

COMMENTARY

International Cognition and Cancer Task Force Recommendations for Neuroimaging Methods in the Study of Cognitive Impairment in Non-CNS Cancer Patients

Sabine Deprez, Shelli R. Kesler, Andrew J. Saykin, Daniel H. S. Silverman,
Michiel B. de Ruiter, Brenna C. McDonald

Affiliations of authors: University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium (SD); Department of Neuro-oncology, University of Texas MD Anderson Cancer Center, Houston, TX (SRK); Center for Neuroimaging, Department of Radiology and Imaging Sciences and Indiana University Melvin and Bren Simon Cancer Center, Indiana University School of Medicine, Indianapolis, IN (AJS, BCM); Ahmanson Translational Imaging Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA (DHSS); Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, the Netherlands (MBdR).

Correspondence to: Brenna C. McDonald, PsyD, MBA, IU Health Neuroscience Center, 355 W. 16th St., GH Suite 4100, Indianapolis, IN 46202 (e-mail: mcdonalb@iupui.edu).

Abstract

Cancer- and treatment-related cognitive changes have been a focus of increasing research since the early 1980s, with meta-analyses demonstrating poorer performance in cancer patients in cognitive domains including executive functions, processing speed, and memory. To facilitate collaborative efforts, in 2011 the International Cognition and Cancer Task Force (ICCTF) published consensus recommendations for core neuropsychological tests for studies of cancer populations. Over the past decade, studies have used neuroimaging techniques, including structural and functional magnetic resonance imaging (fMRI) and positron emission tomography, to examine the underlying brain basis for cancer- and treatment-related cognitive declines. As yet, however, there have been no consensus recommendations to guide researchers new to this field or to promote the ability to combine data sets. We first discuss important methodological issues with regard to neuroimaging study design, scanner considerations, and sequence selection, focusing on concerns relevant to cancer populations. We propose a minimum recommended set of sequences, including a high-resolution T1-weighted volume and a resting state fMRI scan. Additional advanced imaging sequences are discussed for consideration when feasible, including task-based fMRI and diffusion tensor imaging. Important image data processing and analytic considerations are also reviewed. These recommendations are offered to facilitate increased use of neuroimaging in studies of cancer- and treatment-related cognitive dysfunction. They are not intended to discourage investigator-initiated efforts to develop cutting-edge techniques, which will be helpful in advancing the state of the knowledge. Use of common imaging protocols will facilitate multicenter and data-pooling initiatives, which are needed to address critical mechanistic research questions.

Non-central nervous system (CNS) cancer and its treatments are associated with cognitive declines that can be persistent (1–3), with executive functions, processing speed, and memory especially affected (4–7). Neuroimaging studies have demonstrated alterations in brain structure and function (8–11) that correlate with objective and/or subjective cognitive performance (12–14). Important questions remain regarding the role of cancer disease processes (15–17) and treatments other than

chemotherapy (18–20). While most research has focused on breast cancer, other non-CNS cancers have also been studied (21–33). Greater mechanistic understanding of these changes will advance prevention and remediation efforts. Neuroimaging can provide unique and important biomarkers of cognitive changes; however, methodological variability has precluded practice-changing conclusions. Given difficulties inherent in studying cancer patients, multicenter studies and data-pooling

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initiatives are needed to gain sufficient statistical power to address critical research questions (34).

The International Cognition and Cancer Task Force (ICCTF) was founded in 2006 to facilitate international collaborations around cognitive impairment in cancer patients (35). A specific goal of the ICCTF is to create research recommendations and guidelines that increase the homogeneity of study methods to facilitate between-study comparisons, meta-analyses, and data pooling (36) and provide better estimates of incidence, severity, individual risk factors, and causes of cognitive changes (37). In 2011, the ICCTF published recommendations regarding cognitive assessment methods (37). Here the ICCTF Neuroimaging Working Group offers recommendations for magnetic resonance imaging (MRI) and positron emission tomography (PET). We focus on concerns particularly relevant to studies of cancer populations, including study design, timing of assessments, and choice of control groups(s), and we recommend sequences accessible to most institutions thought likely to be fruitful based on the existing literature (Figure 1).

Methodological Considerations

We first discuss general study design concepts formulated in the ICCTF cognitive studies publication (37) that are also critical for neuroimaging studies, then describe additional aspects specific to neuroimaging. Those newly implementing neuroimaging should work with an magnetic resonance imaging (MRI)/positron emission tomography (PET) physicist to optimize sequences (eg, while smaller voxel size increases spatial resolution, other parameters would need to be adjusted to maintain overall signal-to-noise, resulting in increased scan time). Collaboration/consultation with neuroradiology colleagues and/or researchers with neuroimaging expertise in cancer populations may help studies start efficiently and avoid common pitfalls. This Commentary focuses on human neuroimaging studies. Preclinical work is another important component of examination of mechanisms underlying cancer- and treatment-related cognitive changes. Best practices for studies in animal models, including neuroimaging-related considerations, are beyond the scope of this Commentary, but are considered elsewhere (38,39).

General Considerations

Double-blind, randomized, placebo-controlled study designs are optimal, but unethical for cancer patients. Therefore, the optimal approach is a prospective longitudinal design with appropriate control groups, including a minimum of one assessment before and after the treatment under investigation. A longer-term follow-up assessment is also advised to examine persistent or delayed effects. Using intervals similar to those previously published will advance the ability to compare and combine data sets. Acute follow-up intervals have commonly ranged from one to six months postchemotherapy, with longer-term follow-up typically about one year later. Timing of assessments depends on the scientific research questions, taking into consideration potential patient symptoms and side effects and timing of other treatments.

Including control groups is essential, given the absence of appropriate normative data to adequately control for possible confounding factors (eg, variability in neuroimaging equipment and scan sequences). The ideal comparison would be a disease-specific control group differing only in the treatment under

Study design

- Longitudinal: include pre- and post-treatment assessments (near-term and/or longer-term) when possible
- Include disease-specific and healthy control groups if possible
- Address potential future sharing of deidentified data in IRB documents when possible
- Include correction for multiple statistical comparisons or rationale if data are uncorrected
- Include objective and subjective measures of cognitive and behavioral function for correlation with imaging data

Neuroimaging

- Inclusion of a minimal set of MRI sequences to facilitate future data pooling initiatives is encouraged:



- High-resolution T1-weighted anatomical MRI to assess morphological changes



- Resting state functional MRI to assess functional brain changes

For both MRI and PET

- Use the same scanner throughout the study when possible
- Maintain consistent image acquisition parameters and protocols
- Document hardware/software changes of the scanner over time to account for at the time of the analysis when needed
- For multisite studies: consider additional phantom scans to monitor scanner-based calibration across sites and over time

Reporting

To facilitate meta-analysis, researchers are encouraged to report:

- Effect sizes or the necessary data to calculate them
- Three-dimensional (x,y,z) coordinates of the involved brain regions and the stereotactic space

Figure 1. Main recommendations and considerations for incorporation of neuroimaging into studies of cognitive impairment in non-central nervous system cancer patients. IRB = institutional review board; MRI = magnetic resonance imaging; PET = positron emission tomography.

investigation. Given current treatment paradigms, patient groups usually also differ in clinical aspects of disease. Such differences should be documented and considered in analyses. The inclusion of an additional control group of individuals without cancer is also recommended to determine the normal pattern of change in outcome variables over time and if observed effects might be due to technical aspects of neuroimaging (eg, scanner drift).

One challenge for data-pooling initiatives is the need to comply with institutional review board (IRB) requirements for data sharing. We strongly recommend including a section specifically addressing the potential future sharing of deidentified data sets in IRB documents, including informed consents. IRB requirements vary across countries and institutions and change over time. Inclusion of such language facilitates the ability to rapidly participate in multicenter initiatives.

Participant Recruitment

Novice neuroimaging researchers have reported difficulty enrolling participants. The authors have found that a critical component of successful recruitment is having research staff who present the study with confidence and enthusiasm and respond to questions in a positive, knowledgeable, reassuring manner. Offering a mock scanner session or visiting/lying in the real scanner can be useful for hesitant individuals. Providing a picture of the brain to take home, having structural scans read by a neuroradiologist for incidental findings, and offering an

honorarium for time and effort are also helpful. Flexibility in scheduling study visits can make a great difference in recruitment of patients trying to juggle work, personal responsibilities, and medical care. “Piggybacking” imaging onto other studies in cancer populations can also be effective; for example, participants already enrolled in studies of cognition or quality of life may also consider participating in neuroimaging.

Cancer patients tend to be more receptive to research participation when first approached by a member of their clinical team, so involving surgeons and oncologists in study design and efforts to promote the work is crucial. For prospective studies attempting to obtain pretreatment baseline assessments, working with clinicians as early in the diagnostic and treatment process as possible is important. For example, identifying potentially eligible patients via the surgeon may offer a greater window of time to schedule initial prechemotherapy assessments vs identifying patients through the medical oncologist. Financial support of nurse navigators or other clinic staff to support time spent on recruitment can also be very helpful.

MRI Scanner Considerations

MRI should preferably be conducted on a 3T system, using the most advanced headcoil available for maximum signal detection. It is also important to minimize equipment differences. Consistent scan parameters should be maintained across participants and time points, as slight variations can have great effects. Changes in the scanner or equipment (eg, software or hardware upgrades, coil changes) should be documented. Consideration should be given to scanning phantoms relevant to different sequences at regular intervals, as well as after scanner upgrades, to monitor stability. Regular phantom scans can monitor calibration across sites and over time.

It is ideal to use one scanner for all participants and time points. If acquisition cannot be confined to one scanner (eg, for multicenter studies), individual participants should be assessed on the same scanner over time. Patient and control groups should be intermixed across scanners and over time to avoid confounding group with scanner type or scanner changes over time.

MRI Scan Protocol Considerations

It is beneficial to obtain close to isotropic voxels, particularly for high-resolution structural MRI and diffusion tensor imaging (DTI), to avoid directional bias, reduce partial volume effects and registration errors, and allow more precise and accurate measurements. As cancer treatment effects have been detected in distributed brain regions, whole-brain coverage, including the cerebellum, should be obtained unless contraindicated by the specific scan sequence (eg, arterial spin labeling [ASL]). It is advisable to standardize certain scan parameters across sequences. For instance, using the same field of view (FOV) and angulation increases uniformity of the scan protocol and facilitates multimodal analysis.

Motion is extremely detrimental; minimization of head and body motion should be repeatedly emphasized to the participant before and during scanning. Visual inspection of data at the time of acquisition can be helpful to provide participants with feedback on their level of motion and to repeat sequences as necessary. Remaining in close contact with the participant during scanning is also helpful in reducing anxiety and maintaining motivation and arousal (eg, for fMRI tasks).

It is important to maintain a standardized scan protocol order and document any deviations for consideration in analysis. Series that are particularly susceptible to motion might be better placed early in the scanning session. It is recommended that resting state fMRI (rsfMRI) scans be conducted either before or otherwise at a time removed from task-based scans to reduce the effects of cognitive processes on intrinsic networks (40).

Considerations for MRI Sequence Selection

MR technology can be divided into three tiers: 1) conventional techniques in routine clinical use for structural imaging and available on most 3T and 1.5T scanners, such as T1-weighted and T2-weighted volumetric imaging and fluid attenuated inversion recovery (FLAIR) scans; 2) advanced techniques including specialized sequences such as task-based blood oxygen level-dependent (BOLD) and rsfMRI, diffusion, perfusion, and MR spectroscopy—advanced sequences have greater likelihood of equipment, vendor-specific software feature, and hardware performance differences; 3) emerging techniques including leading-edge prototype applications available at academic centers as “work-in-progress (WIP)” software that may become available commercially if proven useful and there is sufficient demand (eg, multiband acquisition software for BOLD and diffusion imaging). These are the most demanding applications in terms of hardware, software, and specialized expertise.

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) and other consortia (eg, Transforming Research and Clinical Knowledge in TBI [TRACK-TBI], International Neuroimaging Data Sharing Initiative [INDI], Brain Development Cooperative Group) have multivendor 3T MR acquisition sequences that are relatively harmonized. Use of such already-vetted sequences might be particularly helpful for multicenter collaborations or investigators with more limited neuroimaging resources. The ADNI sequences are available at <http://adni.loni.usc.edu/methods/documents/mri-protocols/>. ADNI-3 includes T1, FLAIR, fMRI, DTI, and ASL perfusion sequences for multiple vendor platforms, both basic (for most available 3T systems) and advanced (for systems with connectome-level hardware gradients and multiband software).

Recommended Imaging Sequences

These recommendations represent a suggested minimum core set of sequences for sites that may not have the capability for more advanced or emerging sequences, as well as additional series likely to be of interest if the necessary resources are available. We recommend using the most current ADNI sequences, unless relevant expertise is available to optimize sequences for a particular research question. Several considerations were taken into account when selecting the minimum core set of MRI sequences. First, the modalities must have proven to be sensitive to cancer- and treatment-related brain changes. Second, the sequences must be available on most clinical scanners and be accessible to a wide range of users regardless of scanner platform. Third, optimized parameters are publicly available via existing cooperative neuroimaging projects, and multicenter reproducibility has been assessed, making data-pooling easier. Based on these considerations, we recommend including the following minimum set of core MRI sequences:

1. A high-resolution, T1-weighted scan with excellent contrast between gray matter, white matter, and cerebrospinal fluid

allows precise localization of anatomical structures and permits the usage of postprocessing tools that characterize volumetric changes. This series is also routinely used for anatomical reference and spatial normalization procedures for other imaging modalities and for radiologic review for incidental findings. Inclusion of this sequence is recommended as literature has demonstrated differences in gray matter volume, density, and connectivity related to cancer and its treatment (9,41–43).

- rsfMRI allows examination of functional brain changes without requiring the stimulus delivery and response recording equipment necessary for task-based fMRI. Previous work has found rsfMRI useful in demonstrating differences in brain network connectivity after cancer treatment (44–47). A sequence of at least six minutes' duration (ideally 10 minutes or more) is suggested, as is instructing participants to relax, but not to fall asleep. There has been debate about whether eyes should be open or closed (48–51); our consensus recommendation is eyes closed, based on review of the most commonly used procedures.

Investigators are encouraged to consider additional MRI modalities depending on the research questions and available equipment and neuroimaging expertise. Task-based fMRI of working memory has consistently demonstrated alterations in brain function related to cancer and treatment (52–60). Several prior studies have utilized an “N-Back” paradigm, with conditions of increasing working memory load. Use of a visual-verbal N-Back working memory paradigm (eg, the visual analog of the task utilized in [59]) (Supplementary Materials and Supplementary Figure 1, available online) is suggested. fMRI of other cognitive functions of interest should also be considered. Working and episodic memory have been studied most extensively, with some studies examining other aspects of executive functioning (10).

DTI is useful to assess changes in white matter microstructure and has been shown to be sensitive to cancer treatment-related changes (8), though not all scanners may be capable of implementing the parameters necessary for optimal sensitivity. DTI introduces a number of imaging parameters unique to diffusion imaging, including gradient magnitude (b-value) and directions. DTI acquisitions also include nondiffusion T2-weighted images, known as b0 images (61,62), used for artifact removal and tensor fitting. Determination of the number of directions to be acquired and the b-value partly depends on the research question. A minimum of six directions is required for calculating the diffusion tensor (63). A larger number of directions (eg, 30+) is typically required for fiber tracking, with some tracts requiring more directions than others. Multiple sequence runs might be considered to increase signal-to-noise. It is beneficial to acquire as thin a slice thickness and as many directions as possible while being mindful of scan length. DTI was not included in the recommended core minimum set of sequences because it is very sensitive to scanner variability, making it difficult to pool data even when using harmonized sequences.

A 3D FLAIR sequence is useful for detection of white matter hyperintensities as well as radiologic review. Utilization of PET, more advanced diffusion-weighted techniques (eg high angular resolution diffusion-weighted imaging [HARDI], Q-Ball, diffusion spectrum imaging [DSI]), perfusion MRI (eg, ASL, pulsed arterial spin labeling [PASL]), or MR spectroscopy could also be of interest, though, as for DTI, concerns regarding reproducibility between scanners and necessary expertise for reliable

prescription and analysis may limit their generalizability across different sites.

Image Processing, Analysis, and Reporting

Quality Assurance

Image quality, and therefore data analysis and interpretation, can be affected by sources of artifact (64,65), including participant motion (resulting in ringing or blurring of the images), experimenter inaccuracy (eg, susceptibility artifacts related to the presence of ferromagnetic objects, incorrect FOV resulting in wrapping artifacts), and hardware failures and image reconstruction problems (eg, large signal dropouts, noise, spikes, signal inhomogeneity, ghosting). Visual inspection of raw images is recommended (66), and automated quality assurance (QA) procedures can be a useful complementary step (67–69). QA is necessary at various stages in the image processing pipeline, as some artifacts may be more evident at different points. Images with excessive distortions that would corrupt further analysis, such as large signal dropouts or excessive motion, can be easily identified, repaired if possible (70,71), or excluded.

Image Processing for Recommended Core Sequences

T1-Weighted Scans

Voxel-based morphometry (VBM) (72,73) is a commonly used method for examining brain volumes, particularly gray matter. An optimized (74) procedure can be semi-automatically executed using existing software tools such as the VBM Toolbox in the SPM software package. VBM statistical analysis is typically done on a whole-brain basis using statistical parametric mapping within a general linear model (GLM) framework (75).

Surface-based methods for volumetric analysis typically involve automated or semi-automated whole-brain or regional parcellation of cortical and subcortical volumes and provide measurements of cortical thickness, surface area, curvature, and volume for discrete cortical and subcortical structures (76–79).

Manual tracing techniques utilize a standardized approach to delineating regions of interest (ROIs), which typically encompass a particular brain structure. Such protocols rely on anatomic landmarks and conventional boundaries to define ROIs, and tracings must have acceptable inter- and intrarater reliability. These methods can be extremely precise for particular ROIs in a given individual, but they are time- and labor-intensive. The many delineation protocols available can also result in substantial differences in reported ROI volumes (80).

Each approach to quantitative structural analysis has strengths and limitations in terms of objectivity, reliability, time and labor intensity, and other factors. One method may be more advantageous than another for a particular scientific question, and the approaches can be used complementarily to provide convergent validation of a finding.

rsfMRI

rsfMRI is typically used to evaluate functional connectivity between brain regions. In addition to the aforementioned QA procedures, fMRI QA should include inspection of the data time courses to assess any abrupt signal changes. In addition to the standard preprocessing steps required for task-based fMRI described below, rsfMRI data require additional corrections (81). Several statistical approaches for rsfMRI functional connectivity exist, including seed-based correlation (SBC), independent

components analysis (ICA), and atlas-based ROI. SBC seed sizes and locations are not standardized, leading to variability in results (82), and must therefore be carefully considered.

ICA is a data-driven, multivariable method (83) wherein individual components can represent various brain networks or non-neuronal noise. ICA can therefore serve for artifact correction steps (also see task-based fMRI below) as well as for statistical analysis. Identifying relevant components can be challenging, though several methods exist for this purpose (81).

The magnitude of intrinsic brain activity per region can also be measured from rsfMRI. Several methods exist for obtaining information for ROIs and/or in a whole-brain, voxel-wise manner, including amplitude and fractional amplitude of low-frequency fluctuations (84) and regional homogeneity measurement (85); each has advantages and disadvantages (82).

Image Processing for Additional Imaging Sequences of Interest

Task-Based fMRI

Task-based fMRI can assess changes in brain activation while performing a cognitive task in the scanner, and recommended methods for preprocessing fMRI data have been extensively described (86–89). Many options for further preprocessing exist, including B0 field-map correction to correct for geometric distortions due to magnetic field inhomogeneities (relevant for both fMRI and DTI) (90,91) and ICA for removing motion artifacts (92). Similar to VBM, a GLM approach is widely used for whole-brain voxel-based statistical analysis of fMRI data (93).

The interpretation of fMRI activity becomes complicated when fMRI task performance differs between groups, as between-group activation differences could be the result or the cause of low performance accuracy. It is therefore helpful to consider ways to address this concern, for example, by personalizing task difficulty level to ensure similar performance (94) or covarying analyses for task performance.

DTI

Detailed descriptions of DTI preprocessing steps and an overview of the most commonly used DTI analysis methods can be found elsewhere (8). With the diffusion tensor fitted in every voxel, parameter maps, such as those measuring fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD), can be calculated and analyzed.

The diffusion tensor model is a simple model of water diffusion within the brain, and results must be interpreted with care (95). While DTI has the sensitivity to detect microstructural changes and damage, it is not specific in identifying what changes occurred (eg, demyelination vs axonal degeneration). Additionally, the diffusion tensor model is inadequate in the many regions of the brain that contain “crossing fibers.” Higher-order diffusion models can bring additional insights in this regard (62,96), but they require more advanced diffusion sequences (eg, acquiring multiple shells with different b-values and number of orientations).

FDG-PET

FDG-PET serves as a quantitative biochemical marker of glucose utilization rate. Relative levels of FDG uptake are more broadly acquired to index synaptic activity throughout more metabolically active brain tissues (eg, neocortex, thalamus, cerebellar cortex), while little attention has thus far been given to less metabolically active structures (eg, globus pallidus, white matter tracts).

Similar procedures to those discussed above for MRI are recommended to allow collection of data that can be combined in collaborative analyses. Additional considerations for FDG-PET include the following: 1) the participant must fast for a minimum of four to six hours prior to the scheduled time of FDG administration; 2) prior to administering FDG, blood glucose level must be measured and recorded; 3) an intravenous catheter is required for FDG administration; 4) the participant should be accommodated to an environment with minimal sensory stimulation; and 5) PET is acquired while the participant is awake with eyes open.

Specific PET acquisition protocols depend upon various factors related to instrumentation and are thus highly scanner-dependent. Identifying an expert collaborator who can assist in designing these experiments is key to successful PET studies. Preprocessing and analysis of FDG-PET data are highly similar to processing and analysis of fMRI data, including statistical parametric mapping and ROI methods, as described above.

Connectome Analysis

Mapping the brain network, or connectome, has become a focus of increasing attention. Connectomes can be constructed from gray matter volumes (97), DTI (98), and rsfMRI (44), as well as electroencephalogram (EEG) (99) and magnetoencephalography (MEG) (100). Connectome analyses, typically based on graph theory, provide advantages over traditional neuroimaging approaches, including being inherently multivariable, utilizing multiple neuroimaging data modalities, and improved characterization of the brain’s complexity. Connectome properties include global and local metrics of brain organization, efficiency, and connectivity. Additionally, connectomes can be used for more advanced analyses, including network response to simulated neuropathology (98). Connectome analyses can be computationally intensive, however, and thresholding networks of different sizes for comparison remain an area of ongoing debate (101).

Analytic Considerations

Thresholding and Correction for Multiple Comparisons

Analyses of neuroimaging data are typically done at the voxel level across the whole brain, and therefore involve tens of thousands of univariate statistical tests (eg, a t test is performed at each voxel). Options to correct for multiple comparisons include family-wise error (FWE) correction, typically based on an adjusted Bonferroni method, which accounts for the fact that observations for single voxels are not independent; random field theory (RFT), which better accounts for spatial smoothing and correlation in neuroimaging data (102); and false discovery rate (FDR), which often provides greater sensitivity by applying Bonferroni correction in a descending manner across statistically significant voxels, thus adapting to the level of signal present in the data. FWE and RFT control for the chance of any false positives, while FDR controls the proportion of false positives among suprathreshold voxels (103). Permutation methods may offer advantages, especially for small samples (102,104). Threshold-free cluster enhancement (TFCE) is a permutation-based method that identifies areas of spatial continuity while minimizing problems related to arbitrary cluster thresholds and spatial smoothing (105). Alternate approaches include explicit masking as well as ROI extraction to restrict the number of comparisons; however, these approaches inherently downsample the data.

With regard to the concern of adequate consideration of false positives for fMRI (106), recent work suggests that when

an appropriate initial statistical threshold is used, the number of false positive errors is in keeping with what would be predicted statistically (107). With careful consideration of related issues (eg, use of more stringent primary thresholds, transparent reporting practices), methods like cluster-based thresholding can still be useful (108). We recommend that an appropriate method of multiple comparison correction be employed for findings to be considered robust, while also acknowledging the challenges of working with small samples and recognizing that more exploratory analysis can be critical for discovery science.

Considerations for Analyzing Longitudinal Image Data

Two approaches are commonly applied for analysis of longitudinal image data: repeated measures analysis of variance (or within-subject ANOVA) and cross-sectional (GLM-based) analysis of summary measurements such as percent difference (109). If only two time points are being analyzed, baseline measurements can also be included as a covariate when analyzing post-treatment data. Typical methods may be suboptimal, however, as they do not model the covariance structure of serial measurements appropriately, introducing a systematic processing bias (110,111). Some software packages offer solutions for unbiased longitudinal image analysis by using within-subject template creation (110,111). However, commonly used neuroimaging toolboxes make restrictive or unrealistic assumptions when modeling more than two time points per subject (112). More sophisticated methods are being developed to model longitudinal neuroimaging data that account for the within-subject correlation of longitudinal data (109,112–114).

It is important to use the same software version for all analyses to prevent bias. Differences in scanner hardware or software or different acquisition parameters or protocols over time will also influence results (111). A combined scan of subjects and phantoms could allow post hoc correction of these biases, or appropriate covariates reflecting scanner-related differences could be included in the statistical design.

Describing and Reporting Neuroimaging Data

A detailed guide for describing fMRI experiments and results that can be applied to many neuroimaging studies can be found elsewhere (115). It is best to be inclusive regarding details of the study design, data acquisition parameters, QA measures, preprocessing steps, modeling, statistical inference, and any other important methods (eg, ROI definitions). Figures and tables should describe statistics and thresholds used, how anatomical underlays or displayed templates were created, if masking or other such methods were used, the 3D coordinates (x,y,z) of statistically significant clusters, the stereotactic space of these coordinates, statistics for each cluster (eg, Z-value, number of voxels, cluster extent), and anatomical labels for clusters (eg, “left superior frontal gyrus”). To facilitate meta-analyses, we recommend reporting effect sizes or the necessary data to calculate them.

Clinical, Cognitive, and Biomarker Data Considerations

Clinical and Demographic Variables

It is critical to record demographic and clinical data at each study assessment for integration in neuroimaging

analyses. Examples include age, education, sex, handedness, race/ethnicity, and socioeconomic (eg, income level), vocational, menopausal, and marital/social support status. Variables related to cancer and treatment should be documented in as much detail as possible. Examples include type/stage of cancer, disease characteristics (eg, size of tumor, number of affected lymph nodes), details of treatments received (eg, types of surgeries; type and length of anesthesia; chemotherapy regimens, doses, number of cycles completed, and concomitant medications; radiation dose; type, dose, and duration of endocrine therapy). Dates of treatments are needed to calculate relevant intervals for use as covariates. Other medical, psychiatric, and psychosocial data should also be collected, including all medications and vitamins/supplements being taken, other medical or mental health conditions, and ratings of variables such as fatigue, sleep quality, depression, and anxiety.

Cognitive Assessment

A variety of self-report and objective cognitive assessment tools have been shown to correlate with neuroimaging findings (2,11,12,23,24,28,41–47,52–56,94,98,116–130), including measures of attention, memory, and executive function. Some studies have demonstrated correlations with specific tests, while others have utilized cognitive domain scores. While the use of domain scores can be very helpful for dimension reduction of cognitive variables, correlations with neuroimaging variables may be stronger for individual test measures. Specific tests may also be grouped into various cognitive domains, making cross-study comparisons challenging. There has recently been increased emphasis, in the form of a program announcement from the National Cancer Institute, encouraging researchers to leverage cognitive neuroscience to improve assessment of cancer- and treatment-related cognitive changes to better identify and characterize these concerns (eg, potentially via assessment tools targeted toward specific components of cognitive function, or those using more sensitive techniques such as electronic administration). While varying approaches may be taken, incorporation of cognitive assessment is strongly recommended to relate neuroimaging findings to functional status.

Biomarkers

A growing number of articles have evaluated the relationship of neuroimaging to various biomarkers to further elucidate the underlying biology of cancer- and treatment-related cognitive changes (23,41,54,116,125). Preliminary work has also shown genetic variables that relate to cognitive functioning after cancer treatment (23,132–135). Investigators are therefore strongly encouraged to collect blood samples for genotyping and to consider banking plasma and serum for fluid biomarker analyses. While funding or sample size considerations may initially preclude running such analyses, if samples are appropriately processed and stored, which is typically relatively inexpensive, the desired assays may be run later when funding is obtained or potentially via consortium analyses (34). Methodological issues are also important when gathering and storing biomarker data. For example, for cytokine analyses, it is critical to carefully consider factors such as method and timing of sample acquisition (eg, time of day, feeding state and acute stress level of the individual, etc.) as well as processing and storage steps utilized (136). While more speculative in this population at present, consideration might also be given to the correlation of

neuroimaging variables with RNA (eg, via PAXgene tube or other collection vehicles) or telomere length. For any chosen biomarker, standard collection, storage, and processing procedures are readily available, and close collaboration with colleagues with appropriate lab expertise is essential.

Conclusions

A goal of the ICCTF is to provide research recommendations and guidelines in order to increase the homogeneity of study methods in the field of cancer and cognition. Here we offer approaches and recommendations for neuroimaging studies with regard to study design, data sharing considerations, core neuroimaging sequences, and the processing, analysis, and reporting of neuroimaging data. These recommendations are not meant to be prescriptive, to limit innovation, or to otherwise interfere with individual studies, but instead to facilitate comparing and combining neuroimaging data collected across institutions. As multicenter studies seem increasingly likely to become the most effective method to obtain adequate sample sizes to address core research questions in this area (eg, identification of risk factors for cancer- and treatment-related cognitive changes, examination of relative risk of various treatments), harmonization of imaging approaches could be very beneficial to the field. However, it is also critical to recognize that these are a set of core recommendations; studies focusing on innovative technologies to advance the field beyond existing approaches and data are also needed and encouraged.

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