Journal of Nuclear Medicine, published on October 10, 2019 as doi:10.2967/jnumed.119.237578

Long-Term Clinical and Neuronuclear Imaging Sequelae of Cancer Therapy, Trauma, and Brain Injury

April Alcantara[1]

Gholam R. Berenji[1,2]

Carole S. Scherling[3]

Beata Durcanova[1]

Daniel Diaz-Aguilar[1]

Daniel H. S. Silverman[1]

1. Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, CA
2. Department of Radiology, VA Greater Los Angeles Healthcare System, Los Angeles, CA
3. Department of Psychological Science, Belmont University, Nashville, TN

Corresponding Author:

Daniel H. Silverman

ucladgsomdan@gmail.com

Keywords: Neuroimaging; Cancer; Chemotherapy; Post-Traumatic; PTSD; Chronic Traumatic Brain Injury; TBI; Positron Emission Tomography; PET

Running Title: NEUROIMAGING CRCI, PTSD, TBI

ABSTRACT

Neuronuclear imaging has been utilized for several decades in the study of primary neurodegenerative conditions, such as dementia and parkinsonian syndromes, both for research and clinical purposes. There has been a relative paucity of application of neuronuclear imaging to evaluate non-neurodegenerative conditions that can also have long-term effects on cognition and function. This article summarizes clinical and imaging aspects of three such conditions that have garnered considerable attention in recent years: 1) cancer- and chemotherapy-related cognitive impairment, 2) post-traumatic stress disorder, and 3) traumatic brain injury. Further, we describe current research using neuroimaging tools aimed to better understand the relationships between the clinical presentations and brain structure and function in these conditions.

INTRODUCTION

While an extensive literature exists describing neuronuclear imaging studies of long-term cognitive effects of primary neurodegenerative disease on human brain, corresponding publications focused on non-neurodegenerative conditions are relatively sparse. The main purpose of the present paper is to review literature concerning three such conditions – changes in cerebral function associated with 1) cancer and chemotherapy (often referred to as "chemobrain" in lay literature), 2) post-traumatic stress disorder (PTSD), and 3) traumatic brain injury. Clinical aspects of evaluation and therapy are presented in some detail to provide context to the neuronuclear imaging findings to be reviewed for each condition – the latter most often assessed through positron emission tomography (PET) along with some single-photon emission computerized tomography (SPECT) studies of human brain, and also given additional breadth through descriptions of related functional MRI (fMRI) findings, as well as to stimulate future studies with heightened cognizance of current diagnostic and therapeutic limitations.

CANCER PATIENTS AND THE POST-CHEMOTHERAPY STATE: NEUROPSYCHOLOGY

In the United States, approximately 16 million people have a history of cancer (*1*), and cancer/chemotherapy-related cognitive impairment (CRCI) has frequently been reported by cancer patients after concluding treatment, with variable post-therapy duration of deficits ranging from months to years (*2*,*3*). The burden of CRCI has been increasing along with improved survival rates, with up to 35% of chemotherapy-treated patients now experiencing long-term cognitive sequelae (*4*).

Across cognitive studies, changes in memory and executive function are commonly reported (*5*). Some impairment may occur before treatment and, in addition to chemotherapy, factors like surgery, anesthesia, and concurrent endocrine and/or radiation interventions may also contribute to deficits. Generally, affected patients after chemotherapy report expending more effort to complete tasks, especially when facing multiple tasks in high-stress situations, and may suffer from difficulties with concentration, attention, thought processing, working memory, recall, word-finding, reasoning and problem-solving, as well as fatigue and mood dysregulation. Comparisons of typical neuropsychological features of CRCI with those of PTSD or physical trauma are summarized in Figure 1.

Neuropsychological evaluations include both verbal and written tests, with alternate test forms used for repeat administrations. Though magnitudes of neuropsychological deficits are not always well-correlated with patients' global impression of their deficits, a direct correlation specifically with patient memory and problem-solving complaints has been demonstrated (*6*). Dose-dependent side-effects have also been reported, showing a correlation between larger chemotherapy exposure and lower test scores (*7*).

Treatment protocols for CRCI include implementing stress management practices and establishing accommodations in the home and workplace to compensate for impairments and lessen distress. Medications such as antidepressants, anxiolytics and hypnotics, may help with coexisting and exacerbating problems. Some studies have shown promise in lessening cognitive decline and fatigue levels after chemotherapy with the use of stimulants like modafinil (*8*) and methylphenidate (*9*), and efficacy of antidementia drugs such as donepezil and memantine is also being explored (*10*), with the former seeming to be most useful for treating memory-related symptoms. In addition, studies have pointed to cognitive rehabilitation protocols to address specific cognitive sequelae (*11*), and physical activity (*12*) and meditation practices (*13*) may also be employed to lessen CRCI.

CRCI: NEUROIMAGING

While rates of ultimate reversibility of CRCI differ across studies, in part due to differences in the sensitivity and types of cognitive assessments administered, the majority of affected patients appear to normalize within one to two years. CRCI can nevertheless persist for periods exceeding one to two decades, and imaging studies have been performed documenting cerebral alterations across short-term and long-term time frames (Table 1). Although a number of CRCI neuroimaging review articles have been recently published, these have primarily focused upon MR imaging modalities (*14*); none has been previously focused on Nuclear Medicine imaging. The discussion here will concentrate on the latter, highlighting findings particularly from those studies examining metabolism with ^{18}F-fluoro-2-deoxy-D-glucose PET (^{18}F-FDG PET), by far the most well-studied in this field among Nuclear Medicine modalities.

In the first such investigation (*15*), both ^{18}F-FDG- and ^{15}O-water brain PET studies were performed in both healthy control subjects and in breast cancer patients previously treated or

untreated by chemotherapy. Altered functioning of the prefrontal cortex and cerebellum in patients previously treated with adjuvant therapy, 5-10 years after their last dose of chemotherapy, was found. During a short-term verbal memory task, the inferior and superior frontal gyri and posterior cerebellum displayed increased activity in the treated group. Further, each 3% decline in the ^{18}F-FDG resting metabolic activity of left inferior frontal gyrus corresponded to a one standard deviation decline on delayed recall cognitive performance ($p<0.0005$), and only for the chemotherapy-treated group. Chemotherapy patients who were also treated with endocrine therapy (tamoxifen) displayed further reduction of basal ganglia resting metabolism.

Subsequently, Baudino et al. reported altered brain metabolism, first across a variety of hematologic and solid malignancies (*16*), and then focusing exclusively on lymphoma patients (*17*). These studies were notable for examining relationships of regional brain metabolism to time since completion of chemotherapy and to number of chemotherapy cycles (Table 1). Both studies highlighted changes in prefrontal cortex, cerebellum, and limbic regions, negative correlations between number of cycles and metabolic activity, and increased activity with time after last dose of chemotherapy.

A study focusing on Hodgkin's patients by Chiaravalloti et al. (*18*) employed a longitudinal design, acquiring resting ^{18}F-FDG PET studies one week after diagnosis, approximately two weeks after the first two cycles of chemotherapy, and again after four additional one-month cycles. Metabolic reductions in bilateral dorsal anterior cingulate, prefrontal, and orbitofrontal cortex were observed after the first two cycles. Another longitudinal study carried out by Hsieh et al. (*19*) examined patients with pharyngeal squamous cell carcinoma who had been treated primarily with chemoradiation. They identified a number of time-sensitive metabolic alterations, including in the bilateral basal ganglia (Table 1).

A study by D'Agata et al. (*20*) analyzing metabolic data from lymphoma patients using a

network-based approach found significantly diminished metabolism in an identified prefrontal-cerebellar network, which was also capable of distinguishing between groups with 80% accuracy.

In a longitudinal study further extending the range of cancers investigated, Horky et al. (*21*) examined non-small-cell lung cancer survivors before and 11 days after platinum-based chemotherapy completion. Resting hypometabolism after chemotherapy was seen diffusely in gray matter structures, and most profoundly in bilateral frontal lobes.

In another longitudinal study, Hurria et. al (*22*) studied the effect of aromatase inhibition on outcomes of older breast cancer patients before and after 6 months of treatment compared with healthy controls, measuring neuropsychological performance and regional cerebral metabolism in a subset. In addition to hypometabolism near Broca's area in the posterior inferior frontal gyrus, areas of hypermetabolism in bilateral temporal and cerebellar regions were identified in treated subjects. Ponto et al. (*23*) also studied metabolic alterations in older breast cancer survivors compared to healthy controls, including some who had been concomitantly treated with tamoxifen, and also identified areas of regional hyper- and hypometabolism. Most recently, at the other end of the age spectrum, Shrot et al. studied children having non-Hodgkin lymphoma with ^{18}F-FDG PET, also identifying regions of hyper- and hypometabolism, though all of these latter patients' central nervous systems had direct substantial exposure to chemotherapy agents through intrathecal administration, and so potentially involve other mechanisms of injury (*24*).

As seen in discussion of the above, the prefrontal cortex, a part of the brain critical for executive function, has been the most consistently metabolically affected region in patients with CRCI. Limbic/temporal structures, and cerebellum have been the structures next most often reported to be affected by neuroimaging measures and are known to be important for memory, verbal abilities, and visuospatial functions (*25*).

Studies of CRCI have involved a broad array of chemotherapy agents and regimens (Table

1), and specific risks and patterns of neuropsychologic deficits by agent or dose remain mostly undetermined (*26*). Chemotherapy dose-response relationships have been observed, however, when comparing changes in patients to number of doses (*7*), or to magnitude of dose (*27*). There are also several agents that have been implicated in more severe changes in brain function, including carmustine, cisplatin, cytarabine, fludarabine, 5-fluorouracil, and methotrexate (*28*).

Multiple mechanisms could give rise to the observed alterations. These range from direct toxic effects of some chemotherapy agents (which might be expected with higher penetrance across the blood-brain barrier), oxidative damage, metabolic dysregulation and triggering of immune system and inflammatory responses, including through cytokine release. The last of these has been directly tied to alterations in brain metabolism. This is of particular interest since elevated circulating cytokine levels can be present for months to years after initial treatment for cancer and are known to be associated with neurotoxic effects. In a systematic examination with respect to several inflammatory markers, those cytokine levels occurring soon after chemotherapy have predicted patterns of brain metabolism occurring even a year later (*29*). It should also be noted that the mechanisms suggested above are not necessarily competing, but can work in concert, either in parallel fashion or in series. For example, oxidative stress mediated by increasing plasma superoxide levels can in turn trigger release of neurotoxic cytokines capable of penetrating the blood-brain barrier. Moreover, a wide range of chemotherapeutics including anthracyclines, antimetabolites and alkylating agents are known to produce such intermediaries, which helps to explain why multiple classes of chemotherapy agents treating multiple kinds of cancer may lead to such overlapping profiles of cognitive dysfunction and associated patterns of altered brain chemistry.

POST-TRAUMATIC STRESS DISORDER: DIAGNOSIS AND THERAPY

PTSD has been conceptualized as a memory persistence disorder, in which patients "relive their trauma in the form of involuntary recollection," with distressing recollections being "vivid" and "long-lasting" (*30*). The U.S. National Comorbidity Survey Replication found a lifetime prevalence of PTSD of approximately 7% among adult Americans (*31*). Globally, analysis of World Mental Health surveys have found significant differences in prevalence rates of PTSD (*32*). The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria for PTSD (*33*) require the survivor to have been exposed to or threatened by a traumatic event, directly or indirectly. Patients re-experience the events through intrusive thoughts, nightmares, memories, flashbacks and other traumatic recollections. They often demonstrate a distorted sense of blame concerning the traumatic event, decreased social engagement, increased arousal to future threats, concentration difficulties, irritability, anger, sleep dysregulation and hypervigilance. To meet diagnostic criteria, symptoms must persist for at least 1 month, seriously affects one's ability to function and be unrelated to drug use or other medical illness (*33*). PTSD often coincides with other co-morbid conditions such as Traumatic Brain Injury (TBI) (*34*) and depression (*35*), making it more challenging to diagnose or study the disorder, and complicating treatment.

Psychotherapy is the initial basis of treatment for PTSD, and various drug therapies adjunctive to psychotherapy are typically added, though there remains a pressing need for development of new therapies (*36*). Selective serotonin reuptake inhibitors have shown efficacy in symptomatic relief and decreasing rates of relapse, as have norepinephrine reuptake inhibitors (*37*). Other drugs used to treat and resolve ancillary symptoms, such as intrusion and hyper-arousal include alpha- and beta-blockers (*38*), and more recently, novel treatments such as ketamine (*39*). Considered to have strong research support by the American Psychiatric

Association, US Department of Defense and Department of Veterans Affairs, Cognitive Processing Therapy (CPT) has been successful in reducing feelings of fear and culpability in PTSD (*40*). CPT typically consists of twelve 60-90 minute sessions that focus on changing the patients' understanding and conceptualization of their trauma, and recently, intense versions of CPT have demonstrated heightened treatment success and faster recovery times (*41*).

POST-TRAUMATIC STRESS DISORDER: NEUROIMAGING

Neuroimaging studies have been directed toward understanding the biochemical mechanisms that underlie the pathophysiology of PTSD. Several brain areas have been implicated by neuroimaging modalities in PTSD, and here we focus on more recent studies making use of three neuroimaging modalities, most often fMRI, but also PET or SPECT.

Neurocircuitry Model Of PTSD

The hypothalamic pituitary adrenal (HPA) axis is primarily responsible for mediating stress responses and controls the level of cortisol circulating in the body (*42*). Inputs from the amygdala, medial prefrontal cortex (mPFC), and hippocampus activate the HPA axis, and these regions have been widely identified as having altered function or structure in PTSD. Converging lines of evidence from imaging studies indicate that the ventromedial prefrontal cortex inhibits or modulates the activity of the amygdala and anterior insula, suggesting a basis for understanding relationships between these regions in patients with PTSD (*43*). Further roles of key brain regions are highlighted below, with additional details described in Table 2.

Amygdala

The amygdala has consistently been demonstrated to show hyperactivity in PTSD, which manifests in an exaggerated response to traumatic or fearful stimuli (*44*). Recent literature has

moved towards understanding subtle differences in amygdala activity, including studying different trauma types, as they pertain to subregions of the amygdala, and amygdala volume (*45*). In an ^{18}F-FDG PET study on active duty treatment-seeking US Army Soldiers with PTSD, in patients who experienced danger-based trauma decreased metabolism in the left amygdala was associated with PTSD severity. In PTSD patients without danger-based trauma, decreased metabolism in the right amygdala was associated with PTSD severity (*46*). Recent studies have also explored discrete amygdala subregions involved in encoding of emotional events, including the basolateral subdivision and the centromedial amygdala (*47*). (Table 2)

Medial Prefrontal Cortex

The mPFC has been consistently established as a region involved in emotional regulation, and its failure to inhibit the amygdala in PTSD has been thought to lead to impaired fear extinction. An early study using ^{15}O-CO_2 PET imaging in Vietnam veterans who experienced combat or served as nurses in the combat theater found that veterans with PTSD had lower resting cerebral blood flow in the mPFC compared to those without PTSD (*48*), and in general, various neuroimaging studies focused on the prefrontal cortex of PTSD patients demonstrate hypoactivity in this region.

Hippocampus

Neuronal atrophy and synaptic degeneration in the hippocampus can result from stress and trauma (*45*). The largest neuroimaging study to include a focus on PTSD to date, "ENIGMA - Enhancing Neuroimaging Genetics through Meta-Analysis," recently found smaller hippocampal volumes in PTSD subjects compared to trauma-exposed control subjects (*49*), an effect that remained highly significant after adjustment for multiple comparisons. Some studies have also reported diminished hippocampal metabolism and cerebral blood flow associated with PTSD; but although PTSD patients can experience cognitive dysfunction and are at increased risk for

development of AD, its associated pathology appears to be distinct from AD-related pathology with respect to medial temporal atrophy as well as amyloid positivity, when compared to suitable control subjects (*50*,*51*). Since exposure to traumatic events does not always lead to developing PTSD, it has been postulated that functional and structural abnormalities of the hippocampus may predispose an individual to PTSD (*52*). At this point, it remains unclear whether decreased volume and activity of the hippocampus precede or follow development of PTSD.

Functional Connectivity

Functional connectivity is operationally defined in PET and fMRI studies by identifying sets of regions having activity co-varying with each other in individual subjects measured across multiple time points (*53*). Many studies have examined differences in functional connectivity between the amygdala, mPFC, and hippocampus. One such study suggests that the pathogenesis of PTSD may be associated with increased amygdala connectivity with mPFC and hippocampus, and decreased amygdala connectivity with the inferior mPFC and insula (*54*).

Default mode network (DMN) is defined by the set of brain regions having their highest activity levels in a group of subjects during the resting state, which then decrease together during cerebral stimulation. In a number of studies, patients with PTSD demonstrate abnormal levels of activity in these regions during the resting state. Further, ^{11}C-flumazenil PET reveals that patients with PTSD have higher benzodiazepine receptor binding in dorsal and superior anterior cingulate cortex and precuneus, regions known to play a key role in the default mode network (*55*). In brain perfusion SPECT studies of veterans with PTSD, TBI, and PTSD/TBI, the DMN has been found to distinguish between PTSD, which demonstrates hyperperfusion, and mechanical minor traumatic brain injury, which demonstrates hypoperfusion (*56*). However, lack of longitudinal MRI studies and small sample sizes make it difficult to ascertain how soon these findings are

present after trauma occurs. Neuropathological markers that may affect DMN activity are also being examined, such as amyloid-beta deposition, with voxel-based data suggesting that small focal accumulations of amyloid may occur especially in temporal lobes of PTSD patients, despite lack of significant global cortical amyloid accumulation (*57*,*58*).

Imaging Treatment of PTSD

Given that 30-50% of PTSD patients fail to respond positively to treatment, some studies have investigated the use of neuroimaging to predict treatment outcomes. For example, in a fMRI study on war veterans with and without PTSD, increased insula, dorsal anterior cingulate cortex, and amygdala activation predicted persistence of PTSD symptoms after treatment (*59*). In terms of monitoring responses, psychotherapy has been shown to increase prefrontal dorsal anterior cingulate and hippocampal activity, and to reduce amygdala activity (*60*), while ^{15}O-water PET studies of mindfulness-based therapy for combat veterans have pointed to associated increases in anterior cingulate activity, along with decreased insula and precuneus activity (*61*). Changes in the amygdala, insula, and anterior cingulate cortex may also predict response to psychotherapy treatment, with for example higher baseline amygdala activity corresponding to worse treatment response (*62*). Preliminary studies also suggest that intranasal oxytocin may diminish the amygdala and ventrolateral prefrontal cortical functional connectivity (*63*).

TRAUMATIC BRAIN INJURY: NEUROPSYCHOLOGIC EVALUATION AND PROGNOSIS

Traumatic brain injury (TBI) involves mechanical "traumatically induced physiological disruption of brain function," characterized by at least one of the following: loss of consciousness, memory loss for events surrounding the accident, alterations of mental state at the time of the

accident and/or focal neurological deficits. In the United States, TBI has an estimated prevalence of approximately 5 million people and annual incidence of 200 cases per 100,000 people (*64*), though several epidemiological studies have noted difficulties in estimating prevalence and incidence of TBI due to the heterogeneity of age, sex, severity, and methods across studies. In addition, cases of TBI are often not reported by patients or not detected by health care professionals (*65*). The 2008 Rand Report found that 7% of troops who served in Afghanistan and Iraq suffered from TBI with co-morbid PTSD or depression (*66*). Tests for TBI, including a complex battery like the Glasgow Coma Scale (GCS), assess physical injuries, brain and nerve functioning, level of consciousness, speech, language, as well as cognitive and neuropsychological abilities, such as thinking, reasoning, problem solving and memory, ranking these from mild to severe. *Mild* TBI, the main focus here, requires any loss of consciousness to be for less than 30 minutes, period of memory loss limited to less than 24 hours and a GCS of at least 13 out of 15 possible points. Prior studies have found an association between moderate to severe TBI and increased risk of developing dementia. Evidence based on a large, retrospective cohort of veterans indicates that even mild TBI without loss of consciousness may double the risk of dementia diagnosis (*67*).

Cognitive domains typically affected by mild TBI include attention, memory, executive functioning, and information processing (*68*). Behavioral and affective changes can further complicate both diagnosis and treatment, including anxiety, irritability and compromised social functioning, with depression being the most frequent psychiatric diagnosis one year post-injury.

Treatment of TBI is tailored to patient complaints and the extent of injury. Pharmacological treatments may aid in alleviating some TBI symptomatology and lowering some commonly associated risks, such as seizures and sleeping dysregulations. Stimulants, such as methylphenidate, may aid patients in the acute phase regarding concentration, attention and motor memory, and shorten recovery time. A variety of applied behavioral and cognitive therapies have

also been effective for some patients, including physical, occupational, speech, and vocational therapy, as well as psychological counseling, cognitive therapies, and mindfulness training (*69*).

TRAUMATIC BRAIN INJURY: NEURONUCLEAR IMAGING

While imaging is one of the first-line interventions after a head trauma, its application in the post-acute and chronic phases of traumatic brain injury remains controversial. Variability in several factors in TBI pose challenges to interpreting imaging studies. These include mechanism of injury, variable period for manifestation of delayed sequelae, and confounding effects of accompanying factors such as PTSD or substance abuse (*70*).

Performing a computed tomography (CT) or MRI scan can be critical in the acute stages of a head injury to evaluate intracranial bleeding and structural damage. Non-contrast enhanced CT is the modality of choice in moderate and severe TBI for decision on admission to hospital and surgical intervention. MRI is considered as the second imaging modality of choice in moderate and severe TBI, if CT results need clarification. Increased sensitivity in MRI helps to identify brain tissue contusions or further validate negative findings on CT scans. Neither CT nor MRI has been shown to significantly impact evaluation of mild TBI, however, beyond excluding possible structural abnormalities.

Although there has been much interest in evaluating applications of ^{18}F-FDG PET and other neuronuclear imaging modalities in TBI, the clinical utility remains unclear. Some studies report immediate changes in glucose metabolism in whole brain, while patients experiencing a single episode of blunt trauma may have altered patterns particularly of prefrontal and limbic metabolism even years later (*71*). Several other studies have shown abnormally reduced regional metabolism, especially in cerebellum, in patients with blast-induced TBI. Initial patterns of ^{18}F-FDG PET metabolism, however, may substantially differ even among individuals with very

similar mechanisms of injury; such imaging studies may nonetheless lend themselves to intra-individual longitudinal assessments (*72*).

The recent recognition of the magnitude of the problems of TBI and Chronic Traumatic Encephalopathy (CTE) along with their associations with tauopathy has led to increased exploration with other tracers. Along these lines, ^{18}F-FDDNP, ^{11}C-PBB3, ^{18}F-THK5351 and ^{18}F-flortaucipir (also known as ^{18}F-T807 and ^{18}F-AV1451) have been used in evaluation of tau deposits in the brain. For example, ^{18}F-flortaucipir has demonstrated multifocal increased uptake in the gray-white matter junction, corresponding to the tauopathy that is diagnostic for CTE (*73*). Most recently, its uptake has been reported in frontal, parietal, and temporal regions in symptomatic NFL players, as well as in variable distributions in some patients with single TBI episodes, occurring many years prior to PET (*74*,*75*). Further studies in subjects with TBI and CTE are needed to evaluate these radiotracers and their relationship to nature and severity of clinical symptoms, and the bases for wide interindividual variability in their uptake patterns.

Other PET imaging studies, examining post-traumatic neuroinflammation or dopaminergic pathway alterations (*76*,*77*), are now being evaluated in larger cohorts. In an early study of patients with recurrent head trauma, ^{18}F-FDOPA helped to differentiate posttraumatic parkinsonism from Parkinson's disease (*76*). Microglial activation in post-TBI subjects has been evaluated by imaging translocator protein (TSPO) ligands in several studies. For example, ^{11}C-PK11195 has demonstrated increased uptake in subcortical structures including thalami, putamen, and parts of white matter in subjects with chronic single moderate to severe TBI (*78*). Furthermore, these findings have been replicated in additional studies using second-generation TSPO ligands ^{11}C-DPA-713, ^{18}F-DPA-714 (*79*), and ^{11}C-PBR28 (*77*).

GENERAL CONSIDERATIONS

There are a number of issues and limitations that apply broadly across the clinical conditions described above. For example, it should be noted that there are not yet sufficient compelling data to suggest adequate sensitivity or specificity at the individual level to be able to reliably apply the regional brain data in a clinically diagnostic or prognostic manner. Rather, the data have been mostly obtained at the group level to gain some insight on underlying neurological substrates for the syndromes under study. Relatedly, in general, the findings would not be expected to necessarily be identified through visual image readings of individual brains, but rather emerge from either of the two kinds of quantitative methods used in the papers discussed, voxel-based and volume-of-interest based, for which age-matched comparisons are typically applied. Consequently, with respect to who should be imaged and why in a more routine clinical manner, this currently makes the most sense in the context of differentiating these conditions from neurologic changes such as occur in early stages of neurodegenerative disease (particularly in older patients), for which characteristic findings of more established clinical significance have been extensively documented. The reassurance that can be provided to a CRCI patient, for instance, that she or he is not suffering from inexorably progressive comorbid Alzheimer's disease (AD) can be valuable and, conversely, identifying signature neuroimaging findings of that disease, leading to initiation of appropriate treatment, may also be useful.

As it required over three decades of study with neuronuclear imaging methods of even the most common neurodegenerative conditon, AD, before large databases were prospectively amassed that allowed for systematic, generalizable findings, so it is with the current phase of our understanding of the conditions considered here. For example, limitations that are common to neuronuclear imaging studies on CRCI include relatively small sample sizes, the wide variety of

chemotherapy agents and combinations of agents pooled into each analysis (also a necessary function of limited sample sizes), and inherent difficulty of matching patients with similar cancer histologies and stages who have nevertheless been with and without chemotherapy exposure. Neuroimaging studies on PTSD are typically marked by small sample sizes, psychiatric and other comorbidities, a wide range of types of events leading to PTSD, and confounds related to medications used. Similarly, neuroimaging studies on TBI are often limited by relatively small sample sizes, multiple comorbidities (including PTSD), the lack in most studies of correlative neuropathologic data, and frequently lack of longitudinal assessments. In many respects, we are still in relatively early stages of understanding the underlying neurobiologic changes in these conditions, along with how they are related to observed clinical manifestations, and imaging-based studies are playing a leading role in contributing to their elucidation. Moving forward, as we gain a deeper understanding of features of these conditions that may be detected and measured through brain imaging, studies will be needed that individually examine large series of regionally quantified scans, to assess accuracy and incremental value in answering questions clinically pertinent to the treatment and outcomes of patients suffering from them.

DISCLOSURE

No potential conflicts of interest relevant to this article exist.

REFERENCES

1. American Cancer Society. *Cancer Treatment & Survivorship Facts & Figures 2016-2017*; 2016:1.

2. Ruiter MB de, Reneman L, Boogerd W, et al. Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. *Hum Brain Mapp*. 2011;32:1206-1219.

3. Koppelmans V, Breteler MMB, Boogerd W, Seynaeve C, Schagen SB. Late effects of adjuvant chemotherapy for adult onset non-CNS cancer; cognitive impairment, brain structure and risk of dementia. *Crit Rev Oncol Hematol*. 2013;88:87-101.

4. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry*. 2014;26:102-113.

5. Scherling CS, Smith A. Opening up the window into "chemobrain": a neuroimaging review. *Sensors (Basel)*. 2013;13:3169-3203.

6. Ganz PA, Kwan L, Castellon SA, et al. Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. *J Natl Cancer Inst*. 2013;105:791-801.

7. Collins B, MacKenzie J, Tasca GA, Scherling C, Smith A. Cognitive effects of chemotherapy in breast cancer patients: a dose–response study. *Psychooncology*. 2013;22:1517-1527.

8. Kohli S, Fisher SG, Tra Y, et al. The effect of modafinil on cognitive function in breast cancer survivors. *Cancer*. 2009;115:2605-2616.

9. Gong S, Sheng P, Jin H, et al. Effect of methylphenidate in patients with cancer-related fatigue: a systematic review and meta-analysis. *PLoS One*. 2014;9:e84391.

10. Karschnia P, Parsons MW, Dietrich J. Pharmacologic management of cognitive impairment induced by cancer therapy. *Lancet Oncol*. 2019;20:e92-e102.

11. Ferguson RJ, McDonald BC, Rocque MA, et al. Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial. *Psychooncology*. 2012;21:176-186.

12. Fardell JE, Vardy J, Shah JD, Johnston IN. Cognitive impairments caused by oxaliplatin and 5-fluorouracil chemotherapy are ameliorated by physical activity. *Psychopharmacology (Berl)*. 2012;220:183-193.

13. Biegler KA, Chaoul MA, Cohen L. Cancer, cognitive impairment, and meditation. *Acta Oncol*. 2009;48:18-26.

14. Li M, Caeyenberghs K. Longitudinal assessment of chemotherapy-induced changes in brain and cognitive functioning: A systematic review. *Neurosci Biobehav Rev*. 2018;92:304-317.

15. Silverman DH, Dy CJ, Castellon SA, et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5-10 years after chemotherapy. *Breast Cancer Res Treat*. 2007;103:303-311.

16. Baudino B, D'Agata F, Castellano G, et al. Chemotherapy effects on brain glucose metabolism at rest. *Nat Precedings*. 2011. doi: hdl:10101/npre.2011.5637.1.

17. Baudino B, D'agata F, Caroppo P, et al. The chemotherapy long-term effect on cognitive functions and brain metabolism in lymphoma patients. *Q J Nucl Med Mol Imaging*. 2012;56:559-568.

18. Chiaravalloti A, Pagani M, Pietro BD, et al. Is cerebral glucose metabolism affected by chemotherapy in patients with Hodgkin's lymphoma? *Nucl Med Commun*. 2013;34:57-63.

19. Hsieh T-C, Wu Y-C, Yen K-Y, Chen S-W, Kao C-H. Early changes in brain FDG metabolism during anticancer therapy in patients with pharyngeal cancer. *J Neuroimaging*. 2014;24:266-272.

20. D'Agata F, Costa T, Caroppo P, et al. Multivariate analysis of brain metabolism reveals chemotherapy effects on prefrontal cerebellar system when related to dorsal attention network. *EJNMMI Res*. 2013;3:22.

21. Horky LL, Gerbaudo VH, Zaitsev A, et al. Systemic chemotherapy decreases brain glucose metabolism. *Ann Clin Transl Neurol*. 2014;1:788-798.

22. Hurria A, Patel SK, Mortimer J, et al. The effect of aromatase inhibition on the cognitive function of older patients with breast cancer. *Clin Breast Cancer*. 2014;14:132-140.

23. Ponto LLB, Menda Y, Magnotta VA, Yamada TH, Denburg NL, Schultz SK. Frontal hypometabolism in elderly breast cancer survivors determined by [(18)F]fluorodeoxyglucose (FDG) positron emission tomography (PET): a pilot study. *Int J Geriatr Psychiatry*. 2015;30:587-594.

24. Shrot S, Abebe-Campino G, Toren A, Ben-Haim S, Hoffmann C, Davidson T. Fluorodeoxyglucose detected changes in brain metabolism after chemotherapy in pediatric non-Hodgkin lymphoma. *Pediatric Neurology*. 2019;92:37-42.

25. Kaiser J, Bledowski C, Dietrich J. Neural correlates of chemotherapy-related cognitive impairment. *Cortex*. 2014;54:33-50.

26. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J Clin*. 2015;65:123-138.

27. van Dam FSAM, Boogerd W, Schagen SB, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *J Natl Cancer Inst*. 1998;90:210-218.

28. Wefel JS, Schagen SB. Chemotherapy-related cognitive dysfunction. *Curr Neurol Neurosci Rep*. 2012;12:267-275.

29. Pomykala KL, Ganz PA, Bower JE, et al. The association between pro-inflammatory cytokines, regional cerebral metabolism, and cognitive complaints following adjuvant chemotherapy for breast cancer. *Brain Imaging Behav*. 2013;7:511-523.

30. Banich MT, Mackiewicz KL, Depue BE, Whitmer A, Miller GA, Heller W. Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. *Neurosci Biobehav Rev*. 2009;33:613-630.

31. Gradus JL. Epidemiology of PTSD - PTSD: National Center for PTSD. https://www.ptsd.va.gov/professional/treat/essentials/epidemiology.asp. Updated June 6, 2019. Accessed June 25, 2019.

32. Atwoli L, Stein DJ, Koenen KC, McLaughlin KA. Epidemiology of posttraumatic stress disorder: prevalence, correlates and consequences. *Curr Opin Psychiatry*. 2015;28:307-311.

33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington D.C.: American Psychiatric Association; 2013.

34. Mohamed AZ, Cumming P, Götz J, Nasrallah F, for the Department of Defense Alzheimer's Disease Neuroimaging Initiative. Tauopathy in veterans with long-term posttraumatic stress disorder and traumatic brain injury. *Eur J Nucl Med Mol Imaging*. 2019;46:1139–1151.

35. Rytwinski NK, Scur MD, Feeny NC, Youngstrom EA. The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. *J Trauma Stress*. 2013;26:299-309.

36. Forbes D, Pedlar D, Adler AB, et al. Treatment of military-related post-traumatic stress disorder: challenges, innovations, and the way forward. *International Review of Psychiatry*. 2019;31:95-110.

37. Hoskins M, Pearce J, Bethell A, et al. Pharmacotherapy for post-traumatic stress disorder: Systematic review and meta-analysis. *Br J Psychiatry*. 2015;206:93-100.

38. Khachatryan D, Groll D, Booij L, Sepehry AA, Schütz CG. Prazosin for treating sleep disturbances in adults with posttraumatic stress disorder: a systematic review and meta-analysis of randomized controlled trials. *Gen Hosp Psychiatry*. 2016;39:46-52.

39. Liriano F, Hatten C, Schwartz TL. Ketamine as treatment for post-traumatic stress disorder: a review. *Drugs Context*. 2019;8:dic.212305.

40. Asmundson GJG, Thorisdottir AS, Roden-Foreman JW, et al. A meta-analytic review of cognitive processing therapy for adults with posttraumatic stress disorder. *Cognitive Behaviour Therapy*. 2019;48:1-14.

41. Murray H, El-Leithy S, Billings J. Intensive cognitive therapy for post-traumatic stress disorder in routine clinical practice: A matched comparison audit. *Br J Clin Psychol*. 2017;56:474-478.

42. Dunlop BW, Wong A. The hypothalamic-pituitary-adrenal axis in PTSD: pathophysiology and treatment interventions. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;89:361-379.

43. Andrewes DG, Jenkins LM. The role of the amygdala and the ventromedial prefrontal cortex in emotional regulation: implications for post-traumatic stress disorder. *Neuropsychol Rev*. 2019;29:220-243.

44. Im JJ, Namgung E, Choi Y, Kim JY, Rhie SJ, Yoon S. Molecular neuroimaging in posttraumatic stress disorder. *Exp Neurobiol*. 2016;25:277-295.

45. Henigsberg N, Kalember P, Petrović ZK, Šečić A. Neuroimaging research in posttraumatic stress disorder – Focus on amygdala, hippocampus and prefrontal cortex. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;90:37-42.

46. Ramage AE, Litz BT, Resick PA, et al. Regional cerebral glucose metabolism differentiates danger- and non-danger-based traumas in post-traumatic stress disorder. *Soc Cogn Affect Neurosci*. 2016;11:234-242.

47. Patel R, Girard TA, Pukay-Martin N, Monson C. Preferential recruitment of the basolateral amygdala during memory encoding of negative scenes in posttraumatic stress disorder. *Neurobiol Learn Mem*. 2016;130:170-176.

48. Gold AL, Shin LM, Orr SP, et al. Decreased regional cerebral blood flow in medial prefrontal cortex during trauma-unrelated stressful imagery in Vietnam veterans with post-traumatic stress disorder. *Psychol Med*. 2011;41:2563-2572.

49. Logue MW, van Rooij SJH, Dennis EL, et al. Smaller hippocampal volume in posttraumatic stress disorder: a multisite ENIGMA-PGC study: subcortical volumetry results from posttraumatic stress disorder consortia. *Biological Psychiatry*. 2018;83:244-253.

50. Kim S-Y, Chung Y-K, Kim BS, Lee SJ, Yoon J-K, An Y-S. Resting cerebral glucose metabolism and perfusion patterns in women with posttraumatic stress disorder related to sexual assault. *Psychiatry Res*. 2012;201:214-217.

51. Weiner MW, Harvey D, Hayes J, et al. Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: Preliminary report. *Alzheimers Dement (NY)*. 2017;3:177-188.

52. Holzschneider K, Mulert C. Neuroimaging in anxiety disorders. *Dialogues Clin Neurosci*. 2011;13:453-461.

53. Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Functional connectivity: the principal-component analysis of large (PET) data sets. *J Cereb Blood Flow Metab*. 1993;13:5-14.

54. Zhang Y, Xie B, Chen H, Li M, Guo X, Chen H. Disrupted resting-state insular subregions functional connectivity in post-traumatic stress disorder. *Medicine (Baltimore)*. 2016;95.

55. Reuveni I, Nugent AC, Gill J, et al. Altered cerebral benzodiazepine receptor binding in post-traumatic stress disorder. *Transl Psychiatry*. 2018;8:206.

56. Raji CA, Willeumier K, Taylor D, et al. Functional neuroimaging with default mode network regions distinguishes PTSD from TBI in a military veteran population. *Brain Imaging Behav*. 2015;9:527-534.

57. Mohamed AZ, Cumming P, Srour H, et al. Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. *Neuroimage Clin*. 2018;19:716-726.

58. Mohamed AZ, Cumming P, Srour H, et al. Corrigendum to 'Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury' NeuroImage: CLINICAL. 19 (2018) 716–726. *NeuroImage: Clinical*. 2019;22:101829.

59. van Rooij SJH, Kennis M, Vink M, Geuze E. Predicting treatment outcome in PTSD: a longitudinal functional MRI study on trauma-unrelated emotional processing. *Neuropsychopharmacology*. 2016;41:1156-1165.

60. Thomaes K, Dorrepaal E, Draijer N, Jansma EP, Veltman DJ, van Balkom AJ. Can pharmacological and psychological treatment change brain structure and function in PTSD? A systematic review. *J Psychiatr Res*. 2014;50:1-15.

61. Bremner JD, Mishra S, Campanella C, et al. A pilot study of the effects of mindfulness-based stress reduction on post-traumatic stress disorder symptoms and brain responses to traumatic reminders of combat. *Front. Psychiatry*. 2017; 8:157,1-15

62. Szeszko PR, Yehuda R. Magnetic resonance imaging predictors of psychotherapy treatment response in post-traumatic stress disorder: A role for the salience network. *Psychiatry Research*. 2019;277:52-57.

63. Frijling JL, van Zuiden M, Koch SBJ, Nawijn L, Veltman DJ, Olff M. Intranasal oxytocin affects amygdala functional connectivity after trauma script-driven imagery in distressed recently trauma-exposed individuals. *Neuropsychopharmacology*. 2016;41:1286-1296.

64. Popescu C, Anghelescu A, Daia C, Onose G. Actual data on epidemiological evolution and prevention endeavours regarding traumatic brain injury. *J Med Life*. 2015;8:272-277.

65. Nguyen R, Fiest KM, McChesney J, et al. The international incidence of traumatic brain injury: a systematic review and meta-analysis. *Can J Neurol Sci*. 2016;43:774-785.

66. Tanielian T, Jaycox LH, Adamson DM, et al. *Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery.* Santa Monica, CA: RAND Corporation; 2008.

67. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. *JAMA Neurol*. 2018;75:1055-1061.

68. Vanderploeg RD, Curtiss G, Belanger HG. Long-term neuropsychological outcomes following mild traumatic brain injury. *J Int Neuropsychol Soc*. 2005;11:228-236.

69. Bédard M, Felteau M, Marshall S, et al. Mindfulness-based cognitive therapy reduces symptoms of depression in people with a traumatic brain injury: results from a randomized controlled trial. *J Head Trauma Rehabil*. 2014;29:E13.

70. DeKosky ST, Ikonomovic MD, Gandy S. Traumatic brain injury — football, warfare, and long-term effects. *N Engl J Med*. 2010;363:1293-1296.

71. Komura A, Kawasaki T, Yamada Y, Uzuyama S, Asano Y, Shinoda J. Cerebral glucose metabolism in patients with chronic mental and cognitive sequelae after a single blunt mild traumatic brain injury without visible brain lesions. *J Neurotrauma*. 2019;36:641-649.

72. Mendez MF, Owens EM, Reza Berenji G, Peppers DC, Liang L-J, Licht EA. Mild traumatic brain injury from primary blast vs. blunt forces: post-concussion consequences and functional neuroimaging. *NeuroRehabilitation*. 2013;32:397-407.

73. Dickstein DL, Pullman MY, Fernandez C, et al. Cerebral [18 F]T807/AV1451 retention pattern in clinically probable CTE resembles pathognomonic distribution of CTE tauopathy. *Transl Psychiatry*. 2016;6:e900.

74. Stern RA, Adler CH, Chen K, et al. Tau positron-emission tomography in former National Football League players. *N Engl J Med*. 2019;380:1716-1725.

75. Gorgoraptis N, Li LM, Whittington A, Zimmerman KA, Maclean LM, McLeod C, Ross E, Heslegrave A, Zetterberg H, Passchier J, Matthews PM, Gunn RN, McMillan TM, Sharp DJ. In vivo detection of cerebral tau pathology in long-term survivors of traumatic brain injury. *Sci Transl Med.* 2019;11:508.1-508.14.

76. Turjanski N, Lees AJ, Brooks DJ. Dopaminergic function in patients with posttraumatic parkinsonism: an 18F-dopa PET study. *Neurology*. 1997;49:183-189.

77. Coughlin JM, Wang Y, Munro CA, et al. Neuroinflammation and brain atrophy in former NFL players: An in vivo multimodal imaging pilot study. *Neurobiol Dis*. 2015;74:58-65.

78. Ramlackhansingh AF, Brooks DJ, Greenwood RJ, et al. Inflammation after trauma: Microglial activation and traumatic brain injury. *Ann Neurol*. 2011;70:374-383.

79. Hosomi S, Watabe T, Mori Y, et al. Inflammatory projections after focal brain injury trigger neuronal network disruption: An ^{18}F-DPA714 PET study in mice. *Neuroimage Clin*. 2018;20:946-954.

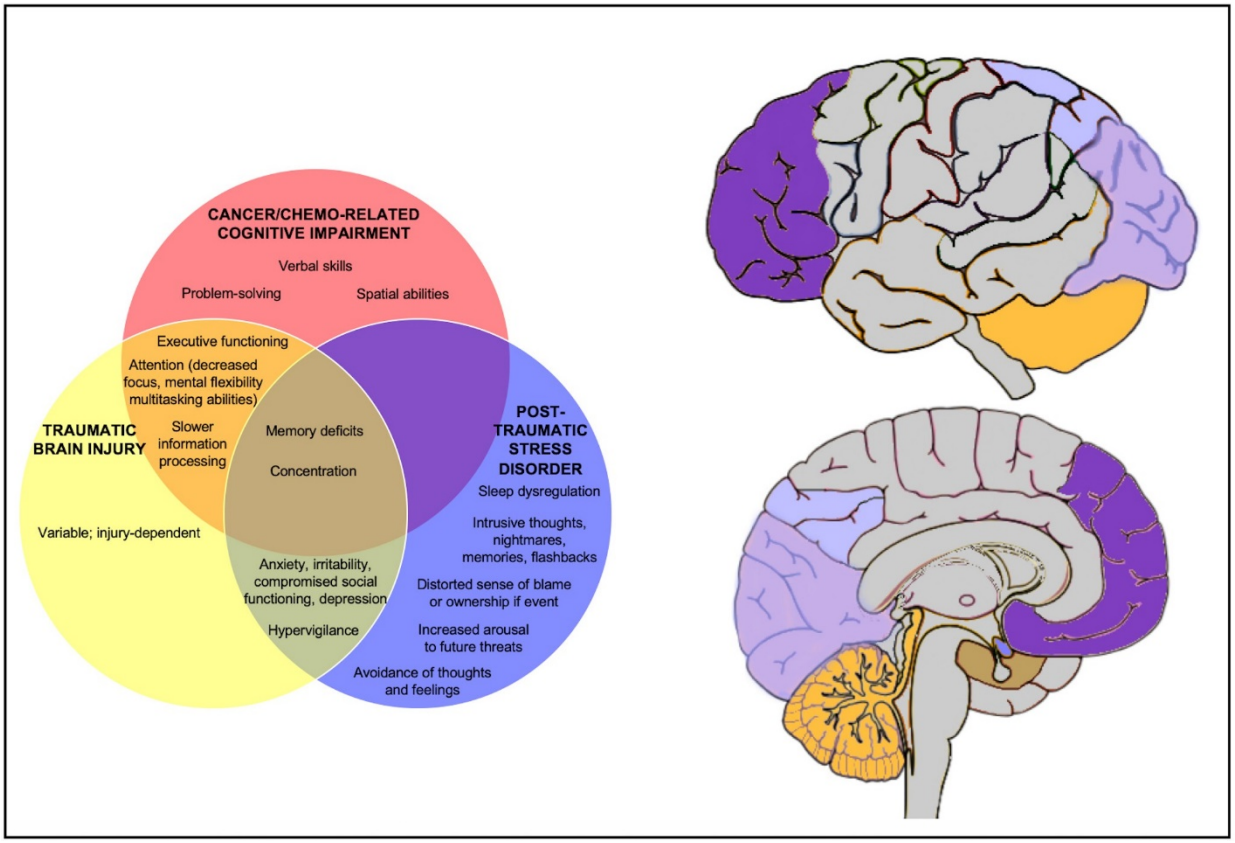

FIGURE 1: Venn diagram describes key clinical features (red = CRCI, blue = PTSD, yellow = TBI). Brain slices on the right show corresponding brain regions implicated in these disorders. Areas in darker shades occur most consistently in literature. Although not depicted due to internal location, basal ganglia structures have also been implicated in several CCRI and PTSD studies.

TABLE 1: Summary of neuroimaging findings in CRCI studies

Reference #	Imaging	Chemotherapeutic Drugs Used (*Not Further Detailed)	Main Findings
(*15*)	^{15}O-water PET and ^{18}F-FDG PET	• cytotoxic chemotherapy* • tamoxifen therapy*	• **INCREASED** activation in prefrontal cortex and cerebellum during short-term memory recall task in chemotherapy-treated patients • **DECREASED** prefrontal cortex resting metabolism in correlation with decreased short-term memory • Basal ganglia resting metabolism **DECREASED** in patients with tamoxifen and chemotherapy-treated compared with chemotherapy-only breast cancer patients or patients without chemotherapy
(*16*)	^{18}F-FDG PET/CT	• Systemic CHT*	• Early High chemo group had **DECREASED** metabolism of prefrontal cortex, white matter, cerebellum, posterior medial cortices, and limbic regions compared to group without chemotherapy • Early High chemo group had **DECREASED** metabolism of right temporal and PFC compared to Late Low chemo group • Number of cycles negatively correlated with rate of metabolism in these regions • Post-chemotherapy time positively correlated with rate of metabolism in these regions
(*17*)	^{18}F-FDG PET/CT	• CHT*	• **DECREASED** metabolism in prefrontal cortex, cerebellum, medial cortex, and limbic regions in chemotherapy group • Metabolism of these regions negatively correlated with number of cycles and positively with post-chemotherapy time • Poorer performance in many frontal functions in chemotherapy group
(*18*)	^{18}F-FDG PET/CT	• ABVD consisting of doxorubicin (Adriamycin) bleomycin, vinblastine, dacarbazine	• Interim PET scan showed **INCREASED** metabolism in right angular gyrus (Brodmann area 39) and **DECREASED** activity in prefrontal cortex bilaterally
(*19*)	^{18}F-FDG PET/CT	• Intensity - modulated radiation therapy (IMRT)	• **DECREASED** metabolism in bilateral basal ganglia and bilateral occipital lobes, even after termination of anticancer therapy • Relative metabolic recovery in bilateral occipital lobes and further deterioration in bilateral basal ganglia • Right prefrontal cortex metabolism **INCREASED** during therapy • **INCREASED** metabolism in right PFC also seen at end of therapy

(*20*)	^{18}F-FDG PET	• CHT group: conventional standard-dose chemotherapy* • HL patients: hydroxydaunorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy • NHL patients: cyclophosphamide, hydroxydaunorubicin and vincristine (Oncovin), prednisone or prednisolone associated with the monoclonal antibody rituximab (R-CHOP) • NHL 2nd line: cyclophosphamide, mitoxantrone (Novantrone), Oncovin, prednisone (CNOP); vincristine, Adriamycin, cyclophosphamide, Oncovin and prednisone (VACOP); and etoposide, Oncovin, cyclophosphamide, hydroxydaunorubicin, (EPOCH) • Corticosteroid and immunotherapy	• Prefrontal-cerebellar system (PCS) metabolism **DECREASED** in chemotherapy group
(*21*)	^{18}F-FDG PET	• Carboplatin/taxol • Carboplatin/gemcitabine/avastin • Cisplatin/etoposide • Cisplatin/gemcitabine • Cisplatin/navelbine • Alimta (pemetrexed) • Carboplatin/taxol/ avastin	• Mean overall metabolic **DECREASE** of 22% in all gray matter structures • Chemotherapy associated with **DECREASED** metabolism in paraventricular and subcortical white matter tracts, corpus callosum, and cerebellar white matter • Most profound **DECREASED** metabolism in bilateral frontal cortex and bilateral olfactory gyri
(*22*)	^{18}F-FDG PET	• Chemotherapy, radiation, hormone replacement therapy	• **INCREASE** in bilateral anterior medial temporal activity, left posterior medial temporal activity, and cerebellar region activity • **DECREASE** in the Broca's area activity following aromatase inhibition therapy • Greatest **INCREASE** in metabolism in right medial temporal lobe

(*23*)	^{18}F-FDG PET	• Chemotherapy • Chemoradiation therapy • standard multi-agent regimens using cyclophosphamide, methotrexate and 5-fluorouracil or an anthracycline (doxorubicin)	• **DECREASED** metabolism in orbital frontal regions in breast cancer survivors compared with healthy controls • Right substantia nigra most profoundly affected in tamoxifen-treated patients • Treated patients showed **INCREASED** metabolism in left postcentral gyrus and corpus callosum

TABLE 2: Summary of neuroimaging findings in PTSD studies

Reference #	Imaging	Main Findings
(*46*)	^{18}F-FDG PET	• **INCREASED** metabolism in right amygdala in danger-based trauma versus control groups • **INCREASED** metabolism in precuneus in non-danger-based traumas versus danger group
(*47*)	fMRI	• **INCREASED** activation of basolateral relative to centromedial amygdala in PTSD group
(*48*)	^{15}O-CO_2 PET	• **DECREASED** regional cerebral blood flow in mPFC in veterans with PTSD during mental imagery of trauma-unrelated stressful personal experiences
(*61*)	rs-fMRI	• Oxytocin **DECREASED** amygdala-left vlPFC functional connectivity after trauma script-driven imagery versus neutral script-driven imagery • Oxytocin **INCREASED** amygdala–insula functional connectivity and **DECREASED** amygdala–vmPFC functional connectivity in both groups • PL-treated participants had **INCREASED** amygdala-left vlPFC functional connectivity following trauma script-driven imagery
(*50*)	SPECT and ^{18}F-FDG PET	• **DECREASED** perfusion and metabolism in left hippocampus and basal ganglia in PTSD group • **INCREASED** cerebellar metabolism in PTSD group
(*51*)	MRI and ^{18}F-AV-45 PET	• Slightly **DECREASED** superior parietal volume in TBI + PTSD group versus controls • **DECREASED** odds of amyloid positivity based on cortical amyloid SUVR in PTSD group versus controls • No evidence for increased brain amyloid associated with TBI • No evidence for medial temporal lobe atrophy in PTSD and/or TBI versus controls
(*54*)	fMRI	• **DECREASED** functional connectivity between left ventral anterior insula and anterior cingulate cortex • **DECREASED** functional connectivity between right posterior insula and left inferior parietal lobe
(*56*)	SPECT	• Hyperperfused DMN in PTSD group • Hypoperfused DMN in TBI group
(*55*)	^{11}C-flumazenil PET and MRI	• **INCREASED** mean ^{11}C-flumazenil binding potential in PTSD group versus healthy controls in medial and superior portion of caudal anterior cingulate cortex and precuneus • **INCREASED** BZD receptor BP in precuneus, and superior and dorsal anterior cingulate cortex in PTSD patients versus healthy controls
(*57*)	^{18}F-AV-45 PET	• **INCREASED** amyloid accumulation in frontal, occipital, and temporal lobes of PTSD, in white matter of TBI + PTSD group, and in cerebellum and precuneus area of TBI group
(*59*)	Active task fMRI	• **INCREASED** activation of dACC, insula, and amygdala in response to trauma-unrelated negative stimuli predicted PTSD persistence after trauma-focused therapy

SUPPLEMENTAL DATA: Glossary

- CRCI: Cancer/Chemotherapy Related Cognitive Impairments
- CT: Computed Tomography
- DMN: Default Mode Network
- fMRI: Functional Magnetic Resonance Imaging
- mPFC: Medial Prefrontal Cortex
- PTSD: Post-Traumatic Stress Disorder
- TBI: Traumatic Brain Injury