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Imaging Brain Networks After Cancer and Chemotherapy:

Advances Toward Etiology and Unanswered Questions

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The study by Kesler and Blayney[1] in this issue of *JAMA Oncology* investigated the impact of anthracycline-based chemotherapy regimens (ANTHR) on cognitive performance and resting state functional magnetic resonance imaging (fMRI) brain connectivity within the default mode network (DMN) in female breast cancer survivors. Brain connectivity has become a major focus in neuroscience that is rapidly translating to the clinical realm where brain disorders are viewed from a system or network perspective rather than as a set of affected regions. The DMN is of particular interest as a measure of the brain's resting state of spontaneous cognition, or thought processes when not task-focused. Disruptions of the DMN have been associated with neurodegenerative disease as well as systemic chemotherapy.[2] Kesler and Blayney[1] found that, compared with breast cancer survivors treated with non–ANTHR-based regimens or breast cancer survivors not treated with chemotherapy (NC), ANTHR was associated with poorer verbal memory, as well as with altered connectivity of the left precuneus region, which is part of the superior parietal lobule involved in episodic memory, visuospatial processing, and aspects of consciousness. Although the finding of lower connectivity of the left precuneus to other brain regions was not specific to the ANTHR group, it was more pervasive. The non-ANTHR group also displayed lower connectivity of this brain region to a frontal region compared with NC. This finding suggests that different chemotherapy regimens may affect DMN connectivity through a similar mechanism, with ANTHR-based regimens having a greater impact, perhaps through an oxidative stress-linked metabolic pathway, as posited by the authors.[1]

The authors[1] infer that lower connectivity of the left precuneus with frontal and/or hippocampal regions may underlie the poorer memory function of ANTHR-treated survivors. Relating the cognitive and imaging findings may have strengthened this argument, but correlations between regional connectivity and memory performance were not reported. The fact that the non-ANTHR group also showed lower connectivity of the left precuneus with a frontal region but did not show decreased verbal memory performance suggests other contributory factors. A subset of patients included in this study[1] also completed task-based

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fMRI. While those results are not included their article, future work integrating task-based fMRI (eg, during episodic memory processing) would be another potential source of convergent data for the authors'[1] hypothesis that altered precuneus connectivity may relate to reduced post-ANTHR memory function. Although task-based analysis may have been outside the scope of the current work,[1] future fMRI studies analyzing memory-induced connectivity changes in relation to task performance could support the authors'[1] interpretation that DMN connectivity is related to cognitive dysfunction. The integration of structural and functional neuroimaging and performance-based measures of cognitive dysfunction is an ongoing effort in cancer- and treatment-related neurocognitive dysfunction research, as well as in neuroimaging research more broadly.

In addition to verbal memory, the authors[1] examined neuropsychological measures of executive function and verbal fluency, neither of which showed significant differences between groups, although the combined chemotherapy-treated groups showed a trend toward lower executive function compared with the NC group. These findings suggest that while chemotherapy regimen may be an important factor in some types of cognitive dysfunction (eg, episodic memory), changes in other cognitive domains may be common to a wider range of treatment regimens, emphasizing the need for studies characterizing the types of cognitive dysfunction linked with various chemotherapy protocols.

Other findings from the study by Kesler and Blayney[1] included similar elevation of patient-reported cognitive dysfunction and psychological distress in both chemotherapy-treated groups compared with the NC group. Future investigation of the relationship between subjective symptoms and connectivity measurements may help elucidate mechanisms driving cognitive concerns after cancer treatment. Understanding this aspect of posttreatment symptomatology would be particularly useful given the finding that both chemotherapy-treated groups showed subjective symptom elevation compared with the NC group, despite the lack of performance deficits in the non-ANTHR group. While this could in part be attributable to relatively small sample sizes, a common challenge for neuroimaging studies, it also highlights broader issues in this research area. Prior studies examining cancer- and treatment-related cognitive effects have shown cognitive changes in patient subsets, with a lack of consistency between subjective and objective cognitive changes. The work of Kesler and Blayney[1] provides important insight into which patients may be more likely to show objective cognitive changes, while the reconciliation of subjective and objective cognitive changes remains a challenge in this and other populations.

Interestingly, Kesler and Blayney[1] found that the dose of ANTHR was not associated with either cognitive performance or resting functional connectivity, suggesting that relatively small differences in standard-dose chemotherapy regimens may not have a significant impact on the degree of cognitive dysfunction compared with previous studies comparing low- and high-dose chemotherapy effects.[3] In addition, endocrine treatment was not associated with either outcome; however, as the authors[1] suggest, this could be due to the high percentage of treated patients in each group (>60%), limiting power for the analysis. Disease stage was also not associated with either outcome, though there was a significant difference in stage distribution between groups, as expected by indication for chemotherapy. This is particularly important in light of studies that have shown differences in brain function during task-based

fMRI between healthy controls and patients with cancer prior to systemic treatment, suggesting that aspects of the cancer disease process or risk factors also may contribute to cognitive dysfunction.[4–6] Immune activation has increasingly been posited as a mechanism for these changes. This hypothesis has been supported by research showing that memory performance was correlated with alterations in proinflammatory cytokines in patients newly diagnosed as having breast cancer prior to treatment.[7] Additional prospective studies are needed to address baseline differences and the impact of specific treatments on cognitive function, the underlying neural substrate, and specific biological pathways.[8] Resolving the pathways leading to cognitive dysfunction will be important for development of targeted interventions.

While previous studies have linked chemotherapy and cognitive decline, and a few other studies have linked treatment with differences in brain connectivity,[2,9,10] there has been very little research comparing cognitive effects of different types and combinations of chemotherapy because most studies have been underpowered to distinguish these effects. This present study[1] builds on preclinical work[11] and, although modest in power to detect regimen differences, represents an important step forward while underscoring the need for larger studies.

Neuroimaging studies have advanced research on cancer and cognitive dysfunction in recent years, providing a biological context to prior neuropsychological and self-report studies. Findings from prospective breast cancer cohorts have shown both cancer- and treatment-related gray matter alterations[12] and demonstrated a relationship between lower frontal gray matter density and increased cognitive complaints[13] and reduced cerebral perfusion.[14] Prospective task-based fMRI studies have also shown cancer- and treatment-related brain activation changes and have been able to demonstrate correspondence of changes in structure and function in frontal brain regions that may underlie the commonly observed cognitive changes in this population.[5] However, pretreatment and posttreatment analysis of resting cerebral perfusion has also shown regions of increased perfusion in patients who received chemotherapy, which correlated with pretreatment neuropsychological performance.[14] These findings emphasize the complex nature of cancer and treatment-related neural changes and underscore the possibility that different physiological mechanisms may be involved in various aspects of these cognitive and brain changes, as also noted by Kesler and Blayney.[1] Given the diverse brain regions reported in various imaging studies as significantly associated with cancer and chemotherapy, the study of connectomics is a logical extension that may integrate these findings into a more coherent picture of alterations in brain network function and cognition related to cancer and its treatment. It will be important for future studies to consider the impact of cancer and related treatments on other known functional brain networks, in addition to the DMN, to gain a more complete understanding of the impact of cancer and treatment on brain function.

Larger, prospective studies are needed, including different studies in patients with types of cancer as well as healthy controls to provide a normative framework so that cancer-specific effects can be identified. In addition to allowing further discrimination of specific treatment regimen effects, larger studies would permit investigation of other patient-specific factors likely to contribute to posttreatment cognitive outcomes, including genetic variability. With

the movement toward precision medicine, it will be important to investigate genetic predictors of cognitive risk for various regimens. Similarly, the roles of cognitive aging and neurodegenerative disorders of aging are largely unexplored in cancer imaging and biomarker studies. Different types of chemotherapy may specifically exacerbate neurotoxic processes present in normal aging and/or neurodegenerative disorders such as Alzheimer or Parkinson disease. Kesler and Blayney[1] discuss elevated molecular markers of aging in patients with breast cancer after ANTHR treatment,[15] as well as the theoretical link between ANTHR-increased oxidative stress and amyloid β accumulation, which could accelerate the progression of Alzheimer disease. However, to date, specific treatment types have not been compared for effects on these important pathways, which have the potential to have a significant impact on survivor quality and length of life. The study by Kesler and Blayney[1] in this issue therefore provides intriguing hypotheses warranting follow-up in larger prospective studies.

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