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SI: NEUROIMAGING STUDIES OF CANCER AND CANCER TREATMENT

Neuroimaging biomarkers and cognitive function in non-CNS cancer and its treatment: Current status and recommendations for future research

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Abstract Cognitive changes in patients undergoing treatment for non-central nervous system (CNS) cancers have been recognized for several decades, yet the underlying mechanisms are not well understood. Structural, functional and molecular neuroimaging has the potential to help clarify the neural bases of these cognitive abnormalities. Structural magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), MR spectroscopy (MRS), and positron emission tomography (PET) have all been employed in the study of cognitive effects of cancer treatment, with most studies focusing on breast cancer and changes thought to be induced by chemotherapy. Articles in this special issue of *Brain Imaging and Behavior* are devoted to neuroimaging studies of cognitive changes in patients with non-CNS cancer and include comprehensive critical reviews and novel research findings. The broad conclusions that can be drawn from past studies and the present body of new research is that there are structural and functional changes associated with cancer and various treatments, particularly systemic cytotoxic chemotherapy, although some cognitive and fMRI studies have identified changes at pre-treatment baseline. Recommendations to accelerate progress include well-powered multicenter neuroimaging studies, a better standardized definition of the cognitive phenotype and extension to other cancers. A systems biology framework incorporating multimodality neuroimaging, genetics and other biomarkers will be highly informative regarding individual differences in risk and protective factors and disease- and treatment-related mechanisms. Studies of interventions targeting cognitive changes are also needed. These next steps are expected to identify novel protective strategies and facilitate a more personalized medicine for cancer patients.

Keywords Neuroimaging · MRI · PET · Cognition · Cancer · Chemotherapy · Genetics · Biomarkers · Personalized medicine

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Two decades of research, primarily in the breast cancer patient population, has confirmed an association between cognitive changes and systemic adjuvant chemotherapy (Ahles et al. 2012; McDonald and Saykin 2011; Nelson and Suls 2013; Wefel et al. 2008) as confirmed by several meta-analyses (Anderson-Hanley et al. 2003; Falleti et al. 2005; Hodgson

et al. 2013; Jansen et al. 2007; Jim et al. 2012; Stewart et al. 2006). Early work focused on cytotoxic chemotherapies and long-term survivor samples, and was followed by prospective studies that also included examination of hormonal therapies. As investigators began to emphasize prospective study designs it became clear that some patients with breast cancer had cognitive abnormalities at pre-treatment baseline (Ahles et al. 2008; Wefel et al. 2004), raising a question of neural effects of breast cancer, other host factors or vulnerabilities that impact the brain, or perhaps shared genetic risk with neurodevelopmental or neurodegenerative disorders (Ahles and Saykin 2007). Across cognitive studies, the specific domains affected have been relatively consistent, and include memory, executive function, processing speed, and verbal and spatial abilities (Anderson-Hanley et al. 2003; Falleti et al. 2005; Hodgson et al. 2013; Jansen et al. 2007; Jim et al. 2012; Stewart et al. 2006). Survival after treatment for early stage breast cancer is high and long-term quality of life of survivors has been identified as an important issue. Although the changes may be relatively mild as measured by current psychometric methods, such mild cognitive dysfunction may have a very significant impact on quality of life. Moderate to severe cognitive deficits have also been reported. While more pronounced changes are often associated with more intensive and prolonged treatment regimens, individual differences in response to treatment are not well understood.

The neural basis of cancer and treatment-induced cognitive changes has been a major question (Ahles and Saykin 2007; Saykin et al. 2003; Vodermaier 2009), as a better understanding of the mechanism(s) of this dysfunction would facilitate selection of alternative therapies, development of preventative strategies, and identification of those patients who may be at elevated risk for cognitive changes. Structural, functional, and molecular neuroimaging have been used to probe the mechanisms underlying observed changes after adjuvant breast cancer chemotherapy (Conroy et al. 2012; Holohan et al. 2013a). In brief, structural changes detected include decreased gray matter density and volume on anatomic MRI (Conroy et al. 2013b; de Ruiter et al. 2012; Hosseini et al. 2012; Inagaki et al. 2007; Koppelmans et al. 2012a; McDonald et al. 2010, 2013; Saykin et al. 2003) and alteration in white matter integrity and volume on diffusion tensor imaging (DTI) (de Ruiter et al. 2012; Deprez et al. 2011, 2013; Koppelmans et al. 2012b). fMRI studies have demonstrated post-treatment changes in brain activation during memory and executive tasks (Conroy et al. 2013b; de Ruiter et al. 2011; Ferguson et al. 2007; Kesler et al. 2009, 2011; Lopez Zunini et al. 2012; McDonald et al. 2012) and in resting brain connectivity pattern (Bruno et al. 2012). Recent arterial spin labeled MRI perfusion data suggests alterations in cerebral blood flow (Holohan et al. 2013b). Further, several fMRI studies have detected abnormalities prior to treatment (Cimprich et al. 2010; McDonald et al. 2012; Scherling et al. 2011, 2012), suggesting a possible substrate for baseline neuropsychological findings observed in some prospective cognitive studies (Ahles et al. 2008; Wefel et al. 2004). PET has also been used to characterize metabolic and cerebral blood flow abnormalities after cancer treatment (Silverman et al. 2007) including post-treatment depression (Kim et al. 2008).

Accumulating evidence indicates there are individual differences in risk for cognitive and brain abnormalities associated with non-CNS cancer and its treatment. An important challenge is determining the sources for these differences in risk for cognitive decline (Ahles and Saykin 2007; McAllister et al. 2004). Limited early data suggest genetic factors are contributory (Ahles et al. 2003; Small et al. 2011). In addition, baseline differences, comorbidities, and psychosocial factors among other variables may play a role. Patient age is likely to be a major factor (Mandelblatt et al. 2013, in press) that has not been well-studied, as most research has focused on middle-aged women. Older patients, including men, are increasingly undergoing cytotoxic and hormonal chemotherapies, and a better understanding of the role of age in modulating the impact of cancer and its treatment on brain structure and function is critical, particularly as patients enter the peak risk period for age-associated neurodegenerative disorders. Better understanding of risk factors and predictors of cognitive and neural outcomes of cancer therapy would facilitate clinical risk/benefit discussions, leading to more personalized medicine as well development of preventative and rehabilitative interventions. Prior studies in this area, particularly those focusing on neural mechanisms, have had relatively small sample sizes, limiting the ability to examine risk and predictive factors.

Papers in this special issue

The series of articles begins with several comprehensive and critical reviews of the use of advanced neuroimaging techniques to study the neural bases of cognitive changes in non-CNS cancers and cancer therapeutics. Most of the existing studies have been completed in patients undergoing treatment for breast cancer and these studies are therefore emphasized. With the high rate of survival in early stage breast cancer, cognitive problems after systemic treatment and their impact on quality of life has been a growing concern. Studies remain to be completed in most other forms of non-CNS cancer, and the present reviews and original research reports mostly but not exclusively concentrate on breast cancer and its treatment.

Reviews

The earliest studies employed quantitative analyses of structural MRI. McDonald and Saykin (2013) review the range of

structural MRI studies, including post-chemotherapy breast cancer survivor study designs as well as the more limited number of recent prospective studies. Methodological considerations are discussed including manual vs. automated analytic approaches to quantify gray and white matter tissue properties and the issue of control or contrast groups included in these studies. Structural MRI studies, as reviewed by these authors, demonstrate lower gray and white matter volume and density after systemic cytotoxic chemotherapy with the most consistent findings shown in the frontal and temporal lobe regions. Much less information is available regarding other therapeutic modalities such as anti-estrogen hormonal treatment, but initial evidence suggests a potential contribution to structural changes on imaging. Some studies have shown a relationship between structural imaging and cognitive changes as well as other biological markers.

Diffusion tensor imaging (DTI) is another important structural MRI-based tool for assessing neuroanatomical changes in non-CNS cancer, particularly for detection of microstructural alterations in white matter. Deprez et al. (2013) provide a detailed review of the fundamentals of DTI methodology and its application to studies of chemotherapy-induced cognitive impairment. Paralleling results employing conventional structural MRI, cross-sectional and longitudinal DTI studies have shown abnormal microstructure in white matter regions important for cognition. DTI results have also been found to correlate with cognitive performance, suggesting a functional connection between reduced "white matter integrity" and cognitive changes after chemotherapy.

Moving beyond brain structure, fMRI has the potential to detect alterations in the neural circuitry and networks subserving cognitive functioning after systemic treatment in cancer patients. de Ruiter and Schagen (2013) provide a detailed analysis of the fMRI studies ($n=14$) of systemic treatment for non-CNS cancers published to date. Long-term breast cancer survivors (5–10 years since therapy) treated with chemotherapy have been compared to other cancer contrast groups and controls in cross-sectional fMRI studies. Studies employing executive function probe tasks have demonstrated prefrontal and parietal hypoactivation whereas fMRI studies of episodic memory have similarly shown hypoactivation during encoding but differ in demonstrating hyperactivation during memory retrieval. The authors discuss the interpretation of these alterations, including reduction of neural function in brain regions that support cognition as a result of chemotherapy and the concept of compensatory hyperactivation to support adequate memory retrieval. The few available prospective fMRI studies of executive functioning and episodic memory show a more complex pattern of hypo- and hyperactivation that may be related to the closer temporal proximity to systemic treatment or other mechanisms. de Ruiter and Schagen also discuss the data emerging in fMRI studies of patients being treated for prostate cancer which show preliminary evidence for decreased activity after androgen deprivation therapy. These authors conclude by discussing multiple testing, sample size and power considerations, among other methodological issues for fMRI studies.

Pomykala et al. (2013a) review recent imaging studies of cancer- and chemotherapy-related cognitive changes focusing on a comparison of findings across modalities (various MRI and PET techniques) in studies of changes in brain structure and function associated with chemotherapy. The authors emphasize the similar changes in brain activation in parietal regions identified by functional PET (Silverman et al. 2007) and fMRI (de Ruiter et al. 2011) studies in survivors 5–10 years after systemic chemotherapy. Similarly cross-sectional [O15]PET findings in frontal cortex (Silverman et al. 2007) were noted to be similar to prospectively assessed changes in frontal gray matter density one month after chemotherapy (McDonald et al. 2010).

Another window to the neural bases of cognitive changes associated with cancer and systemic therapy is preclinical studies employing small animal models of chemotherapy neurotoxicity. Seigers and colleagues (2013) review recent advances from animal studies highlighting the role of the blood–brain barrier in cognitive impairment and issues related to the development of neuroprotective strategies. Although human imaging studies can provide important longitudinal structural, functional and molecular information, small animal models have the advantage of permitting detailed histological analysis on a microscopic level to more fully characterize the biological significance of any findings. Seigers et al. summarize research studies that examined implicated biological processes including apoptosis, vascular supply, CSF composition, electrophysiology, histone acetylation, inflammation, morphology, neurogenesis/gliogenesis, neurotransmitter/monoamine release and oxidative stress. Given the ability of animal studies to address these fundamental mechanisms, preclinical methods are highly complementary with human neuroimaging. In the future, prospective small animal neuroimaging studies are likely to provide even better integration of preclinical and clinical research.

New research findings

Neuroimaging data using various samples, techniques and study designs is accruing at a rapid pace, as reflected by the reports of novel findings in this special issue. Lopez Zunini and colleagues (2012) used fMRI to investigate verbal memory recall in breast cancer patients receiving chemotherapy and controls in a prospective design, and report on differences at baseline as well as changes one month after chemotherapy. Their paper describes reduced activation in the anterior cingulate in patients on baseline fMRI scans compared to controls during memory retrieval. Patients treated with

chemotherapy also showed decreased activation in several regions (bilateral insula, the left inferior orbitofrontal cortex and the left middle temporal gyrus) as well as less activation compared to controls in several frontal and temporal regions. A notable feature of the Lopez Zunini study is the careful attention to potential confounding factors such as depression, anxiety, and fatigue, which accounted for some of the observed changes in activation patterns.

Dumas and colleagues (2013), also using fMRI to prospectively study patients being treated for breast cancer, analyzed functional connectivity to examine neural processes underlying the reported executive and attentional deficits observed in cognitive studies. Measures of functional connectivity can be extracted from a task-free or resting state fMRI or from task-based paradigms, as in the present study. Functional connectivity analyses typically employ a seed-based approach or independent components analysis (ICA) to determine the interconnectivity of brain regions based on their temporal correlation. The report by Dumas et al. describes the results of a small study employing a seed-based analysis of task related fMRI using a 3-back task, similar to that employed in prior studies (McDonald et al. 2012), in nine women who were scanned before and one month and one year after chemotherapy. To examine connectivity changes, the dorsal anterior attention network was targeted by placing a seed in the intraparietal sulcus (IPS), whereas the default mode network was targeted by a seed in the posterior cingulate cortex (PCC). Dumas et al. report a reduction of functional connectivity a month after chemotherapy with partial return to baseline on one year follow-up. The authors also described an increase in subjective memory complaints, although this was not directly analyzed in relation to connectivity changes. Results of this small and uncontrolled prospective pilot study are intriguing and consistent with other reports suggesting that there may be altered brain connectivity after chemotherapy (Bruno et al. 2012; Hosseini et al. 2012).

MRS provides another window into cerebral function, in this case at the level of neurochemistry. Kesler et al. (2013b), studying breast cancer patients, compared proton (1H) MRS metabolites and metabolite ratios in 19 survivors treated with chemotherapy to those in 17 controls. The authors describe novel results including increased prefrontal levels of the myo-inositol (MI) and choline (Cho) metabolites and decreased N-acetylaspartate (NAA)/Cho and NAA/mI ratios in the breast cancer group. Of note, the Kesler group found a relationship in both groups between subjective memory functioning and metabolite levels.

The papers by Lopez Zunini et al., Dumas et al. and Kesler et al. in this issue demonstrate the complementary nature of task-based fMRI, functional connectivity and metabolic signals in demonstrating changes in patients who have undergone chemotherapy. Numerous hypotheses have been proposed for cancer and chemotherapy-induced changes in cerebral function (e.g., Ahles and Saykin 2007) and one of the most obvious and important biological alterations relates to altered neuroendocrine function.

In this issue, Conroy and colleagues (2013a) report prospective fMRI changes in breast cancer patients focused on the issue of chemotherapy-induced amenorrhea (CIA), a common occurrence in pre- and peri-menopausal patients. Data from the 3-back working memory task (McDonald et al. 2012) collected at pre-treatment baseline and one month after chemotherapy was used to compare changes in brain activation and deactivation patterns in patients who underwent CIA to those who were post-menopausal, as well as to pre- and post-menopausal healthy controls. The authors describe increased pre- to post-chemotherapy fMRI activation that was specific to the CIA group, which was also strongly correlated with change in processing speed on neuropsychological testing, suggesting this increase in brain activity reflects effective compensatory processes. An important aspect of this study is the finding that the pattern of change in brain activity from pre- to post-chemotherapy varies according to pre-treatment menopausal status, which has potential implications for risk appraisal and development of prevention or treatment strategies for cognitive changes in CIA.

Researchers are just beginning to integrate blood-based biomarkers and neuroimaging in studies of cancer and cognition. Silverman and colleagues (Pomykala et al. 2013b) examined relationships between circulating proinflammatory cytokines (IL-1ra, sTNF-RII, CRP, and IL-6), regional cerebral metabolism on FDG PET, and cognitive complaints in 33 early stage breast cancer patients (23 treated with chemotherapy) at baseline and one year after adjuvant chemotherapy. At baseline, left medial frontal and right inferior lateral anterior temporal cortices were correlated with inflammatory markers within the chemotherapy group only. On one year follow-up, there were persisting correlations in the medial frontal cortex and the temporal cortex with some spatial shifting. Memory complaints were associated with metabolism on PET and cytokine analyte levels in chemotherapy-treated patients. This is an important inroad building on limited prior work correlating cognitive changes and proinflammatory cytokine levels (Ganz et al. 2013; Kesler et al. 2013a; Myers 2010; Walker et al. 2012).

Neuroimaging can be used to investigate many aspects of cancer and cognition as well as other related survivorship issues. In a novel study, Versace and colleagues used fMRI to investigate the basis of the loss of sexual desire and arousability often reported by breast cancer survivors (Versace et al. 2013). Neural responses to erotic and other emotional stimuli in survivors with and without distress were studied to test the hypothesis that cancer or treatment for cancer damages brain reward circuitry. The authors found that women who were distressed about their desire had reduced brain responses to erotica in reward-associated regions

including the anterior cingulate and dorsolateral prefrontal cortex. Further work will be needed to determine if this is related to chemotherapy, hormone therapy, and/or menopausal status.

High dose conditioning regimens for cancer patients requiring hematopoietic stem cell transplantation (HSCT) for hematologic cancers have received little prior study. Correa et al. report prospective structural neuroimaging and cognitive data in adult stem cell transplant recipients (Correa et al. 2013). These authors examined regional gray matter and ventricular volumes and cognitive function before and one year after HSCT in 28 patients and 10 healthy controls. Patients showed evidence of reduced gray matter volume in the middle frontal gyrus bilaterally and in the left caudate nucleus, as well as a significant increase in left lateral ventricle volume and in total ventricle volume in the patient group relative to healthy controls. This is important in identifying changes in a particularly high risk group for cognitive impairment associated with treatment.

Another important application of neuroimaging and related tools is to serve as biomarkers to monitor the effects of cognitive interventions for cancer patients. Ercoli and colleagues examined the feasibility of a cognitive rehabilitation program in breast cancer survivors who had persisting cognitive complaints 18 months to five years after treatment (Ercoli et al. 2013). The intervention included once-weekly group cognitive training for five weeks. Multiple outcome measures and follow-up time points were included. These authors reported significant reductions in total and memory-specific cognitive complaints from pre-intervention to post-intervention that were maintained at four months post-intervention. In a small but novel substudy, eight of the participants were evaluated prospectively with quantitative resting state electroencephalography (qEEG). Absolute alpha power over the course of the intervention was associated with reduced complaints at several outcome intervals, suggesting that qEEG may serve as a potential biomarker for improvement in self-reported complaints.

Recommendations to advance research on cancer- and cancer treatment-associated cognitive dysfunction

Much has been learned from past studies including the new work included in this special issue of *Brain Imaging and Behavior.* In the final section, the special issue editors outline a series of recommendations based on work to date in cancer and other fields that has implications for moving research on cancer and cognition to the next level. Although it will not be appropriate or feasible to incorporate all of the following methods or design features in any particular study, these suggestions are offered to stimulate broader and more powerful approaches to the problems of cancer- and cancer treatment-associated neurocognitive dysfunction. In particular, we believe that many key gaps in current knowledge could be addressed by larger-scale multicenter studies that include refined phenotypes paired with advanced neuroimaging, genetics and biomarkers.

Refined cognitive phenotype definitions are needed

1. Cognitive assessment should include reliable psychometric tests with good sensitivity and specificity that cover key domains reviewed above with established relevance to cancer and cancer treatment (e.g., executive function, processing speed, working memory, episodic memory, verbal and spatial abilities). No specific tests have been conclusively demonstrated to outperform others but there is good evidence to support the relevant domains. Inclusion of some computer-based tests assessing response times might be considered. Attention to ecological validity in terms of impact of measured domains on activities of daily living is another important consideration. These concepts are generally consistent with prior consensus group recommendations for studies of cancer and cognition (Tannock et al. 2004; Wefel et al. 2011).
2. Ratings of cognitive concerns should be included, such as subjective and informant/study partner/clinician-based perception, as in some cases these may be among the earliest and most sensitive indicators of alterations in cognition. An emergent model from the MCI/prodromal Alzheimer's disease research field is defining subjective cognitive decline (SCD) based on self-perception. Individuals whose self-perceived concerns are validated by a family member, friend, co-worker or clinician, or who have other risk factors for cognitive decline are classified as "SCD-plus" and have been found to be more likely to demonstrate positive findings on imaging and other biomarkers. In general, careful tracking of subjective and informant concerns or "complaints" is consistent with the patient reported outcomes (PRO) model widely applied to cancer research. Ascertainment of informant ratings has been underrepresented in cognitive research on cancer and chemotherapy effects but should be relatively easy to add. This can be expected to provide potentially important complementary information to subjective changes and psychometric data.
3. Standardized definition of abnormal performance. For comparison across studies, whether observational or clinical trials, some standardization or harmonization of classification is important. Cut-off scores between low normal and impaired psychometric performance, although arbitrary, are often employed in research studies of cognitive dysfunction, driven by the perceived need for a standard metric to define binary classification of subjects into

impaired and unimpaired categories. The criteria for defining cutoffs for cognitive scores is a challenging area in the absence of a clear outcome such as measureable disease progression used in other contexts. In the definition of mild cognitive impairment (MCI) occurring in prodromal Alzheimer's disease, scores of 1.5 standard deviations (SD) or more below normal age, education and gender adjusted performance are considered abnormal. In some cases scores 1.0 SD below are considered sensitive to early changes as in work on early amnestic MCI (Risacher et al. 2013), but that greater sensitivity is purchased at the price of lower specificity. Many investigators consider the presence of deficits to ultimately be a clinical decision based on all available information. An alternative basis for achieving binary classification for the sake of defining inclusion criteria or outcomes for research studies is to compare an individual's cognitive performance not to population norms in the manner delineated above for defining MCI, but relative to that individual's own normal level of cognitive performance, or to determine whether performance is declining to a degree greater or faster than would be expected for normal aging (Ahles et al. 2012; Silverman et al. 2008). In prospective cancer treatment studies this can be accomplished by including baseline psychometric data. In post-treatment studies investigators should attempt to include a more accurate analysis of baseline abilities based on continuing educational achievement, occupation and professional and social activities over time. Self- and informant-based ratings of cognitive concern or complaints can also be potentially classified using standardized cutoffs but the same caveat applies in terms of decline being assessed relative to the individual's own baseline. It is also important to keep in mind that some studies ask only 1–2 questions whereas others employ detailed scales with a large number of items.

4. The role of psychosocial factors deserves more attention, including more sophisticated conceptual models of the interaction of social, self-regulatory and biological factors (Arndt et al. 2013). Social networks, studied with regard to cancer survival (Kroenke et al. 2006), could also be analyzed for bidirectional relationships with cognitive function.
5. DSM-5, the recently released edition of the Diagnostic and Statistical Manual (American Psychiatric Association 2013) includes the categories of mild and major neurocognitive disorder. Cognitive changes associated with non-CNS cancer and chemotherapy-associated cognitive changes are likely to fall under the DSM-5 mild neurocognitive disorder framework, although in some cases more pronounced changes would meet criteria for major neurocognitive disorder. In either case it would be important to record which DSM-5 criteria are met for harmonization across future studies.

Sample composition

6. The majority of neuroimaging studies to date have included patients undergoing treatment for breast cancer. Future brain imaging studies are needed to address changes in brain structure and function associated with other non-CNS cancers.
7. Extension to broader age and education ranges and more demographically diverse samples. The role of age, hypothesized accelerated aging, and interactions with aging processes has been discussed but under-investigated. Similarly, the role of education, occupation and other factors related to cognitive reserve warrant further attention as potential moderators of cognitive outcomes. More attention to socioeconomic, racial/ethnic and language-related factors would also be useful to extend the generalizability of findings in future research.

Study design, scanning and sample collection

8. Prospective neuroimaging studies are needed. Most research to date has focused on survivor cohorts with the follow-up intervals ranging from one year to several decades. Inclusion of baseline scans prior to systemic treatment with cytotoxic chemotherapy or hormonal therapy is highly desirable despite the challenges in obtaining these data. Where feasible, baseline scanning followed by early post-treatment imaging (e.g., within the first 1–6 months after treatment) with subsequent longer term follow-up scans a year or more after the conclusion of treatment is recommended. Limited existing data reviewed above suggest acute effects on brain structure and function with partial recovery by one year, as well as residual changes observed in the long-term survivor studies. Ultimately, the issue of optimal time points for neuroimaging studies warrants further investigation.
9. Large well-powered, multicenter neuroimaging studies are needed in research on cancer and cognition. Most neuroimaging studies to date have modest sample sizes. When considering the relationships to cognitive performance, biomarkers and especially potential genetic moderators of cognitive outcome, imaging studies will need to be quite large to have sufficient power to detect the influence of these factors after controlling for multiple testing. A parallel to studies of Alzheimer's disease and MCI is informative. Early MRI and PET studies typically included relatively small samples. In 2004, the Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched across 59 sites in the US and Canada with standardized clinical, cognitive, structural MRI, genetics and biofluid data collection, with FDG PET and later

amyloid PET scans obtained in a subsample. In ADNI-2 all participants undergo the detailed MRI, FDG and amyloid PET, genetics, CSF and blood biomarker studies. This large data set made publicly available to the scientific community has resulted in nearly 400 publications to date (Weiner et al. 2013), reflecting the power of comprehensive "big data" sets to drive research. ADNI included genome-wide association study (GWAS) genotype data (Saykin et al. 2010) and recently whole genome sequencing data has been added. The combination of genetic data (APOE or GWAS) with imaging and other phenotypes led to over 100 publications by the end of 2012 (Shen et al. 2013). This open, collaborative, and highly productive paradigm can provide a model for advancement of research into the cognitive and neural effects of cancer and cancer treatment.

10. Standardization of MRI and PET methods has been demonstrated by ADNI and other large scale multicenter studies. For studies of cognition changes associated with cancer and cancer treatment, a common core of scan sequences should be developed to facilitate cross-study comparison and potentially inclusion in a large multicenter study. MRI and PET methods have been standardized across the major vendor platforms and models (i.e., GE, Philips and Siemens scanners). At present, a minimal approach would be inclusion of a high resolution 3D volumetric MRI such as the T1-weighted MPRAGE sequence used in ADNI (for detailed protocols for ADNI-1 and ADNI-2 see: http://adni.loni.usc.edu/methods/documents/mri-protocols/). Similarly, for assessment of white matter hyperintensities and other age associated microvascular changes, a 3D FLAIR sequence might be included. Recent studies described in this special issue and elsewhere suggest that several advanced MRI techniques may be particularly sensitive to cancer- and treatment-associated changes. These include diffusion imaging (e.g., DTI and DSI), resting state (task free) fMRI, memory and executive task-based fMRI, MRS and arterial spin labeled perfusion. Employing these techniques across sites in a multicenter framework is more challenging, although each has been used in such studies spanning different scanners and software platforms. Multimodality imaging across MRI techniques, and potentially also including PET studies, is likely to be particularly informative for differentiating treatment and disease mechanisms.
11. Special imaging databases, processing pipelines and analytic techniques are also needed for standardization or harmonization in multicenter studies. There is ample proof of concept that these methods are effective in multicenter studies of other disorders, suggesting that they can be applied in future cancer studies. High throughput automated analyses of structure and function will be needed and are available, as are meta-analytic approaches for imaging data. A particularly promising area includes analyses of alteration of the structural and functional "connectome" (Sporns 2013a, b; Sporns et al. 2005) or network properties of the brain after cancer treatment (Bruno et al. 2012; Dumas et al. 2013; Hosseini et al. 2012).
12. There is a paucity of PET studies addressing the cognitive effects of cancer and cancer treatment. Although PET requires minor exposure to ionizing radiation this technique has the distinct advantage of permitting specific molecular targeting. Many of the candidate mechanisms for cancer-associated cognitive dysfunction (Ahles and Saykin 2007; Saykin et al. 2003) such as alterations in inflammation/immune activation, vascular function and growth factors, efflux transporters, hormones, neurotransmitters and receptors, proliferation/neurogenesis, DNA damage/repair and plasticity markers, as well as abnormal proteins could all be potentially studied using targeted molecular imaging. Although a powerful tool, a limitation of PET is that only one molecular target can be assessed at a time, so that a limited number of hypotheses can be tested in a given study. Once there is a strong hypothesis PET could be used in a targeted manner to pursue a particular mechanism.
13. Standardized clinical/cognitive, genetic and biomarker collection approaches are well established for large scale studies and could readily be included along with neuroimaging for studies of cancer and cognition. Biorepository banking of blood samples for DNA, RNA, plasma and serum could greatly enhance studies of cancer and cognition. Recent analyses of proinflammatory cytokines (Pomykala et al. 2013b) and DNA damage markers (Conroy et al. 2013b) from blood samples are already proving informative. Proteomics analyses can be used to study many analytes in blood plasma or serum or CSF when available. Analytes related to relevant biological pathways can be measured prospectively including endocrine, immune, oxidative stress, growth factors, apoptosis, and many other pathways. Many other assays such as analysis of telomere length and accelerated aging effects in relation to imaging data become possible if DNA samples are banked and available. Similarly, a range of other host factors can be studied including variation in candidate genes for cognition and genes from targeted biological pathways, and ultimately GWAS and whole genome or exome sequencing for less common variants can be undertaken. RNA sequencing or expression profiling from accessible peripheral blood may be revealing as a marker for dynamic changes in the transcriptome, and may in part reflect transcriptional changes in brain given conservation of gene expression. MicroRNAs, small RNAs that are

important regulators of transcription, play a significant role in cancer and neurodegenerative disorders such as AD (Holohan et al. 2012). Finally, the gut-brain relationship is receiving increasing attention in cancer and neurodegeneration research and assays of the microbiome are likely to prove informative if samples are banked.

Intervention studies

14. Therapeutic and preventative strategies targeting cognitive changes in cancer patients, including pharmacological as well as behavioral/psychosocial interventions such as cognitive rehabilitation, exercise, diet and other lifestyle factors, could all be studied with the neuroimaging and other biomarker methods discussed above, to examine the impact on physiological processes and mechanisms.

Ethical, legal and social issues

15. Ethical, legal and social issues (ELSI) will need to be addressed. Investigators will need to consider what participants should be told about results of imaging, genetics and other biomarker studies designed to address cognitive risks and changes, if anything. The methods discussed above are largely experimental at present, but in the future at least some are very likely to prove to be predictive and become part of personalized cancer medicine, including diagnostic, prognostic and therapeutic aspects. ELSI research is needed to better understand the implications of returning or not returning such results to research participants.
16. Another important ELSI relates to informed consent with regard to data sharing. There is increased recognition that data sharing greatly facilitates scientific research. The NIH mandates data sharing plans for larger studies and for all GWAS and a similar plan for required biorepository deposition is being developed for genome sequencing studies. ADNI, discussed above as an example of open and collaborative science, makes all data available to qualified investigators around the world with a low barrier for obtaining data, and this has proven to be extremely productive in facilitating progress. Yet making genomic, imaging and other potentially identifiable data broadly available is not without some degree of risk. Involvement of ELSI experts will be important to help the field appropriately manage risks, provide appropriate informed consent, and address national and international data sharing.

Conclusions

We hope that readers will enjoy the thorough reviews of existing neuroimaging research on cancer and cancer treatment as well as the novel findings reported in this special issue of *Brain Imaging and Behavior*. In addition, we hope that investigators will find the above recommendations useful for advancing neuroimaging research on cancer and cognition as part of a comprehensive systems biology framework.

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