Received: 11 September 2017 | Accepted: 29 September 2017

DOI: 10.1002/pon.4564

WILEY

INVITED EDITORIAL

New Challenges in Psycho-Oncology Research IV: Cognition and cancer: Conceptual and methodological issues and future directions

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Funding information
National Cancer Institute, Grant/Award Number: R01 CA172119, R01 CA129769 and U54CA137788; National Cancer Institute, Cancer Center Core Grant, Grant/Award Number: P30 CA008748; Breast Cancer Research Foundation, Grant/Award Number: R01 CA14063

1 | INTRODUCTION

Evidence for the cognitive impact of cancer and cancer treatments has grown over the last 20 years based on studies ranging from prospective assessments with neuropsychological tests, imaging, and biomarkers to animal model studies.[1] Research examining the cognitive impact of brain tumors and treatments that directly affect the brain (cranial surgery and radiation therapy) has a long history.[2] Additionally, there is a substantial literature examining cognitive deficits in children treated for cancer[3] and a growing literature on cognitive functioning in adult survivors of childhood cancers.[4] However, evidence for cancer associated cognitive decline (CACD) for the common non-CNS cancers in adults (breast, colon, lymphoma, and prostate) has significantly broadened the scope of the field. Research has examined cognitive change across a variety of cancer types (primarily, breast cancer, but increasingly in colon, prostate, and hematological cancers) and across a variety of treatments (standard and high dose chemotherapy with stem cell transplant, endocrine / hormone ablation therapies, and local radiation). Cancer is frequently treated with multiple modalities, which complicates the study of CACD and the identification of the components of treatment responsible for cognitive change. Treatment for many cancers may consist of a combination of surgical resection, systemic chemotherapy, and local radiation therapy, with additional treatments for specific cancers (eg, endocrine therapy for breast cancer and hormone ablation for prostate cancer), and emerging evidence suggests that all of these treatments can potentially impact cognitive function.[5] Therefore, even though many researchers have assumed that they are studying the cognitive effects of chemotherapy ("chemobrain"), in reality, most of the research has examined the cognitive impact of the entire package of treatment exposures. The goals of this manuscript are to describe the conceptual and methodological challenges and emerging issues in the study of cognition and cancer.

2 | MULTIPLE DETERMINANTS OF COGNITIVE DECLINE IN CANCER PATIENTS

Initially, researchers in this area conceptualized the problem of chemotherapy-induced cognitive decline from a pharmacotoxicology perspective, ie, patients diagnosed with cancer would have normal cognitive functioning prior to treatment that would be adversely affected by exposure to certain chemotherapeutic agents. However, several findings have challenged this conceptualization including the identification of (1) pretreatment cognitive problems in a subset of patients, (2) evidence that multiple components of treatment potentially affect cognitive function, and (3) multiple risk factors including age, cognitive reserve, genetic polymorphisms (APOE, COMT, and BDNF), pathologic tumor markers, and comorbidities. Additionally, although not well studied in this area, research from other areas suggests that the biological impact of stress and low socioeconomic status and racial / ethnic factors may also influence risk for cognitive decline in cancer patients.[5] Figure 1 provides a conceptual model that outlines the multiple factors that may contribute to post-treatment cognitive decline. One implication of this model is that sociodemographic, life style, psychological, physiological, and genetic factors as well as the "wear and tear" on the biological system related to coping with the demands and stress of life (allostatic load)[6] may be as important in determining the risk of post-treatment cognitive decline as the specific treatments received. Further, it is possible that particular constellations of risk factors may make one patient more vulnerable to the side effects associated with chemotherapy, whereas another set of risk factors may make another patient more sensitive to the side effects of endocrine therapy.

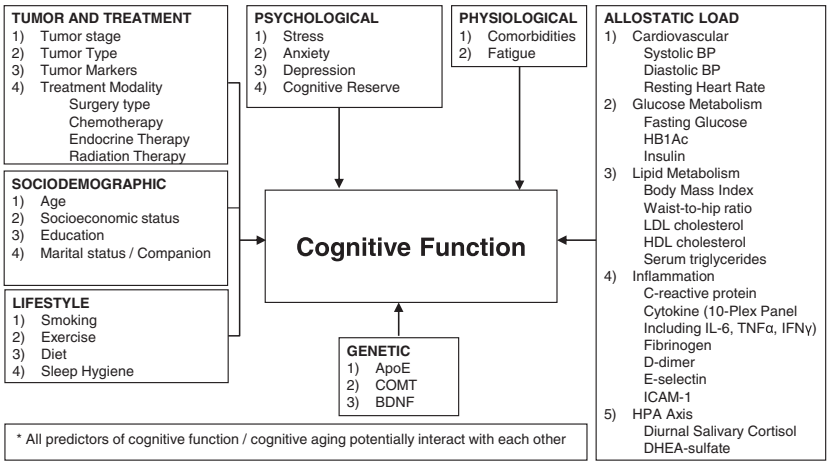

FIGURE 1 Conceptual model: Predictors of cognitive change in cancer survivors

3 | AGING, COGNITION, AND CANCER

Life expectancy has increased dramatically over the last 100 years.[7] As a result, older adults make up an increasingly large proportion of the total population. At the turn of the century, 13% of the population was aged 65 and over, amounting to around 35 million individuals; by 2050, this number is projected to double to 70 million individuals, which will represent approximately 20% of the US population.[8] As cancer is a disease of aging,[9] the changing demographics of the nation will result in an increase in the number of individuals diagnosed with and surviving cancer. Indeed, there is a projected 67% increase in cancer incidence in patients aged 65 and older from 2010 to 2030,[10] and older adults will make up 60% of the cancer survivors in the USA.[11]

Most of the research on CRCD has been done in patients with breast cancer and breast cancer survivors comprise nearly 25% of all survivors over the age of 60. Although increasing evidence suggests that exposure to systematic breast cancer treatments (chemotherapy and endocrine therapy) may be associated with long-term cognitive deficits in a subgroup of cancer survivors, most studies have been conducted with younger cancer patients (mean age 40–50).[12] Hence, little is known about the long-term impact of adjuvant treatment on cognitive function, or the risk factors for treatment-driven cognitive decline. Therefore, a critical gap in knowledge relates to the impact of cancer and cancer treatment on cognitive functioning in older patients with breast cancer.

It is especially important to study the association between cancer therapy and cognitive decline in older adults because among the side effects that older patients fear most from cancer therapy is the prospect of diminished cognition.[13] In a recent study conducted by Soto-Perez-de-Celis and colleagues, 51% of older patients (age 65+) with cancer agreed with the statement, "I would rather live a shorter life than lose my ability to take care of myself," and 84% of patients agreed with the statement, "it is more important to me to maintain my thinking ability than to live as long as possible."[14] Even minor changes in cognitive ability can impact function, the ability to live independently, and quality of life. It is therefore imperative that we understand the potential links between cancer therapy and cognitive decline so that we may determine risk factors, devise interventions, and enable patients to make better-informed decisions about their treatment.

Recently, there has been increasing interest in the intersection of chronic diseases (eg, HIV, diabetes, and cancer) and the biology of aging.[15] Cancer, cancer treatments, and aging, including cognitive aging, are linked through a variety of biological changes including increased cell senescence, DNA damage, oxidative stress, inflammation, and decreased telomere length (telomerase activity).[16] Consistent with the conceptual model described earlier, several factors independent of cancer and cancer therapy may impact cognitive function including lifestyle,[17] psychological state,[18] comorbidity,[19,20] genetic variation,[21] and sociodemographic status.[22] Hence, it can be difficult to discern what part of cognitive decline is due to the cancer and/or cancer therapy versus other causes. Normal cognitive aging is a process that occurs throughout an individual's lifespan[23] and is marked by a decrease in cerebral blood flow, white matter atrophy, and impairments in processing speed, sequence-learning ability, short-term memory, and increased reaction time,[24] impairments frequently seen in cancer survivors.

Of the few studies on the association between cancer therapy and cognition that focused on older patients, results are somewhat inconsistent. In a longitudinal study of 1280 breast cancer survivors, Mandelblatt et al[25] found that the majority of older survivors self-reported good cognitive function while only a small subset of older survivors exposed to chemotherapy self-reported accelerated cognitive decline. Heck and colleagues performed an analysis using the Surveillance, Epidemiology, and End Results—Medicare database and found a long-term association between a diagnosis of dementia and chemotherapy in women over age 65,[26] and Schilder et al[27] found that 1 year of tamoxifen was associated with worsening cognitive function with patients age ≤ 65 performing worse than healthy controls on executive functioning and those > age 65 performing worse than healthy controls on verbal memory and information processing speed. Minisini et al[28] prospectively measured cognitive function in older patients with breast cancer who received no adjuvant treatment or were treated with chemotherapy with or without endocrine therapy and found that more patients in the chemotherapy group showed worsening memory skills, and more patients in the endocrine therapy and chemotherapy group experienced reduction in attention scores.[28] Other studies have raised concerns about the short and long-term impact of chemotherapy in older adults with breast cancer.[29-32]

On the other hand, some studies found no association between cancer therapy and self-reported cognitive function,[33] or found inconsistency between patient-reported and demonstrated, objective evidence of cognitive decline. In a pilot longitudinal study of the cognitive effects of chemotherapy in older (>65) patients with breast cancer, 50% of patients reported decline in cognitive functioning post-chemotherapy and 25% demonstrated evidence of a decline in performance from pre-treatment to post-treatment on neuropsychological tests.[30,31,34] In another study,[35] no significant decline in cognitive function was detected among individuals receiving aromatase inhibitors from pretreatment to 6 months post-treatment compared with healthy controls; however, changes in PET activity were notable most significantly in the medial temporal lobe.

Recent studies[36] have demonstrated that breast cancer chemotherapy (anthracycline-based regimens) affects biomarkers of aging (p16INK4a and ARF). The investigators suggest that the level of activation of these biomarkers equates to 10.4 years of chronological aging. Animal studies have also demonstrated that the administration of cyclophosphamide and doxorubicin to rats increases activation of markers of aging and stress (Erk1/2 and AKT).[37] Consequently, researchers have speculated that cancer treatments may affect specific brain regions and the biology of aging, including cognitive aging.[1,38] Therefore, as our population ages, a critical research question is whether the diagnosis of cancer and exposure to cancer treatments has an initial post-treatment effect on certain domains of cognitive function and regions of the brain followed by age-associated cognitive decline that parallels those of older adults with no cancer history (phase shift hypothesis) or follows a steeper slope of decline (accelerated aging hypothesis) (Figure 2). These hypotheses are not mutually exclusive in that survivors with 1 or more vulnerability factors (eg, hypertension, inactive lifestyle, APOE4+) may demonstrate the accelerated aging trajectory, whereas survivors with no vulnerability factors may demonstrate the phase shift trajectory.

4 | LIMITATIONS OF TRADITIONAL NEUROPSYCHOLOGICAL TESTING

One reason for some of the inconsistencies in results seen in the literature may be related to limitations in neuropsychological tests. Traditional neuropsychological measures commonly used in cognitive research were developed originally to determine lesion location and impairment in patients with overt neurological injuries and illnesses with moderate to severe dysfunction (eg, traumatic brain injury or dementing conditions). The cognitive impact of treatment in survivors, by contrast, is relatively subtle, and measurement error alone could obscure true changes in survivors. Recent studies have examined the extent to which poor sensitivity might be due to measurement error and low test-retest reliability in 2 control samples, where no change in cognitive function is expected, collected as part of research projects in 2 different labs (USA and the Netherlands).[39] Results of neuropsychological testing over 6-month and 1-year intervals indicated attenuated test-retest reliability compared with published reliability values during standardization that are derived from shorter intervals (ie, 1–3 weeks). Reliability values generally fell below $r \geq 0.8$ with a subset of measures exhibiting reliability values as low as $r = 0.23$ to 0.35. The range of random variation between time 1 and time 2 in the healthy control samples represents medium to large effect sizes, in contrast to much smaller expected changes in survivors. As a result, the inherent "noise" of measurement error, here represented by low test-retest reliability, may obscure the "signal" of true treatment-related change.

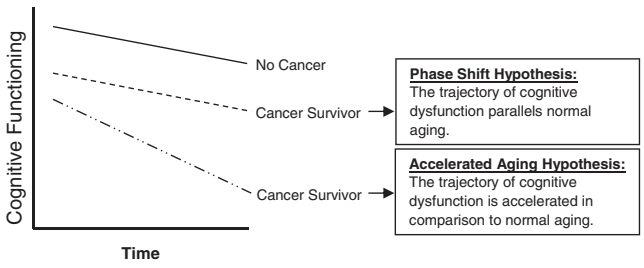

FIGURE 2 Trajectories of cognitive change

5 | LACK OF CORRELATION BETWEEN SELF-REPORT OF COGNITIVE PROBLEMS AND PERFORMANCE ON NEUROPSYCHOLOGICAL TESTING

Many studies have reported low or no correlation between patients' self-report of cognitive problems and performance on neuropsychological testing. The pattern typically is of patients reporting cognitive problems in the context of normal performance on testing. This has led some in the field to question the existence of true cognitive changes associated with cancer and cancer treatments. However, recent research has suggested potential reasons for this apparent discrepancy.

5.1 | Compensatory activation

Imaging research has demonstrated that, in the face of alterations to structure or function, the brain has the capacity for compensatory activation that allows for recruitment of alternate brain regions in order to maintain cognitive performance. Compensatory activation has been observed in normal aging[40] and in cancer survivors.[41] Cancer survivors frequently report that cognitive tasks require more effort and are more easily disrupted in the real world of distractions, stress, etc.[42] However, standard neuropsychological tests are administered in an environment designed to minimize distraction and maximize performance. Therefore, survivors' perception of cognitive problems in their day-to-day lives may well be accurate; however, performance is maintained in the neuropsychological testing setting which likely maximizes compensatory mechanisms.

5.2 | Memory versus attention

Another explanation for this discrepancy is related to survivors' experience of cognitive change and the actual cognitive processes that are altered by cancer treatments. As stated earlier, most cancer survivors describe memory deficits but tend to score in the normal range on neuropsychological tests of memory. Recently, researchers

have investigated specific learning and memory processes that might contribute to greater reports of memory dysfunction. The subjective experience of forgetting can be due to failures to retain information, to retrieve information, or to acquire information at the time of learning. This may suggest that patient reported memory complaints are driven by initial learning difficulties that are misidentified as actual forgetting by patients in daily activities. This hypothesis was confirmed in 2 separate studies of clinically referred survivors[43] and a research dataset of survivors[44] in which serial list learning measures were administered. Serial learning measures include multiple trials for acquisition of information and allow for decomposition of single trial learning, multiple trial learning, retention, and recall of information so that specific areas of weakness can be identified. In both studies, survivors exhibited lower initial learning of information (Trial 1 performance) that is indicative of problems in attention, compensation through repetition (Trial 5 performance), and normal recall of this information following a delay (Long Delay Free Recall). True-forgetting rates in each study were equivalent to normative and healthy control performance. Therefore, survivors' perception of memory problems is accurate but related to deficits in earlier stages of information processing related to attention rather than memory per se.

These findings suggest that initial attention, registration, and encoding of information may be altered in survivors, and argue for a greater emphasis on attentional processes and sub-processes. Recent studies have found increased variability of attention across longer go/no-go tasks, with particularly variable attention in low-challenge conditions, and increasing variability in the latter portions of the task both before[45] and following treatment.[46] This suggests that survivors tended to lose focus throughout the task, particularly in relatively unstimulating conditions, as well as in later phases of the task.

At this point, the precise mechanism(s) for learning difficulties have not been defined; however, we and others have proposed that changes in attentional processes both pre-attentive and volitional (orienting, shifting, disengaging, and inhibiting attention) interfere with efficient and effective encoding of information in memory.[5]

5.3 | Leveraging cognitive neuroscience

The limitations of traditional neuropsychological measures and the potential importance of attentional processes, including pre-attentive processes underlying cognitive decline, suggest the need for a different approach to the assessment of cognitive function in cancer survivors. Similar issues have arisen in other clinical areas leading to the development of cognitive-experimental measures to better assess cognition associated with clinical syndromes (NIH Examiner[47]) and schizophrenia (CNTRICS[48]). The National Cancer Institute has also encouraged researchers to leverage cognitive neuroscience measures to improve assessment of cancer and cancer treatment-related cognitive impairment[49] (https://grants.nih.gov/grants/guide/pa-files/PAR-16-212.html).

5.4 | Statistical issues

The lack of correlation between self-report of cognitive problems and performance on neuropsychological tests may also be related to limitations of statistical approaches used to evaluate this association. Conventional statistical methods rely on aggregating item responses into total scores or sub-domains and submitting these to traditional, correlation-based analyses. A recent study has identified significant associations between self-reported dysfunction and traditional neuropsychological measures using latent regression Rasch modeling.[50] The latent Rasch approach: (1) directly models individual, item-level, cognitive symptom ratings, whereas the conventional approach aggregates over symptom ratings to form subscale or global scores, obscuring specific patterns of symptoms and (2) weights the endorsement of rare symptoms more highly than commonly reported symptoms, whereas the conventional approach weights all symptoms identically. Use of the Rasch approach revealed that changes in objective performance from pre-treatment to post-treatment predicted self-report of cognitive problems, whereas traditional correlations were low or non-significant.[50] Consistent with the proposed role of attention, self-reported memory problems correlated with performance on measures of attention and processing speed rather than measures of memory.

5.5 | Treatment implications

These considerations also have treatment implications. Most cognitive rehabilitation approaches have focused on strategies to enhance memory and compensation. However, researchers from other areas have focused on experimental methods designed to enhance the ability to focus on relevant information and filter out irrelevant information in order to improve memory processes. For example, perceptual training designed to improve signal to noise discrimination generalized to improvement in working memory performance. Further, improvement in working memory was correlated with EEG recordings (N1 amplitude), a pre-attentive measure of more efficient encoding of stimuli.[51] Approaches like perceptual training have yet to be tested in the treatment of CACD.

Transcranial direct current stimulation (tDCS), used in other disorders, may also enhance the impact of approaches like perceptual training. tDCS delivers a minimal electric current by means of electrodes placed on the scalp and exerts its effect by lowering the threshold at which action potentials are generated.[52] As such, combining tDCS with cognitive training may "open windows of neuroplasticity" in effected areas that are supportive of a given cognitive task, eg attentional function.[6]

6 | EMERGING ISSUES

6.1 | Inverse association with cancer and neurodegenerative diseases

As a counterpoint to the discussion on the interaction of cancer treatments and aging, several population studies have suggested an inverse relationship between cancer and various neurodegenerative diseases, including Alzheimer's disease. There are limitations to these studies, including heterogeneous samples of cancer patients and lack of specific diagnostic and treatment information. However, there is increasing speculation of plausible biological mechanisms that may explain the inverse relationship, including biological processes that

increase the tendency toward cellular proliferation versus aggregation ([53] for review). On the other hand, as discussed previously, there is increasing evidence that cancer treatments accelerate the aging process on a biological level. Therefore, there may be an overall inverse relationship between cancer and Alzheimer's disease; however, there may be individuals with certain vulnerability factors for Alzheimer's disease (eg, APOE4 genotype) whose risk is increased if exposed to certain types of cancer treatments. Additional research is clearly necessary to sort out these complicated relationships; however, from a clinical point of view, answers to these questions are important because cancer survivors with a family history of dementia frequently ask whether exposure to chemotherapy will increase their risk for dementia.

Even if future research verifies the inverse association between cancer and neurodegenerative disease, having one disorder does not completely protect one from the other. As our population ages, increasing numbers of cancer patients will present with significant cognitive problems at diagnosis that may or may not be related to their cancer. Given the increasing complexity of cancer treatments and the need for high patient compliance, the presence of cognitive difficulties can present challenges in treatment planning and care for older adults with cancer. Geriatric oncology is an emerging field that is helping to define appropriate care for older cancer patients with multiple comorbidities / frailty through the development of geriatric assessment tools.[54] Additional research examining the impact of cognitive dysfunction on treatment decision-making and the supportive services (eg, family, visiting nurses, etc.) to ensure patient safety is clearly necessary.

6.2 | Tipping point

Although expansion of the conceptual model may be a more accurate portrayal of the multiple factors that can lead to the experience of cognitive decline in cancer survivors, it makes research in the area much more complicated. If post-treatment cognitive deficits are determined by a complex interaction of specific impacts of cancer treatments on brain structure and function, innate (eg, genetic) and acquired risk factors, and aging, the determination of specific mechanisms of CACD becomes a significant challenge. However, research related to the concept of tipping points in complex systems may be relevant.[55,56]

Many complex systems, ranging from climate change, to financial markets, to social networks, have tipping points at which there is an abrupt change from one state to another. Prediction of these transitions is difficult because of the complexity of the system and because the system may show little evidence of change prior to the transition. However, early-warning signs for critical transitions have been identified which relate to the phenomenon in dynamic systems theory known as "critical slowing down".[55,56] Characteristics of critical slowing include (1) overall slowing of the system; and either, (2) increased autocorrelation (ie, because of slowing of the system, the rate of change decreases, hence the state of the system at any given time is more similar to past states); or (3) increased variability. Examination of cognitive performance seen in cancer patients has demonstrated (1) slowing of processing speed[57]; (2) decreased ability to benefit from practice (performance from Time 1 to Time 2 remains similar; which may be a sign of higher autocorrelation)[58]; and (3) increased intra-individual variability on reaction time tasks seen both before[45] and following treatment.[46] At least 2 questions for future research emerge from this conceptualization. First does "critical slowing" prior to treatment, represented by slowed processing speed, inability to benefit from practice, and/or increased variability in reaction time, predict vulnerability to post-treatment cognitive decline? Second, neuropsychology researchers commonly dichotomize survivors into impaired or not impaired. However, another hypothesis is that all patients are affected at the same level by a given treatment in terms of brain structure and function, but only a subgroup reaches a tipping point where the cognitive system shifts to a new state that is no longer sufficient to maintain pre-diagnosis task performance and cognitive deficits are measurable. Future research is necessary to determine the validity of these hypotheses and the utility of this conceptualization.

7 | CONCLUSION

Despite advances in the field, the effects of cancer and cancer treatment on cognitive function clearly need further research. Cognitive decline can lead to a deterioration of functional status and independence particularly in older adults. There are persistent gaps in knowledge regarding aging and cognition in older adults with cancer. Much information is needed to more fully understand how cancer and cancer therapy may affect both physiological aging and cognitive aging, and how this impact can vary based on patients' age at treatment, comorbid conditions, and overall health status. We suggest that future research needs to address the complex, interacting factors that influence cognitive function in cancer survivors, examine both the direct effects of cancer treatments on brain structure and function and the impact on cancer treatments on the biology of aging, and address conceptual and methodological issues that may explain inconsistencies in research findings and limit progress in the field.

ACKNOWLEDGEMENTS

Preparation of the manuscript was supported by grants from the National Cancer Institute (R01 CA172119, R01 CA129769, U54CA137788), the Breast Cancer Research Foundation (R01 CA14063), and the Cancer Center Core Grant (P30 CA008748).

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How to cite this article: Ahles TA, Hurria A. New Challenges in Psycho-Oncology Research IV: Cognition and cancer: Conceptual and methodological issues and future directions. *Psycho-Oncology*. 2018;27:3–9. https://doi.org/10.1002/pon.4564