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Review

Default mode network as a potential biomarker of chemotherapy-related brain injury

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ABSTRACT

Chronic medical conditions and/or their treatments may interact with aging to alter or even accelerate brain senescence. Adult onset cancer, for example, is a disease associated with advanced aging and emerging evidence suggests a profile of subtle but diffuse brain injury following cancer chemotherapy. Breast cancer is currently the primary model for studying these "chemobrain" effects. Given the widespread changes to brain structure and function as well as the common impairment of integrated cognitive skills observed following breast cancer chemotherapy, it is likely that large-scale brain networks are involved. Default mode network (DMN) is a strong candidate considering its preferential vulnerability to aging and sensitivity to toxicity and disease states. Additionally, chemotherapy is associated with several physiological effects including increased inflammation and oxidative stress that are believed to elevate toxicity in the DMN. Biomarkers of DMN connectivity could aid in the development of treatments for chemotherapy-related cognitive decline.
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1. Brain aging, cancer, and chemotherapy

With age, the brain undergoes numerous degenerative changes that tend to result in a decline of cognitive function. Cognitive decline occurs on a continuum with dementia being at the pathologic extreme. Age is the most consistent predictor of pathologic cognitive decline including mild cognitive impairment (MCI) and dementia (Kravitz et al., 2012). However, age is also a primary risk factor for several major, noncentral nervous system (CNS) medical conditions. Many of these conditions and/or their treatments could potentially trigger an altered or accelerated brain aging process.

Cancer is a common, age-related disease with most diagnoses originating outside the CNS. Approximately 1 in 2 adults will be diagnosed with cancer during their lifetime with a median age at diagnosis of 66 years (Howlader et al., 2013). Advances in cancer treatments, such as chemotherapy, have resulted in significantly improved survival rates leading to a large and growing cohort of chemotherapy-exposed older adults. Chemotherapy is often associated with persistent cognitive decline affecting an estimated 78% of patients with non-CNS cancer (Wefel and Schagen, 2012). Neuroimaging studies provide insight regarding the effects of chemotherapy on cognition by demonstrating subtle but diffuse brain injury (de Ruiter and Schagen, 2013; Kaiser et al., 2014; Koppelmans et al., 2013; McDonald and Saykin, 2013; Pomykala et al., 2013a; Scherling and Smith, 2013; Simo et al., 2013).

Thus far, most neuroimaging studies have focused on breast cancer, which has become an initial model for investigating chemotherapy-related brain injury in adult onset, non-CNS cancer. Possible mechanisms of brain injury following breast cancer chemotherapy (BCC) include direct toxicity to neural progenitor cells (Monje and Dietrich, 2012), elevation of cytokine release and oxidative stress (Conroy et al., 2013b; Ganz et al., 2013; Kesler et al., 2013a; Pomykala et al., 2013b; Vardy et al., 2007), DNA damage and epigenetic alterations (Conroy et al., 2013b), deficient estrogen-related protection of healthy brain cells (Hogervorst, 2013) following chemotherapy-induced menopause (Conroy et al., 2013a), and altered cerebral blood supply through blood vessel damage (Seigers et al., 2010) and/or chemotherapy-induced anemia (O'Shaughnessy, 2003). Chemotherapy-related mechanisms interact with other factors including cancer pathogenesis (Kesler et al., 2011), allostatic load (Miller et al., 2008), and genetic variations (Ahles and Saykin, 2007). Therefore, BCC research has broad implications for neuroscience in terms of the effects of various physiological factors on brain-behavior relationships. This research

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is also forging new ground in terms of the relevance of cognitive neuroscience for non-CNS medical conditions and provides an opportunity for interdisciplinary approaches to intervention including neuropsychological rehabilitation, physical activity, and nutrition, among others.

Many of the candidate mechanisms for BCC-related brain injury overlap significantly with those involved in aging (Ahles 2012; Koppelmans et al., 2013; Mandelblatt et al., 2013). Accordingly, older patients tend to have poorer cognitive outcome following BCC (Ahles et al., 2010). Gray matter atrophy following BCC is analogous to approximately 4 years of aging on the brain (Koppelmans et al., 2012). Roughly 30% of BCC patients demonstrate a new onset of a previously nonexistent cognitive deficit at long-term follow up, suggesting possible progressive decline (Wefel et al., 2010). The presence of the APOE ε4 allele is a common risk factor for both dementia and BCC-related cognitive dysfunction (Ahles et al., 2003).

Aging is associated with microglial activation, causing increased release of proinflammatory cytokines (Lynch, 2010), and chronic neuroinflammation is associated with dementia (Herrup, 2010). BCC survivors show elevated neurochemical markers of microglial activity (i.e., myo-inositol) (Kesler et al., 2013b) and increased peripheral proinflammatory cytokines levels (Ganz et al., 2013; Kesler et al., 2013a; Pomykala et al., 2013b; Vardy et al., 2007). Compared with healthy women, BCC survivors show increased proinflammatory cytokine levels with increased age (Kesler et al., 2013a). Therefore, BCC is an interesting model for examining the interactions among disease, aging, and neurodegeneration.

If chemotherapy accelerates the brain aging process, chemotherapy-treated patients could be at higher risk for dementia. Accordingly, one study suggested that BCC survivors are 20% more likely to be diagnosed with dementia (Heck et al., 2008). Subsequent reports have not supported this finding (Baxter et al., 2009; Du et al., 2010; Raji et al., 2009) though methodological issues make conclusions difficult (Koppelmans et al., 2013) and further research in this area is imperative. Dementia risk could be diagnosis-specific given that treatment regimens have been linked with dementia incidence in colon cancer (Gupta and Lamont, 2004) but not breast cancer (Raji et al., 2009). Neuroimaging biomarkers may offer significantly increased sensitivity and reliability in predicting cognitive outcome following BCC.

2. Aging and the default mode network

One of the most promising neuroimaging biomarkers of age- and disease-related cognitive decline is reduction of default mode network (DMN) connectivity (Damoiseaux, 2012). The increasing investigation of large-scale brain networks such as DMN signals a shift beyond theories relying on discrete cortical localization of cognitive function and dysfunction. It is now known that specialized brain regions do not operate in isolation but participate in integrated networks. These networks are dynamically coordinated with specialized regions contributing to different networks in an adaptive, context-specific manner (Hutchison et al., 2013; Sporns, 2011). Brain networks are organized such that they are simultaneously highly segregated and integrated allowing for optimal efficiency of information processing and learning (Bullmore and Sporns, 2012).

Even at rest, several different large-scale brain networks demonstrate spontaneous, synchronous neuronal activity. These intrinsic or "resting state" networks show higher activity during rest and tend to be anti-correlated with activity in task-positive networks (Fox et al., 2005; Raichle, 2011). Intrinsic network regions show attenuation or "task-induced deactivation" (TID) and are believed to modulate allocation of neural resources to support goal-oriented processes (Sambataro et al., 2010). The DMN, one of the most commonly observed resting state networks, includes precuneus, posterior cingulate, medial frontal, middle temporal and lateral parietal regions, as well as hippocampus (Damoiseaux et al., 2006). DMN is believed to support processes such as implicit learning, autobiographical memory, prospection, monitoring the external environment, creativity, and self-reflection (Abraham, 2013; Agnati et al., 2013; Qin and Northoff, 2011; Raichle, 2011; Takeuchi et al., 2012). Both DMN functional connectivity and TID tend to decrease with age and are markedly decreased in individuals with MCI or Alzheimer's disease (Damoiseaux et al., 2012; Greicius et al., 2004; Sheline et al., 2010). Disruptions of DMN precede amyloid beta toxicity, the hallmark molecular pathology associated with neurodegeneration, identifying individuals who are cognitively normal but at high risk for dementia (Sheline et al., 2010).

Amyloid beta accumulation naturally increases with age and DMN is preferentially vulnerable to this toxicity (Buckner et al., 2005). DMN regions are hubs, areas that participate in a large number of functional interactions (Cole et al., 2010b) and therefore have significantly high metabolic demands (Lord et al., 2013). DMN's high energy requirements may make it more susceptible to the reduction of physiological resources that occurs with age including reduced metabolic capacity, cerebral blood flow, and glucose metabolism (Yao et al., 2011; Kapogiannis and Mattson, 2011). Additionally, inflammation increases with age and is associated with elevated amyloid beta accumulation (Herrup, 2010). Lower cognitive reserve also appears to degrade the DMN faster by increasing amyloid beta deposition (Bero et al., 2011).

Alternatively, it has been suggested that amyloid beta toxicity may be a consequence of neurodegeneration rather than a cause (Armstrong, 2011). Amyloid beta is produced from amyloid precursor protein, which shows neuroprotective functions following brain injury (Blennow et al., 2012). Therefore, the mechanism underlying DMN's increased vulnerability to age is not entirely clear. DMN susceptibility to amyloid beta accumulation could result from a combination of factors including both metabolic changes and neuroprotective mechanisms that become dysregulated in the aging brain, which has decreased ability to adequately return to homeostasis (Herrup, 2010). Additionally, APOE status influences amyloid beta clearance (Verghese et al., 2013) indicating genetic moderation of DMN vulnerability to amyloid beta toxicity.

3. Measuring DMN

DMN is primarily measured using functional magnetic resonance imaging (fMRI) (Cole et al., 2010a; Margulies et al., 2010; Zhang and Raichle, 2010) but has also been assessed using positron emission tomography (PET) (Buckner et al., 2008), electroencephalography (Chen et al., 2013), and near-infrared spectroscopy (Sasai et al., 2012). Structural connectivity of DMN can be measured using volumetric magnetic resonance imaging or diffusion tensor imaging (Alexander-Bloch et al., 2013).

3.1. Functional connectivity

If neural activity in a set of anatomically distinct brain regions is synchronous, these regions are believed to be coordinating into a functional network. Resting state fMRI (rsfMRI) is typically used to assess functional connectivity of DMN and simply requires the participant to lie passively in the scanner. A minimum duration of 5 minutes is associated with stable correlation strengths (Van Dijk et al., 2010). However, robust brain network metrics can be achieved using a scan time of as little as 2 minutes if necessary (Whitlow et al., 2011). RsfMRI is ideally acquired before task-based

fMRI scans conducted within the same session to reduce the effects of specific cognitive processes on the resting state networks (Waites et al., 2005; Northoff et al., 2010). Uncertainty remains as to whether rsfMRI should be acquired with eyes open or closed as the 2 conditions can yield different results (Liu et al., 2013). Instructions given to participants during rsfMRI, including whether or not to close the eyes, should be consistent as findings can vary based on instruction content (Benjamin et al., 2010). There are several other potential participant-related confounds such as body weight and caffeine consumption (Duncan and Northoff, 2013). However, rsfMRI functional connectivity measures show strong stability and test-retest reliability (Van Dijk et al., 2010).

Preprocessing of rsfMRI data is similar to that of task-based fMRI including motion correction, spatial normalization, and smoothing. However, rsfMRI data must be filtered to the <0.1 Hz range of spontaneous activity (Raichle, 2011; Whitfield-Gabrieli and Ford, 2012). Because intrinsic activity occurs in such a low frequency range, rsfMRI signal has increased susceptibility to nonneuronal noise (Hutchison et al., 2013). Several approaches have been described for minimizing these artifacts including independent component analysis (ICA) (Boubela et al., 2013), principal component analysis (Behzadi et al., 2007), and model-based methods (Chang and Glover, 2009).

The 2 most common statistical approaches for rsfMRI functional connectivity are seed-based correlation (SBC) and ICA. SBC is a model-driven, univariate analysis where the time course of a region of interest or seed, is correlated with the whole brain in a voxel-wise manner at the individual participant level. The resulting correlation matrix is typically normalized and can then be evaluated at the group level (Whitfield-Gabrieli and Ford, 2012). SBC seed sizes and locations are often ambiguous leading to variability in results (Cole et al., 2010a). One group recently introduced a data-driven seed selection method that uses regional homogeneity (Yan et al., 2013). Another data driven method, seed-based iterative cross-correlation uses the voxels from an SBC-generated group level connectivity map as a new seed, repeating this process until the results converge (Yang et al., 2013).

ICA is a data-driven, multivariate method that works by decomposing the unknown, mixed fMRI signal sources into maximally independent temporal or spatial activation maps (components) (Calhoun and Adali, 2012). Individual components can represent various brain networks as well as nonneuronal noise. Therefore, components associated with DMN must be selected before moving on to group level analyses. One approach is to observe the power spectrum for each component and identify those with a peak frequency in the intrinsic activity range (e.g., 0.008–0.09 Hz). An automatic template matching procedure calculates the "goodness of fit" of a component with a spatial template of interest (Greicius et al., 2004). Group ICA involves concatenation of individual participants' components and then back-reconstructing them to ensure that components are consistently ordered and can then be sorted temporally or spatially (Calhoun et al., 2009). Partner-matching selects components by clustering them based on similarity measures of spatial patterns across multiple within or between participants' data sets (Wang and Peterson, 2008). Another automatic component selection method combines spatial map filtering, statistical tests, and spectral analysis (Storti et al., 2013).

Intrinsic functional connectivity can also be extracted from task-based block design or event related data (Fair et al., 2007). These methods include concatenation of interleaved rest epochs or removal of task-induced variance via regression (leaving the underlying spontaneous activity) (Fox et al., 2006). There are several disadvantages to such emulation of rsfMRI including exclusion of the lower intrinsic frequencies and possible contamination by previous task conditions (Fair et al., 2007). However, emulation is advantageous for research groups with large existing data sets that did not include rsfMRI.

Graph theory analysis provides a mathematical representation of brain network topology as a system of interconnected elements defined by nodes (regions) and edges (connections) (Hosseini et al., 2012a; Sporns, 2011). Brain networks tend to demonstrate an efficient, "small-world" organization where local connectivity (clustering) is high and long-range connections (path lengths) are economical (Sporns, 2011). Both global and local network metrics can be calculated including modularity, which provides an assessment of sub-networks (Stevens et al., 2012), hub analysis to identify regions that are central to the network's organization, and attack analyses, which measure the network's resilience (Hosseini et al., 2012a). Methodological considerations include parcellation scheme (Shen et al., 2013), choice of benchmark networks (Hosseini and Kesler, 2013b), and thresholding (van Wijk et al., 2010).

Multivoxel pattern analysis (MVPA) uses machine learning, a branch of artificial intelligence, to automatically find multivariate patterns of brain structure and/or function that accurately predict categorical or continuous variables (Mahmoudi et al., 2012; Orru et al., 2012). MVPA is a highly sensitive method because of its ability to use subtle signals across voxels that tend to be undetectable by univariate analyses (Kamitani and Tong, 2005). The functional connectivity correlation matrix or other extracted rsfMRI measures can be used as features (i.e., input variables) for MVPA classification (Craddock et al., 2009). Linear support vector machine is currently the most common MVPA approach because of its ability to handle large, high-dimensional data sets (Orru et al., 2012). Like all the above methods, region of interest or feature selection, can significantly influence MVPA results (Mahmoudi et al., 2012).

3.2. Task-induced deactivation

Intrinsic network activity is attenuated during active tasks in a dose-dependent manner with increased TID occurring with increased task difficulty (Newton et al., 2011). Thus, TID can be measured by identifying regions where activation is greater during passive or low-load conditions compared with active or higher-load conditions. In fMRI analyses, statistical modeling is generally accomplished by creating contrasts or subtractions of various task-related conditions or events. The aim is to examine activation patterns associated with the effect of interest after removing irrelevant or nuisance activations. These nuisance activations tend to be accounted for using a control condition such as the 0-back epochs in an n-back paradigm, for example. TID can be measured by subtracting active task conditions from these control conditions (Buckner et al., 2008). Because DMN TID occurs across tasks (Sambataro et al., 2010), any fMRI task paradigm could potentially be used.

4. DMN and chemotherapy

BCC-related cognitive dysfunction may represent a brain network disorder given the widespread brain alterations that are noted even decades after the treatment has ended (Pomykala et al., 2013a). The coordinated, dynamic brain network response that supports cognitive function depends critically on stable structural networks (Sporns, 2011). Accordingly, intrinsic functional connectivity is dependent on the underlying structural connectivity (Damoiseaux et al., 2012; Hosseini and Kesler, 2013a). BCC is associated with widespread reductions in white matter pathway integrity in regions including cingulum and superior frontal occipital fasciculus (Deprez et al., 2013), which connect DMN regions.

Deficits in white matter structure reduce brain network functional integration. BCC survivors also demonstrate reduced gray matter volumes of DMN regions including precuneus, cingulate, lateral parietal cortex, medial frontal gyrus, and hippocampus (Pomykala et al., 2013a). Alterations in gray matter structure reduce brain network functional specialization.

Most neuroimaging studies of BCC to date have involved task-based fMRI methods. Although these studies did not aim to examine DMN, they may collectively suggest reduced task-related response of DMN regions. To investigate this possibility, a quantitative, anatomic likelihood estimate meta-analysis was performed using GingerALE software version 2.3.2 (http://www.brainmap.org/ale/) (Laird et al., 2011). A threshold of $p < 0.05$, false discovery rate (nonparametric p-value) corrected with a 40 mm minimum cluster volume was used. All studies that used task-based fMRI to study BCC and neurobiologic status were included. PubMed searches included the keywords "cancer and chemotherapy and brain" or "cancer and chemotherapy and brain and MRI". Studies were also identified using recent reviews (de Ruiter and Schagen, 2013; Pomykala et al., 2013a; Scherling and Smith, 2013; Simo et al., 2013). Six studies were identified (36 total foci, 258 total participants) (Conroy et al., 2013b; de Ruiter et al., 2011; Kesler et al., 2009, 2011; Lopez Zunini et al., 2012; McDonald et al., 2012). Meta-analysis indicated that abnormality of regions involved in DMN was the most consistent finding, particularly in the precuneus and medial frontal gyrus (Fig. 1). It is important to note that DMN activity is reduced during tasks, not extinguished. Task-related functional activation is believed to reflect a combination of spontaneous intrinsic network activity and response to cognitive load (Fox et al., 2006). The present meta-analysis suggests disrupted modulation of the DMN during various executive and memory tasks following BCC. However, these findings are an indirect assessment of DMN function and precuneus and medial frontal gyrus participate in other brain networks as well.

Application of graph theory in neuroimaging provides novel insight regarding the topology of large-scale brain networks. Increased age tends to be associated with reduced global efficiency of large-scale brain networks, which is believed to represent a high risk for dysconnectivity syndromes such as MCI and dementia (Wu et al., 2013). Altered organization of large-scale structural and intrinsic functional brain networks has been demonstrated in patients with brain tumor (Bartolomei et al., 2006; Bosma et al., 2009; Heimans and Reijneveld, 2012) and patients exposed to intrathecal chemotherapy (Hosseini et al., 2012a) as well as following BCC.

Hosseini et al. (2012b) examined organization of the large-scale gray matter network in 37 BCC survivors compared with 38 healthy female controls. Breast cancer survivors had completed chemotherapy an average of 4.5 years before the study enrollment. Using graph theoretical analysis of 90 anatomic regions of interest, a structural correlational brain network was constructed for each group. Brain network statistics were computed, including mean clustering coefficient, a measure of network segregation, characteristic path length, a measure of network integration and small-worldness, a measure of the network's ability to balance segregation and integration. A permutation distribution was created based on 1000 benchmark networks to determine the significance between group differences in network measures. Results indicated that the BCC group demonstrated significantly reduced mean clustering ($p = 0.03$) and marginally reduced small-worldness ($p = 0.08$). Further, the control group demonstrated expected hub regions in DMN including precuneus and middle temporal gyrus whereas the BCC group did not. These findings suggest that chemotherapy may disrupt participation of DMN regions in the structural brain network.

A follow up study of the same cohort, demonstrated that organization of the global resting state functional brain network is also disrupted following chemotherapy (Bruno et al., 2012). Consistent with the previous study, mean clustering was significantly reduced

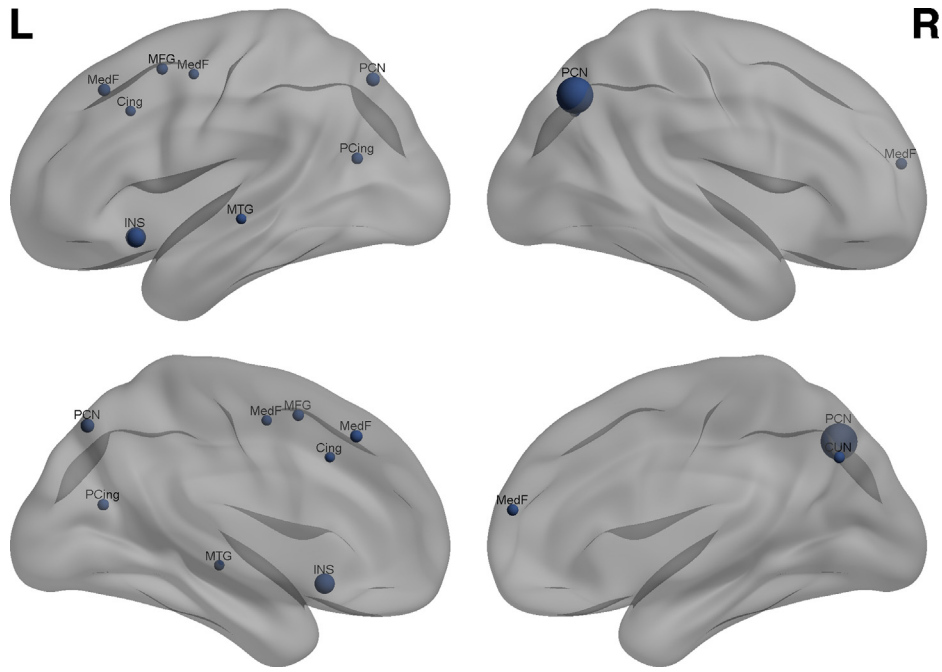

Fig. 1. Meta-analysis results showing regions of significant ($p < 0.05$ corrected) overlap across fMRI studies of BCC-related brain activation abnormality. Increased region marker size indicates increased cluster volume. PCN: precuneus (MNI coordinates: 40, −68, 42; −16, −72, 48), INS: insula (−32, 18, −12), MedF: medial frontal gyrus (−6, 30, 44; 4, 56, 16; −16, −4, 50), PCing: posterior cingulate (−28, −66, 18), CUN: cuneus (8, −68, 36), MFG: middle frontal gyrus (−26, 8, 52), MTG: middle temporal gyrus (−56, −22, −5), Cing: cingulate (−10, 20, 36). Figure created using BrainNet Viewer (http://www.nitrc.org/projects/bnv/). Abbreviations: BCC, breast cancer chemotherapy; fMRI, functional magnetic resonance imaging.

in BCC ($p = 0.03$) with a marginal reduction in small-worldness ($p = 0.06$). Additionally, characteristic path length was decreased in the BCC group ($p = 0.05$) indicating inefficient functional network integration. Again, the BCC group showed an altered hub profile with hippocampus not participating effectively in the functional brain network. There were no significant correlations between network measures and cognitive or demographic factors. Although neither of these brain network studies examined DMN specifically, they provide evidence that BCC negatively impacts large-scale brain networks, particularly with respect to DMN connectivity. However, without a non-chemotherapy comparison group, it is not possible to conclude from these studies that alterations in DMN are specific to chemotherapy.

Altered brain network organization not only results in cognitive impairment, but also reduces the brain's resilience (Achard et al., 2006; He et al., 2008; Hosseini et al., 2012a; Rubinov et al., 2009) consistent with the frail phenotype of aging and reduced cognitive reserve, both significant predictors of pathologic cognitive decline (Mandelblatt et al., 2013; Steffener and Stern, 2012; Stern 2012; Whalley et al., 2004). Thus, even if a patient does not demonstrate symptoms of chemotherapy-related cognitive dysfunction at the time of initial evaluation, she may have increased vulnerability for cognitive decline because of later disease, injury, and aging. Decreased brain resilience may help explain the new onset of previously nonexistent cognitive impairment and progressive worsening of existing symptoms that have been noted in some chemotherapy-treated breast cancer survivors (Wefel et al., 2010).

Two PET studies from the same research group examined both task-related and resting-state cerebral metabolism in BCC (Pomykala et al., 2013b; Silverman et al., 2007). The latter study involved 16 BCC survivors 5–10 years post-chemotherapy and 8 healthy female controls (Silverman et al., 2007), whereas the earlier study involved 23 chemotherapy-treated and 10 non-–chemotherapy-treated breast cancer patients assessed after completing chemotherapy and 1 year later (Pomykala et al., 2013b). Differences in PET activation were measured using whole-brain voxelwise as well as region of interest analyses. There were no between group differences or longitudinal differences in resting metabolism in either study although regions of interest included some DMN regions. However, the study did not actually aim to measure DMN and did not use TID or functional connectivity methods. Therefore, it is not likely that DMN would have been detected. PET studies provided the original evidence of DMN through meta-analysis of TID (Buckner et al., 2008). PET's limited spatial and temporal resolution prevents functional connectivity analysis at the individual participant level (Greicius et al., 2007) and may result in inconsistent DMN results compared with fMRI (Di et al., 2012).

Very few direct investigations of DMN in BCC have been conducted to date. A case study by LaViolette et al. (2009) examined change in DMN functional connectivity of a patient with breast cancer from pre-chemotherapy to 3 months post-chemotherapy compared with 5 control participants. RsfMRI was used to measure functional connectivity and arterial spin labeling was used to measure cerebral blood flow. DMN connectivity was defined via SBC of posterior cingulate. Functional connectivity between posterior cingulate and medial temporal cortex and hippocampus were significantly reduced post-chemotherapy ($p < 0.005$). Additionally, cerebral blood flow was decreased in the lateral parietal cortex and precuneus ($p < 0.001$). This study preliminarily demonstrates that BCC-related DMN changes can be measured at the individual level, potentially providing valuable patient-specific information.

In a longitudinal study, Conroy et al. (2013a) investigated the effect of chemotherapy-induced amenorrhea on task-induced activation as well as TID during an n-back working memory task in 9 post-menopausal BC patients undergoing chemotherapy, 9 pre- or peri-menopausal BC patients undergoing chemotherapy and 6 healthy female controls. TID was used to define DMN. There were no significant differences in activation or deactivation among the groups. However, the chemotherapy-induced amenorrhea group showed a significant increase in the summed magnitude of activation and deactivation from pre-chemotherapy to 1 month post-chemotherapy ($p = 0.011$). This study suggests that alteration in DMN TID may play a role in working memory dysfunction following BCC and that menopausal status is an important factor to consider when evaluating the effects of BCC on DMN. However, the study was very limited by the small sample size and lack of separation between the contribution of task-induced activation versus DMN TID to the overall findings.

Dumas et al. (2013) conducted an SBC analysis using an fMRI n-back task in 9 patients with breast cancer before chemotherapy, 1 month and 1 year after completion of chemotherapy. Task-related activation was removed via regression. An intraparietal sulcus seed was used to interrogate dorsal attention network connectivity and a posterior cingulate seed was used to investigate DMN. Dorsal attention network connectivity was decreased at 1 month with partial recovery at 1 year ($p < 0.001$, uncorrected). DMN connectivity was also decreased at 1 month, specifically in the precuneus, and did not recover at 1 year ($p = 0.001$, uncorrected). N-back performance did not change over time but self-rated memory difficulties decreased across all 3 time points. The authors did not correlate fMRI and cognitive-behavioral data so it is unknown if changes in connectivity were related to changes in memory complaints. This study was limited by the emulation method of resting state connectivity, small sample size, lack of control group, and uncorrected statistical threshold. However, it provides further preliminary evidence that DMN may show increased vulnerability to chemotherapy characterized by limited recovery compared with other brain networks.

To examine the specificity of BCC on DMN, Kesler et al. (2013c) conducted MVPA of DMN functional connectivity in 30 BCC and 27 non-chemotherapy treated breast cancer survivors (4.9 ± 3.4 years post-chemotherapy) as well as 24 healthy female controls. RsfMRI temporal correlations were calculated between 19 functional regions of interest. Data were corrected for age, education, psychiatric symptoms, and gray matter volume. The MVPA classifiers were tested for each group pair as well disease stage (breast cancer group only) using leave-one-out cross-validation. Permutation analysis was conducted to determine classifier significance at an alpha level adjusted for multiple comparisons.

Patterns of DMN connectivity significantly distinguished chemotherapy from both non-chemotherapy survivors and healthy females with 90%–91% accuracy ($p < 0.0001$, receiver operating characteristic [ROC] effect sizes: 0.97–0.98). The non-chemotherapy group could not be distinguished from the healthy control group and disease-stage classifiers also were not significantly better than chance. Connectivity within DMN regions as well as connectivity between DMN and prefrontal regions contributed the most to the classifiers indicating that these connections were the most important for distinguishing the groups. The classifiers were significantly correlated with memory complaints ($p < 0.002$) indicating that the more similar a participant's DMN connectivity to that of the chemotherapy group, the lower the memory function. This study was limited by its cross-sectional design but provides evidence that DMN may be preferentially vulnerable to chemotherapy.

There are multiple different brain networks and chemotherapy could potentially affect several of these. In fact, the profile of BCC-related cognitive impairments strongly suggests deficit of central

executive network and several studies have demonstrated altered prefrontal cortex structure and function following chemotherapy (de Ruiter and Schagen, 2013). Hosseini and Kesler (2013c) examined prefrontal functional connectivity in 27 chemotherapy treated and 29 non-chemotherapy treated breast cancer survivors and 30 healthy females. fMRI data were obtained during an executive function task. Functional connectivity was calculated between 12 frontal and parietal executive network regions of interest. MVPA was conducted as described previously.

The MVPA classifiers significantly distinguished between the chemotherapy group and both the non-chemotherapy and health female group with 71%–72% accuracy ($p < 0.01$, ROC: 0.71–0.72). The classifier for non-chemotherapy and healthy females was not significant. Connections between prefrontal and parietal regions contributed the most in discriminating the chemotherapy group from healthy females, whereas connections within prefrontal regions had the greatest weight for discriminating the 2 breast cancer groups. ROC effect sizes were much lower than those obtained for the DMN classifier (Kesler et al., 2013c). Additionally, the prefrontal classifier was associated with disease stage ($p < 0.05$) whereas the DMN classifier was not. These findings provide further evidence that DMN may be preferentially vulnerable to chemotherapy versus disease severity or alternate treatments (e.g., radiation) compared with other networks. However, prospective and longitudinal studies are needed to further evaluate these findings.

5. Conclusions and future directions

Thus far, studies of DMN in BCC have been very limited. Many have involved cross-sectional designs, small sample sizes, and/or lacked appropriate comparison groups. However, indirect as well as direct neuroimaging evidence suggests that DMN represents a promising potential biomarker of chemotherapy-related brain injury. The inclusion of rsfMRI in prospective study designs will allow investigation of longitudinal changes in DMN connectivity. Thus far, most neuroimaging studies of BCC have involved middle-aged women (Ahles, 2012). Future efforts should focus on longitudinal evaluation of very long-term survivors and/or older patients to examine how BCC may moderate the effect of age on DMN status.

To address the issue of small sample sizes, a standard neuroimaging battery analogous to that proposed by the International Cognition and Cancer Task Force for harmonizing studies of cognitive status (Wefel et al., 2011) is needed. This would allow multisite research groups to combine data and increase statistical power. This review suggests that the inclusion of rsfMRI is indicated. RsfMRI can be used to assess multiple brain systems using 1 brief acquisition (Fox and Greicius, 2010). Resting state networks closely correspond to a variety of active networks (Smith et al., 2009) and rsfMRI has been used to decode networks associated with various cognitive states including memory, executive control, and salience, among others (Shirer et al., 2011). The simplicity of rsfMRI makes it easy to standardize across sites and more feasible for a wider range of participants, including older adults. Additionally, task-related changes in brain metabolism tend to be quite small compared with the brain's large resting state energy consumption (Raichle and Mintun, 2006). RsfMRI may therefore provide a more robust source of disease-related signal change (Fox and Greicius, 2010; Raichle and Mintun, 2006).

As noted previously, amyloid beta deposition is a key element in the pathology of age-related cognitive decline and neurodegeneration (Herrup, 2010), but it is unknown if this toxicity plays a role in BCC-related brain injury. Chemotherapy may theoretically increase amyloid beta accumulation through elevation of inflammation and oxidative stress (Cai et al., 2011), altered glucose metabolism (Baudino et al., 2011), and/or other factors. Future studies combining APOE status, PET-based amyloid beta markers (i.e., Florbetapir), and rsfMRI are required to examine the interactions between aging, amyloid accumulation, genetic risk, intrinsic brain networks, and chemotherapy.

The increased application of multivariate neuroimaging analyses to the study of chemobrain would significantly advance this field of research. Most studies thus far have used mass univariate methods, which are very limited with respect to evaluation of large-scale networks as well as prediction of individual patient outcome. Chemotherapy treatment is the only situation where it is known in advance that a potential brain injury is about to occur. With further refinement of MVPA algorithms, baseline neuroimaging could be used to predict which patients are at highest risk for persistent chemotherapy-related brain injury. This information could potentially inform treatment regimen decision-making and prioritize patients for early interventions. The inclusion of multimodal DMN biomarkers, such as a combination of rsfMRI and diffusion tensor imaging, may also improve prediction accuracy. MVPA methods could help separate the neurobiological effects of different treatments (e.g., chemotherapy vs. endocrine therapy) as well as psychiatric symptoms (e.g., depression, fatigue vs. chemotherapy).

Finally, further study of DMN's role in chemotherapy-related cognitive decline could aid in the development of interventions. Both cognitive and physical exercise have been shown to increase DMN functional connectivity in healthy adults (Takeuchi et al., 2013; Voss et al., 2010). Medication that has shown promise in improving chemobrain symptoms (i.e., modafinil) improves DMN TID in healthy adults (Minzenberg et al., 2011). Additionally, given the strong link between DMN decline and metabolic processes, DMN biomarkers associated with chemotherapy may provide an important opportunity for assessing nutritional interventions. For example, regulators of mitochondrial metabolic activity (e.g., B-vitamins) and dietary energy restrictions may reduce or prevent amyloid beta toxicity in the brain (Kapogiannis and Mattson, 2011; Yao et al., 2011).

Disclosure statement

The author has no conflicts of interest.

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