** (Wechsler, 2009)), are
14 available in a digital platform, Q-interactive. The WAIS-IV was developed to provide a
15 measure of cognitive ability (4 scales) and the WMS-IV focuses on the assessment of memory
16 (various indexes, Table 3). Equivalence studies between the traditional and electronic versions
17 were conducted in healthy subjects (Daniel, 2012; Daniel, 2013) but there is no data in
18 patients.

19 The electronic version of the MoCA (Nasreddine et al., 2005), a cognitive screening test, is
20 available. **eMoCA** is very similar to the paper version with some additional features
21 (instructions of presented onscreen, computation of the execution time, etc.). The comparison
22 between electronic and paper version is ongoing.

23 The d2 is a test frequently used to assess attention (Brickenkamp, 1998). An electronic
24 version of the revised version (**d2-R**) is available. Normative data of this test exist on a large
25 sample however the electronic version did not include subjects aged ≥ 55 years (Brickenkamp,

1 Schmidt-Atzert, & Liepmann, 2015). The manual of the editor contains reliability data but not
2 validated data (Brickenkamp et al., 2015).

3 The Computerized Speed Cognitive Test (CSCT) assesses processing speed similar to the
4 digit/symbol substitution of the WAIS Digit Symbol or the Symbol Digit Modalities test
5 (Ruet et al., 2013). It allows limited effect related to practice due to the generation of new
6 keys and forms at each session and to instant classification of scores according to normative
7 values.

8 **COGBAT** of the Vienna Test System includes familiar cognitive tests and can provide a brief
9 assessment of attention, executive functions and memory.

10

11 **2.3. Phone based cognitive assessment**

12 Recently, a study on cognitive training in breast cancer patients used a phone based cognitive
13 assessment testing (Damholdt et al., 2016). Phone based tests are usually completed with the
14 supervision of a professional (paced auditory serial addition test, Rey auditory verbal learning
15 test, digit span forwards, digit span backwards, digit ordering, letter fluency, etc.). To reduce
16 risk of cheating, the participants were instructed not to take notes, and the assessors registered
17 any signs of cheating.

18

19 **3. Cognitive assessment in animal models**

20 Although clinical observations are essential for establishing the role of combinatorial
21 chemotherapy and new anti-cancer therapy, they will not make it possible to establish a direct
22 physiopathological link of causality between chemotherapeutic molecules and the appearance
23 of the cognitive dysfunctions observed during longitudinal follow-up of patients. The use of
24 animal models allowed evaluation of the direct impact of cancer therapy on cognitive

1 functions and its interaction with factors such as aging and emotional status (Lee et al., 2006;
2 Dubois et al., 2014; Reiriz et al., 2006).

3 Thus, the behavioral approach used corresponds to selected behavioral tests focusing on tasks
4 dependent on the hippocampus and the prefrontal cortex, in addition to the spontaneous
5 activity and emotional reactivity (supplementary material).

6 **The open field** test assesses rat or mouse spontaneous activity through recording of their
7 natural behavior towards an inherent fear of empty, new and open space. This test helps
8 detecting potential toxicity and well-being, evaluating anxiety-like behavior.

9

10 **3.1. Hippocampus and prefrontal cortical cognitive tests**

11 Cognitive assessment in chemotherapy-treated animals involves standardized cognitive tests
12 evaluating cognitive functions related to the hippocampus and the prefrontal cortex. The
13 recent ICCTF preclinical recommendations proposed battery of standard operating Procedures
14 for behavioral tests in rodents (Winocur et al., 2018).

15 The **Morris water maze** (MWM) addresses context-dependent spatial learning and memory
16 (de Toledo-Morrell, Morrell, & Fleming, 1984), but also behavioral flexibility (Morris, 1984).

17 The **contextual fear conditioning test** assesses non-spatial memory through the ability to
18 learn basic associations involving the functioning of the hippocampal memory (contextual
19 fear conditioning), basic conditioning related to the amygdala (cued fear conditioning), and
20 the learning of suppressing a fear response once it has been learned (Anagnostaras, Maren, &
21 Fanselow, 1999).

22 The **novel object recognition test** (NOR) is also used to assess short-term and long-term
23 memory (working or prefrontal or hippocampal memory function) (Ennaceur & Delacour,
24 1988). This task measures the preference of animals to detect and explore a new object
25 compared with familiar ones in their environment.

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3.2. Emotional reactivity tests

Preclinical research should help to take-into account co-occurring symptoms associated with chemotherapy, and their relationship to cognitive performance. In rodents, emotionality, stress-related responses, motivation or impulsivity/risk assessment have been tested reliably in the neuroscience field. The **elevated plus maze** evaluates anxiety-like behaviors (in a forced situation) (Lister, 1987) by requiring the animal to choose between secure parts of the maze (two enclosed arms) and aversive parts of the maze (open arms).

Other reliable tests for measuring aspects of emotional reactivity in rodents include the **forced swim test** (FST) (Castagne, Porsolt, & Moser, 2009), which measures immobility in inescapable stressful situations and models depressive-like behavior or the **tail suspension test** (TST) (Steru, Chermat, Thierry, & Simon, 1985) an alternative to the forced swimming test in mice.

3.3. Non-human primate model

Non-human primates might be considered the species of choice to study anticancer therapy-induced cognitive deficits because of similarities with human in terms of general physiology, brain structure and metabolism, grey to white matter ratio, immune system, and behavioural repertoire. Complex cognitive behaviours in the marmoset (*Callithrix jacchus*) have been investigated, using manual (Marshall et al., 2003; Roberts & Wallis, 2000) as well as automated touch screen systems such as the CANTAB (Spinelli et al., 2004). As a result, it has been shown that marmosets are able to be trained at a high and stable level of performances on a variety of cognitive tasks (Le Gal, Bernaudin, Toutain, & Touzani, 2017), thus sustaining future development with these non-human primate models.

1 **4. Cognitive training in cancer patients and other pathologies**

2 Although there are still no preventive interventions, different methods of managing cognitive
3 impairment are being assessed: pharmacological, physical, behavioral and cognitive ones.
4 Among these approaches, cognitive rehabilitation appears most promising (Chan et al., 2015).
5 Cognitive management exists both through electronic programs (which can be performed by
6 the patient alone) or *via* internet platforms providing cognitive training at home and enabling
7 to be coached by a professional. Overall, the first outcomes of cognitive management studies
8 based on small cancer patient samples, showed an improvement of cognitive complaints
9 rather than performances on cognitive tests (Table 4).

11 **4.1. Cognitive training based on electronic program**

12 The use of electronic cognitive training programs makes it possible to have a precise follow-
13 up of the patient performances and to be able to standardize the support. Among the tools
14 available, the most common are BrainHQ/InSight®, LUMOSITY® and HAPPYNeuron®.
15 All are available in several languages, allowing cross-language comparisons.

17 **4.1.1. Electronic training in oncology**

18 **BrainHQ/InSight®** is a learning program based on the neuroplasticity model to improve
19 processing speed. It has been mainly used in healthy adults, elderly adults and schizophrenia
20 patients. These benefits were assessed in a large randomized study in cancer survivors
21 showing a decrease in cognitive complaints without benefits on objective tests (Bray et al.,
22 2017).

23 **LUMOSITY®** has been developed partly from neuropsychological tasks. It has been mainly
24 used in older adults. First results have also been published in breast cancer survivors and

1 showed improvement of executive functions, processing speed and executive complaints
2 (Kesler et al., 2013).

3 **HAPPYNeuron®** program has been developed by a team of neurologist, speech therapists
4 and psychiatrics and proposed varied exercises. A study in breast cancer survivors did not
5 show significant effect on cognitive complaints but objective performances of verbal learning
6 and working memory improved from 5 months after training (Damholdt et al., 2016).

7 Other electronic trainings were currently proposed in other pathologies including RehaCom®
8 or Cogmed but not yet in oncology.

9

10 **4.2. Cognitive training in oncology without electronic program**

11 Regarding the non-electronic cognitive rehabilitation programs used in oncology, the problem
12 resides in the small sample of cancer patients, even if they allow improving cognitive
13 complaints and objective performances for at least one score or one domain.

14 The **Memory and Attention Adaptation Training (MAAT)** was based on cognitive-
15 behavioral therapy and aimed to enhance cancer patients' skills for self-managing and coping
16 with cognitive impairment in daily life. Results showed that patients improved in verbal
17 memory performances and some aspects of quality of life after intervention (Ferguson et al.,
18 2012; Ferguson et al., 2007).

19 A second program **Promoting Cognitive Health Program** consists in individualized face-to-
20 face education and focused on changing dysfunctional cognition and maladaptive behaviors
21 and on developing problem-solving and coping skills, to play a role in the prevention of
22 cognitive decline. A pilot study showed benefits in breast cancer patients undergoing
23 chemotherapy on objective and subjective cognition (Park, Jung, Kim, & Bae, 2017).

24 Programs of **group-based cognitive rehabilitation** also exist. The one used by Cherrier and
25 colleagues (2013) included consecutive workshop sessions which included memory aids as

1 well as development of memory skills and one session on mindfulness meditation. In cancer
2 survivors, improvement on attention and cognitive complaints were observed after
3 intervention.

4 A second program, Responding to Cognitive Concerns (**ReCog**), was based on a group of
5 self-regulatory cognitive rehabilitation (Schuurs & Green, 2013). The program was composed
6 by sessions focusing on psychoeducation, and followed by a thematic group discussion. The
7 second half of each session emphasized developing and applying skills. A feasibility study in
8 cancer survivors was followed by a randomized trial showing that the rehabilitation group
9 increased only performance in TMT A and in one subscale of cognitive complaints
10 questionnaire (King & Green, 2015).

11 Another program was based on **psychoeducation and home cognitive exercises** (Ercoli et al.,
12 2013). It includes group session of education, technique instruction, in-class and homework
13 exercises and goal setting. In breast cancer survivors, a significant effect was observed on
14 cognitive complaints and memory functioning (Ercoli et al., 2015).

15 Advanced Cognitive Training for Independent and Vital Elderly (**ACTIVE®**) consisted in a
16 memory training (Jobe et al., 2001) based on memory strategies and exercises on small group
17 dedicated to elderly. A randomized study in breast cancer survivors compared the use of
18 ACTIVE and INSIGHT program (processing speed training only) and showed broader
19 benefits on cognitive complaints, memory and processing speed performance with the latter
20 program (Von Ah et al., 2012).

21

22 **5. Contributions of the cognitive training with animal model**

23 The current core of data obtained in preclinical models should help testing and investigating
24 strategies of intervention and prevention of cancer therapy-induced cognitive deficits. For
25 example, based on the clinical studies previously showing that physical activity improves

1 quality of life and cognitive functioning, two main studies demonstrated in rats that physical
2 exercise improves neurogenesis and cognitive functions altered by chemotherapy (Fardell,
3 Vardy, Shah, & Johnston, 2012; Winocur, Wojtowicz, Huang, & Tannock, 2014).

4

5 **6. Propositions for cognitive study in oncology**

6 The multidisciplinary group aimed at discussing and proposing the most relevant tools
7 including the use of new electronic batteries of tests to apply to cancer patients and to use in
8 animal models to assess cognitive dysfunctions induced by treatments.

9 **6.1. Cognitive assessment in patients**

10 Cognitive assessment in oncology studies depends on the research question, the study design,
11 the cognitive domains, patients' characteristics, the psychometric properties of the tests but
12 also the presence of a neuropsychologist, essential to make the interpretation of results. The
13 propositions are presented as followed:

14 a) Memory, processing speed and executive functions, which are most impaired domains
15 after cancer treatments (Joly et al., 2015), should be evaluated systematically and the battery
16 of tests should not be too long

17 b) Cognitive assessment should as far as possible be performed by a neuropsychologist,
18 using validated and standardized cognitive tests, able to make appropriate feedback to patients
19 and potentially dissociating cognitive impairment due to cancer treatments to those related to
20 different etiology.

21 c) For the use of pencil-and-paper tests, tests should be available and validated in each
22 national language and exhibit normative data. For example, for patients speaking French, the
23 first choice should be the battery proposed by the GREC-ONCO, based on ICCTF's
24 recommendations (Wefel et al., 2011) and according to normative data. The electronic
25 versions of traditional pencil-and-paper tests can also be used (Table 3), with the advantage to

1 have a more precise measure of the reaction time and an automatic calculation of raw scores
2 or even z-scores.

3 d) In the absence of a neuropsychologist, studies can include a screening cognitive
4 assessment and an evaluation of cognitive complaints (Figure 1). Some batteries of electronic
5 tests could also been proposed. Some of them are relatively weak in terms of psychometric
6 development but some have been used in cancer clinical trials, from which CogState has been
7 validated in oncology. More studies using these electronic batteries should be conducted to
8 assess their sensitivity and specificity and to assess relationship with standard
9 neuropsychological tests. With the self-administration of tests, feedbacks to patients are
10 necessary with a suitable manner. This approach also needs follow-up screening of cognitive
11 difficulties. The disadvantages to these batteries also include the lack of familiarization for
12 some patients with electronic tools, especially older patients. Even so, these electronic
13 cognitive batteries (Table 2) could be used for large database implementation. They present
14 the advantage of having little verbal material, thus reducing the impact of the practice in
15 longitudinal studies with repeated assessment and tests could more easily be proposed in a
16 random order

17 e) Cognitive assessment performed by phone, based on tests with known psychometric
18 properties, could be an alternative to electronic tests performed without a neuropsychologist,
19 even if cautions should be taken to reduce the risk of cheating by taking notes.

20 f) Cognitive complaints are not always related to performances in cognitive tests, but
21 they are frequently associated with psychological factors and fatigue (Hutchinson, Hosking,
22 Kichenadasse, Mattiske, & Wilson, 2012). For this reason, these factors should be
23 systematically assessed among patients with cognitive complaints, and used as covariates in
24 studies, to better identify the origin of the difficulties and potentially propose specific care.
25 Furthermore, patients' perceptions of cognitive difficulties are important because of their

1 significant effect on quality of life. Self-reported questionnaires such as Functional
2 Assessment of Cancer Therapy Cognitive Scale (FACT-Cog), Hospital Anxiety and
3 Depression Scale (HADS) and Functional Assessment of Chronic Illness Therapy-Fatigue –
4 FACIT-Fatigue (FACIT-F) could be used to assess respectively cognitive complaints,
5 anxiety/depression and fatigue (Wagner, Sweet, Butt, Lai, & Cella, 2009; Zigmond & Snaith,
6 1983; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997; Wagner et al., 2009; Zigmond &
7 Snaith, 1983; Yellen et al., 1997).

8 g) In addition to psychological factors and fatigue, factors such as co-morbidities should be
9 assessed (e.g. with Charlson questionnaire (Charlson, Pompei, Ales, & MacKenzie, 1987))
10 and taken into account, especially in older patients, as well autonomy data (with Instrumental
11 Activities of Daily Living (Lawton & Brody, 1969)).

12 **6.2. Cognitive training in cancer patients**

13 Among the methods of management of cognitive difficulties, the non-pharmacological
14 approach shows the best benefit (Chan et al., 2015). All interventional studies reported in this
15 review demonstrated cognitive complaints improvement; however their effect in objective
16 cognitive performances is less clear. Cognitive management studies should include a control
17 group with a different kind of cognitive training, or combine alternative approaches like
18 physical activity which also showed benefits in humans and in animals (Zimmer et al., 2016;
19 Winocur et al., 2014), mindfulness based cognitive therapy or programs used in other
20 diseases.

21 Further research is needed about the length of training program, to question whether the
22 duration of 4-12 weeks is sufficient to maintain benefit on cognition. All these programs need
23 standardization, more specifically when non-electronic ones are used.

24 In any case, professional assistance is strongly encouraged. Indeed, if patients with difficulties
25 are following the program alone, some exercises could spark off stress or decrease self-
26 confidence. Furthermore, for studies focusing on elderly patients, who are less familiar with

1 electronic tools, feasibility and acceptance rate on cognitive training with electronic interface
2 need to be assessed.

3 4 **6.3. Cognitive assessment with animal model**

5 To explore and verify potential cognitive impacts of cancer treatments in animal models, a
6 battery of cognitive and emotional tests are likely recommended (Winocur et al., 2018). It
7 should include reliable tests of memory and executive functions related to hippocampal and
8 prefrontal cortex dysfunctions, e.g. MWM and NOR (Table 4). The NOR appears interesting
9 in the sense that it can be used to evaluate the impact of cancer/treatments in a longitudinal
10 way, without bias due to test and retest procedures on the same animals. Anxiety-like and
11 resigned-depressive like behaviors should be tested systematically, such as elevated plus maze
12 and FST (Table 4), to evaluate cancer therapy because emotional status i) may be directly
13 impaired by the neurobiological mechanism of chemotherapy and thus consequently would
14 interfere with cognitive test evaluations and ii) can constitute a risk factor predictive of
15 chemotherapy-induced cognitive dysfunctions.

16 Thus more studies should be directed to better adapt the dose of chemotherapy regimen, the
17 combination of diverse chemotherapy currently in use in clinical protocols (FOLFOX, Folfiri,
18 FEC, etc...), potential toxicities in animals and also to adjust the delay between last treatment
19 injection and the behavioral experiments. Thus, it is likely that investigation of learning
20 memory or behavioral flexibility should be investigated at different time post-treatment
21 corresponding to different mature status of new produced neurons.

22 Until now, it is interesting to note that from the animal model literature, few evidence indicate
23 that anxiety and depressive-like behaviours can be directly affected by chemotherapy, but
24 some confounding factors such as age should be taken into consideration. In addition, new
25 targeted therapy such as kinase inhibitors or new hormone therapy, may interfere with
26 emotional reactivity, and as a consequence, impact the results of cognitive tests. For instance,

1 patients treated with some hormone therapy may suffer from fatigue, while cognitive
2 impairment is currently assessed in clinical trials (Lange et al., 2017). A pre-clinical study can
3 be proposed by adapting the animal model by working on aged animals, bearing a tumor and
4 treated by hormonotherapy after surgery, to better understand the physiopathology of
5 “fatigue” or cognitive impairment, in side of the cancer itself and/or the co-morbidities,
6 confounding aspects in clinical trials.

7 According to research question, if the animal model should assess higher-order executive
8 functions, the non-human primate model, such as the marmoset model, have the advantage to
9 have cognitive skills which cannot be evaluated in other species. Moreover, the
10 pharmacokinetics and pharmacodynamics in primates are often very different from those in
11 rodents, thus placing marmoset as a reasonable intermediate model to examine the effects of
12 anticancer therapies on cognitive performances on brain functions with the same noninvasive
13 neuroimaging techniques used in the clinic.

14 15 **6.4. Perspectives**

16 In addition to development of cognitive assessment with electronic battery of tests, virtual
17 reality, more ecological, or exergaming are other promising approaches for assessment and
18 training. Since cognitive complaints are frequent, some other cognitive domains than those
19 monitored by ICCTF and GREC-ONCO batteries can be investigated such as prospective
20 memory or social cognition.

21 Methodological quality of clinical trial on cognitive management could be improved by
22 comparing cognitive programs and different management approaches, such as cognitive
23 training and physical activity or multimodal approaches.

24 The recommendation is to favor more sophisticated preclinical animal models mimicking the
25 longitudinal course of the cancer treated patients should now include stress and anxiety prior
26 to tumor transplantation/development, anesthesia and surgery, and then chemotherapy and/or

1 new cancer therapy administration, also based on different development stages (juvenile,
2 young and aged), including both sex. It will greatly help to understand and evaluate the
3 transitory or long-term impact on cognition of the cancer situation and to test and evaluate
4 pharmacological or ecological rehabilitation strategies.
5

1 Supplementary material: Table: Common cognitive/emotional test in rodent animal models.
2 Modified and adapted from Winocur et al., 2018

3

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5

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7 ML, HC, JLF, MB, OT, JP, MD, RLG and IsL, have provided review of the literature. ML,

8 HC, JLF, DM, MB, OT, JP, IdL and FJ wrote the article. LT, IL, BG, CB and DR edited the

9 manuscript. All authors approved the final version of the manuscript.

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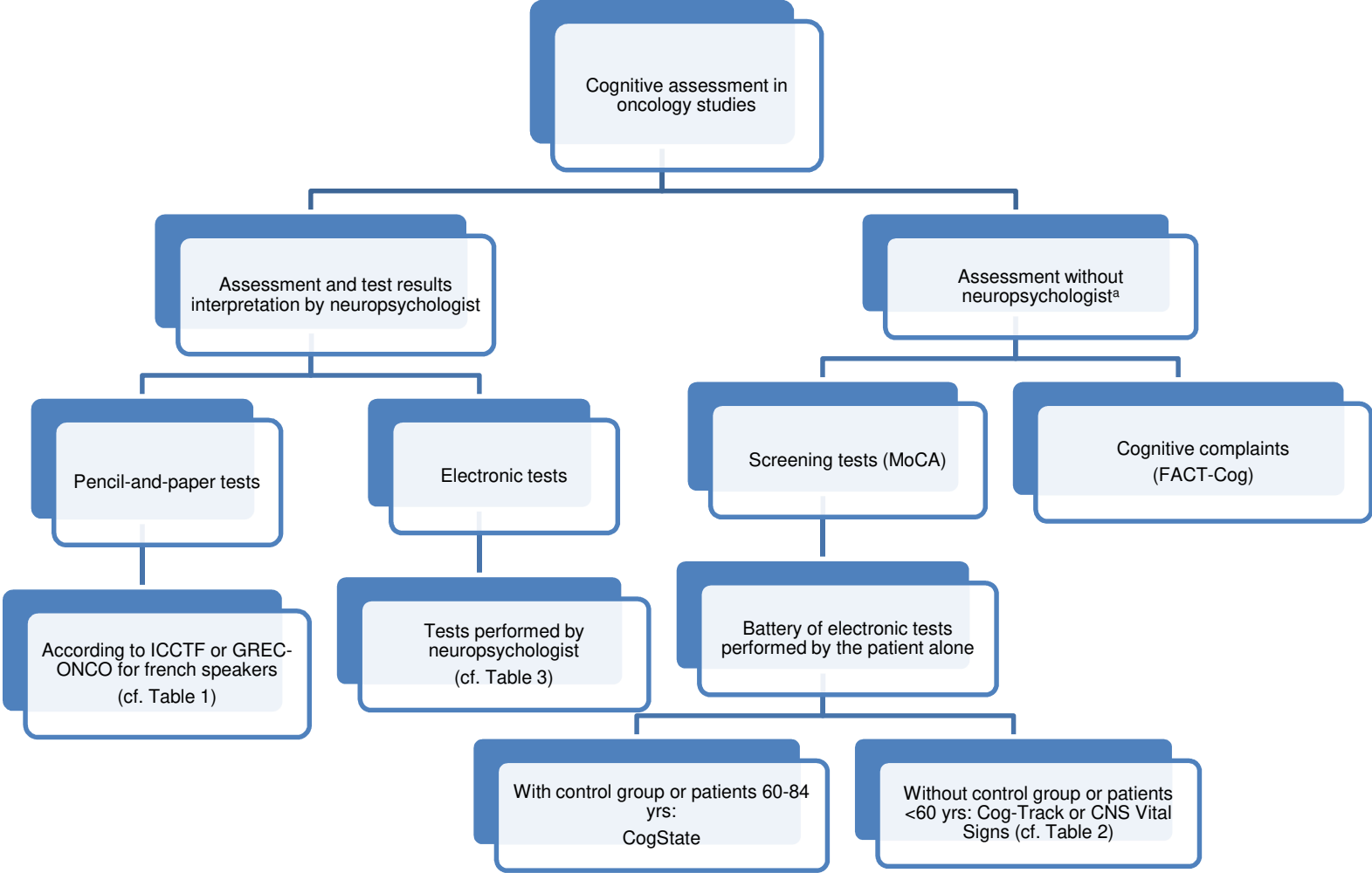
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Figure 1: Choice of tools for cognitive assessment in oncology studies



Legend Figure 1.

Figure 1: Choice of tools for cognitive assessment in oncology studies. The final choice depends on research question, study design, cognitive domains assessed and patients' characteristics.

^a Nevertheless, the presence of a neuropsychologist is essential to make the interpretation of test results

Table 1: Battery of pencil-and-paper tests proposed to patients who speak French without CNS tumor to assess cognition (GREC-ONCO battery)

Tests	Cognitive domains	Time to performed (min)	Notes
Core battery			
fNART ¹³	Premorbid IQ	3	Only at baseline
MoCA ¹⁵	Global cognitive functioning	7	
RL/RI-16 items ^{16,92} Or HVL ^{17,93}	Verbal memory	20	2 equivalent parallel versions; learning control
		10	5 parallel versions in French; no learning control Validation (n=30; <64 yrs old)
CSCT ¹⁹ Or Digit Symbol ²⁰	Processing speed	< 2	CSCT must be the first choice if a computer is available
		3	
Digit span (forward and backward) ²⁰	Memory	5	
Spatial span (forward and backward) ²²		5	
TMT, parts A and B ²¹	Executive functions	7	
Stroop ²¹		5	
Categorical verbal fluency (animals; 2 min) ²¹		3	
Phonological verbal fluency (letter P; 2 min) ²¹		3	
Optional tests			
Copy of the Rey's figure ¹⁸	Constructive praxis	3	
3 minutes recall of the Rey's figure ¹⁸	Visual memory	3	

fNART: french adaptation of the National Adult Reading test, IQ: Intellectual Quotient, MoCA: Montreal Cognitive Assessment, HVL: Hopkins Verbal Learning test, CSCT: Computerised Speed Cognitive Test

Table 2: Summarize of characteristics of electronic cognitive tests used in oncology studies

Cognitive tests/battery	Nb of subtests Assessed cognitive domains	Psychometric properties		Self-administration (Yes/No) & time ^a	Normative data: age (sample)	Available language	Oncology field ^b	Advantages	Disadvantages
		Reliability	Validity						
(CDR)/ Cog-Track 23,24	7 subtests Attention Concentration Vigilance Episodic memory Working memory Executive control	√	√	Yes <20 min	18-87 (n=7751)	6	Effect of modafinil on cognition, breast cancer ²⁵	- Large normative data	- Handheld and touchscreen devices under development - Lack of comparison with traditional tests - Graphic interface little optimized
CANTAB 26,94-98	13 subtests Attention Working memory Episodic memory Executive function Decision making Emotion recognition	√	√	Yes ≈3-10 min/subtest	21-79 (n=341) for 10/13 subtests	30	Longitudinal study, effect of CT, colorectal cancer ^{28,29}		- Validity: moderate correlations with pencil-and-paper tests - Adequate assessment of “general” cognition but not specific domain - Limited normative data - Overall, few data on reliability and low test-retest reliability for some subtest - Possible weak association with traditional tests
CNS Vital Signs 30	10 subtests Verbal and visual memory Processing speed Executive function Attention Reasoning	√	√	Yes ≈30min for the 1 st 7 subtests	7-90 (n=1069)	60	Effect of CT, breast cancer, lymphoma survivors ³³ , ³⁴	- Detailed psychometric characteristics and comparison with traditional tests	- Available online & iPad application - Lower reliability than CogState ³¹ - Graphic interface few optimized

	Emotion recognition Working memory								
CogState 35-38,99,100	13 subtests Attention Processing speed Working memory Episodic memory Executive function Emotion recognition	√	√ notably in breast cancer patients	Yes ≈3-7 min/subtest	60-84 (n≈700)	100 (with dialects)	Effect of HT, breast cancer Cognitive rehabilitation program ³⁹⁻⁴¹	- Recent design - Better reliability than CNS Vital signs ³¹ - No impact of the absence of professional for assessment on data quality ¹⁰¹	
BrainBase line	14 subtests Attention Processing speed Working memory Executive function		NK	Yes	NK	At least english	Relation with physical activity ⁴²		- Available only on IPAD - No known data on psychometric properties nor normative data

CDR: Cognitive Drug Research, CANTAB: Cambridge Neuropsychological Test Automated Battery, CT: Chemotherapy, NK: not known, √: Assessed previously

References for psychometric properties are not exhaustive.

^a Mean time with healthy subjects

^b Only study in adult patients and excluding CNS cancer

Table 3: Summarize of characteristics of electronic cognitive tests used apart from oncology field

Cognitive tests/battery	Assessed cognitive domains	Psychometric properties		Self-administration (Yes/No) & time ^a	Normative data: age	Available language	Advantages	Disadvantages
		Reliability	Validity					
WAIS-IV Q-Interactive 43	Verbal comprehension Perceptual reasoning Working memory Processing speed	Only equivalence studies between paper and digital administration formats		No 60-90 min for main subtests	16-90	27	- Very known and frequently used battery in paper version	- Lack of equivalence study in patients, - Need to buy 2 IPAD, - Available only on IPAD, - Some subtests available only in paper-pencil form (e.g. WAIS: cubes)
WMS-IV Q-Interactive 44	Memory (immediate, delayed, visual, auditory, working memory)			No 90-150 min for all the battery	16-90	17	- Known and frequently used battery in paper version	
MoCA 15	Screening test Visuospatial / executive Naming Memory Attention Language Abstraction Orientation	Comparison between eMoCA vs paper MoCA is planned		No 10 min	No yet	English only - More languages to come	- Screening test frequently used in paper version	- Waiting for publication of psychometric properties/normative data and translation
					18-55	At least		- Lack of normative data

d2-R 46	Attention	√	No assessed	No <5min		5		of electronic over 55 years - No validity data for the electronic version - No article published on psychometric properties - Only assesses attention
CSCT 19	Processing speed	√	√	No <2 min	18-≥65	At least French	- Limited practice effect - Quick to administer	- Only assesses processing speed
<u>Vienna Test System COGBAT</u>	<u>Attention, executive functions, language, memory, processing speed...</u>	<u>√</u>	<u>√</u>	<u>Yes</u> <u>53 min</u>	<u>16-80</u>	<u>11</u>		

CSCT: Computerised Speed Cognitive Test, WAIS: Wechsler Adult Intelligence Scale, WMS: Wechsler Memory Scale, MoCA: Montreal Cognitive Assessment, √: Assessed previously

Table 4: Commonly used cognitive and emotional test in rodent animal models treated by cancer therapy. Modified and adapted from Winocur et al., Accepted, Cancer Treatment Reviews.

Tests	Cognitive domains	Involved brain area
Cognitive functions		
Morris Water Maze (MWM)	Spatial learning and memory ^{51,52}	Hippocampus
	Novel Location Recognition-behavioral flexibility (purge and relearn new strategy) ⁵¹	Hippocampus-prefrontal cortex
Barnes Maze (BM)	Spatial learning and memory ¹⁰²	Hippocampus
Context Fear Conditioning (CFC)	Contextual learning and memory ^{103,104}	Hippocampus-dependent associated learning-Prefrontal cortex (<i>trace fear conditioning</i>)
Conditioned Emotional, Response (CER)	Emotion associated learning	Amygdala-hippocampal connection
Novel objet recognition test (NOR)	Recognition memory ⁵⁴	Hippocampus-Prefrontal cortex
Passive avoidance learning (PAL)	Inhibitory processes ¹⁰⁵	Hippocampus-Prefrontal cortex
Conditional associative learning (CAL)	Executive function ¹⁰⁶	Prefrontal cortex
Non-matched sample (NMS)	working memory ¹⁰⁷	Prefrontal cortex
Emotional reactivity		
Elevated Plus Maze (EPM) Open field	Anxiety, Risk assessment ^{55,108}	Amygdala
		Prefrontal Cortex
Light-dark transition (LDT)	Emotionality, Anxiety, Conflict Resolution	
Tail Suspension Test (TST) Forced Swim Test (FST)	Stress, Depressive Behaviour ^{57,109}	Anterior Cingulate Cortex
Sucrose preference test (SPT)	Anxiety impulsivity, Anhedonia	Infralimbic Cortex Hypothalamus
Resident Intruder Aggression Test	Impulsive -Compulsive Behaviour ¹¹⁰	Raphe Nuclei
Marble Burying Test	Obsessive-Compulsive behaviour ¹¹¹	Infralimbic Cortex

Table 5: Summarize of characteristics of cognitive training programs

Cognitive program	Cognitive domains	Self-administration (Yes/No) & Time	Available language	Oncology field ^a		Advantages	Disadvantages
				Design	Main outcomes		
Electronic program							
BrainHQ/ InSight	29 exercises Processing speed Attention Memory	Yes Adjustable	9	Cancer survivors ⁴⁰ Intervention group (n=121) vs. standard care (n=121) Assessments: before, post-intervention and 6 months follow-up	Improvement of cognitive complaints No significant effect on neuropsychological tests	Self-administration, Automatic complexity level adjustment	Need internet connection
Lumosity	>25 exercises Attention Processing speed Memory Executive functions Problem solving	Yes Adjustable	7	Breast cancer survivors ⁶⁴ Intervention group (n=21) vs. waitlist (n=20) Assessments: before and post-intervention	Improvement of executive functions and processing speed and executive complaints	Multiple domains trained, App format, Self-administration	Need internet connection
HAPPYNeuron	41 exercises Attention Processing speed	Yes Adjustable	11	Breast cancer patients ⁴⁷	No significant effect of program on primary	Multiple domains trained, 9 levels,	

	<p>Learning and memory</p> <p>Working memory</p> <p>Executive functions</p> <p>Language</p> <p>Problem solving</p>	le		<p>Group web-based cognitive training + phone support (n=94) vs. Wait List (n=63)</p> <p>Assessments: before, post-intervention and 5 months follow-up</p>	<p>outcome (PASAT, working memory) and cognitive complaints</p> <p>Improvement: verbal learning + 1 measure of working memory (digit span) at 5 months</p>	<p>Automatic complexity level adjustment,</p> <p>>40 exercises,</p> <p>Varied exercises,</p> <p>Multilanguage,</p> <p>Only health care professionals could purchase access (except some “games” for public),</p> <p>Self-administration,</p> <p>Version off-line available</p>	
Rehacom	<p>20 modules</p> <p>Vigilance</p> <p>Processing speed</p> <p>Attention</p> <p>Memory</p> <p>Executive functions</p> <p>Visual field</p>	<p>Yes</p> <p>Adjustable</p>	21	Trial in process in breast cancer patients		<p>Multiple domains trained,</p> <p>Graphic interface little optimized,</p> <p>Self-administration</p>	<p>Cost,</p> <p>Big keyboard for training</p>
Cogmed	<p>25 sessions</p> <p>Attention</p> <p>Working memory</p>	<p>Yes but coach-supported</p> <p>5 weeks</p>	10	Not known with adult patients		<p>Automatic complexity level adjustment</p>	Only training of 2 cognitive domains
No electronic program							

Memory and Attention Adapting Training (MAAT)	Education Self-awareness Stress management and self-regulation Cognitive compensatory strategies	No 8 weeks	English	Breast cancer patients ⁶⁸ MAAT group (n=19) vs. waitlist (n=21) Assessments: before, post-intervention and 2 months follow-up	Improvement of verbal memory and spiritual well-being No significant effect on cognitive complaints nor other cognitive domains		Few information on the precise content of the program
Promoting Cognitive Health Program	Education Self-awareness Cognitive compensatory strategies	No 12 weeks	Korean	Breast cancer patients ⁷⁰ Intervention group (n=27) vs. waitlist (n=27) Assessments: before CT, post-intervention and CT and 6 months follow-up	Improvement of some objective scores (Immediate & delayed memory, verbal fluency) and cognitive complaints	Face to face education coaching, Scripted intervention protocols, Checklists and bi-weekly supervision	Only available in Korean, Difficult to control intervention adherence at home
Group-based	<i>7 workshop group sessions</i> Memory aids	No	English	Cancer survivors ⁷¹	Improvement of cognitive	Group program	Only memory training,

cognitive rehabilitation	Memory skills Mindfulness meditation Homework	7 weeks		Intervention group (n=12) vs. no intervention group (n=16) Assessments: before and post-intervention	complaints and attention only		Group program, No manualized program
Responding to cognitive concerns (ReCog) ⁷²	<i>4 group sessions</i> Psychoeducation Cognitive-behavioral and compensatory strategies Psychosocial support	No 4 weeks	English	Cancer patients ⁷³ Intervention group (n=16) vs. waitlist (n=13) and no cancer participants (n=16) Assessments: before, post-intervention and 3 months follow-up	Improvement in only one cognitive test (TMT A) and one subscale of cognitive complaints questionnaire	Group program, Program was manualized	Group program,
Psychoeducation and home cognitive exercises ⁷⁴	<i>5 group sessions</i> Psychoeducation Cognitive rehabilitation	No 5 weeks	English	Breast cancer survivors ⁷⁵ Intervention group (n=32) vs. waitlist (n=16)	Improvement of cognitive complaints and memory only	Group program, Program was manualized	Group program,

				Assessments: before, post- intervention and 2 months follow-up			
Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) ⁷⁶	<i>10 sessions</i> Memory compensatory strategies Exercises	No 6-8 weeks	English	Breast cancer survivors ⁷⁷ ACTIVE group (n=26) vs. Insight group (n=27) and waitlist (n=29) Assessments: before, post- intervention and 2 months follow-up	Improvement of cognitive complaints with 2 programs Larger memory and processing speed improvement with Insight	Group program, Developed for elderly participants, Certified trainer administration	Only 1 cognitive domain trained, Group program, Developed for elderly participants, One language, Certified trainer administration, Less benefits than Insight program

CT: Chemotherapy, TMT: Trail Making test

^a Only study in adult patients and excluding CNS cancer