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

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Abstract

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

An expert group presents the state of the art and a guide to help the choice of appropriated tools to assess patient cognition in studies on oncology and neurobehavior in animal models. In addition, current cognitive rehabilitation programs currently under evaluation are also discussed.

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

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

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

Highlights

- Cognitive assessments in oncology studies depend on various methodological issues
- Some batteries of electronic tests are weak in terms of psychometric development
- Preclinical models have showed the impact of cancer treatments on cognition
- Cognitive rehabilitation appears the most promising method of cognition management

1. Background

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

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

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

promising method (Chan, McCarthy, Devenish, Sullivan, & Chan, 2015) among various cognitive programs which have not yet been compared with each other's.

Experimental works performed in animal models are complementary to clinical studies and especially useful to assess the direct impact of anticancer agents on cognition regardless of the cancer itself, the surgery, anxiety/depression and/or additional co-morbidities. It should help investigating underlying neurobiological mechanisms and the influence of some parameters such as stress, mood and aging on potential therapy-induced cognitive dysfunctions (Dubois et al., 2014; Winocur, Johnston, & Castel, 2018; Seigers & Fardell, 2011).

In this context, an expert group of neuropsychologists, oncologists, geriatrics, neurologists, neuroscientists and biostatisticians, from the International Cancer and Cognition Platform, the Reflection Group on Cognitive Evaluations in Oncology (GREC-ONCO) and/or the French speaking association of Neuro-oncologists (ANOCEF), present the CRCI state of the art and a guide to help the choice of appropriated tools to assess objective cognition in oncology studies in patients and animal models. Cognitive rehabilitation programs were discussed and the main propositions of the expert groups are presented hereafter.

2. Cognitive assessment in cancer patients

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

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

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

2.1. Standard pencil-and-paper tests

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

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

To assess verbal memory, two tests can be used depending on the patients' age, the follow-up, and/or the time available for cognitive assessment, e.g. the RL/RI-16 items (Grober, Buschke, Crystal, Bang, & Dresner, 1988) or the Hopkins Verbal Learning test (HVLT) (Brandt, 1991). The last one, recommended by the ICCTF, has few normative data in French as in other languages. The Rey's figure delayed recall can be used to assess visual memory (Rey, 1959).

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

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

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

2.2. Electronic cognitive tests

2.2.1. Electronic cognitive tests used in oncology

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

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

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

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

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

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

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

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

2.2.2. Electronic cognitive tests used in other pathologies

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

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

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

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

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

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

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

2.3. Phone based cognitive assessment

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

3. Cognitive assessment in animal models

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

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

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

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

3.1. Hippocampus and prefrontal cortical cognitive tests

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

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

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

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

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.

4. Cognitive training in cancer patients and other pathologies

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

4.1. Cognitive training based on electronic program

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

4.1.1. Electronic training in oncology

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

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

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

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

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

4.2. Cognitive training in oncology without electronic program

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

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

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

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

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

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

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

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

5. Contributions of the cognitive training with animal model

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

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

6. Propositions for cognitive study in oncology

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

6.1. Cognitive assessment in patients

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

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

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

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

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

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

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

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

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

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

6.2. Cognitive training in cancer patients

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

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

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

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

6.3. Cognitive assessment with animal model

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

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

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

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

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

6.4. Perspectives

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

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

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

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

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

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ML, HC, JLF, MB, OT, JP, MD, RLG and IsL, have provided review of the literature. ML, HC, JLF, DM, MB, OT, JP, IdL and FJ wrote the article. LT, IL, BG, CB and DR edited the manuscript. All authors approved the final version of the manuscript.

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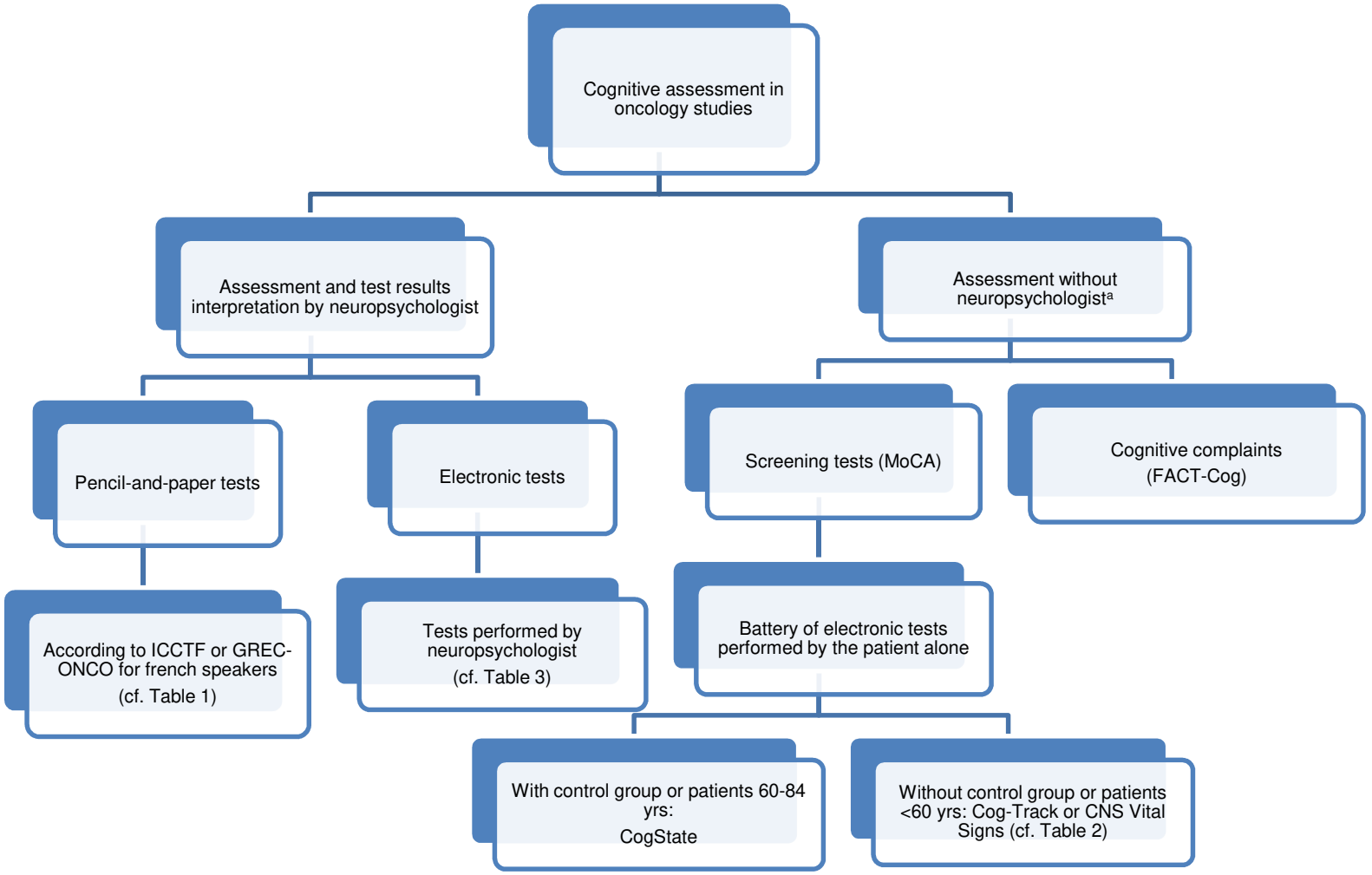
Figure 1: Choice of tools for cognitive assessment in oncology studies



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]	Verbal memory	20	2 equivalent parallel versions; learning control
Or HVLT[17,93]		10	5 parallel versions in French; no learning control Validation (n=30; <64 yrs old)
CSCT[19]	Processing speed	< 2	CSCT must be the first choice if a computer is available
Or Digit Symbol[20]		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 Addult Reading test, IQ: Intellectual Quotient, MoCA: Montreal Cognitive Assessment, HVLT: 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 1st 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]	
BrainBaseline	*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
Vienna Test System COGBAT	Attention, executive functions, language, memory, processing speed…	√	√	Yes 53 min	16-80	11		

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 (*trace fear conditioning*)
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 Adjustab	11	Breast cancer patients[47]	No significant effect of program on primary	Multiple domains trained, 9 levels,	

	Learning and memory Working memory Executive functions Language Problem solving	le		Group web-based cognitive training + phone support (n=94) vs. Wait List (n=63) Assessments: before, post-intervention and 5 months follow-up	outcome (PASAT, working memory) and cognitive complaints Improvement: verbal learning + 1 measure of working memory (digit span) at 5 months	Automatic complexity level adjustment, >40 exercises, Varied exercises, Multilanguage, Only health care professionals could purchase access (except some "games" for public), Self-administration, Version off-line available	
Rehacom	*20 modules* Vigilance Processing speed Attention Memory Executive functions Visual field	Yes Adjustable	21	Trial in process in breast cancer patients		Multiple domains trained, Graphic interface little optimized, Self-administration	Cost, Big keyboard for training
Cogmed	*25 sessions* Attention Working memory	Yes but coach-supported 5 weeks	10	Not known with adult patients		Automatic complexity level adjustment	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	*7 workshop group sessions* 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]	*4 group sessions* 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]	*5 group sessions* 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]	*10 sessions* 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