Functional and effective connectivity of default mode network is disrupted in chemotherapy-treated patients with breast cancer

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Introduction

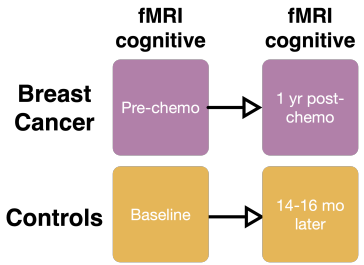
Cognitive impairment is common after chemotherapy treatment, affecting an estimated 60% of patients [1]. Patients with cognitive impairment tend to have lower quality of life, increased psychological distress and significantly shorter survival rates compared to those without cognitive impairments [2]. The default mode network (DMN) is particularly vulnerable to toxins as well as aging. The median age of adult onset cancer diagnosis is 66 years and therefore chemotherapy-related injury may exacerbate normal brain aging. We previously showed that disrupted functional connectivity of DMN regions was predictive of chemotherapy history [3] and future cognitive outcome [1]. However, there have been very few studies to date of DMN connectivity in patients with breast cancer.

Research Goal

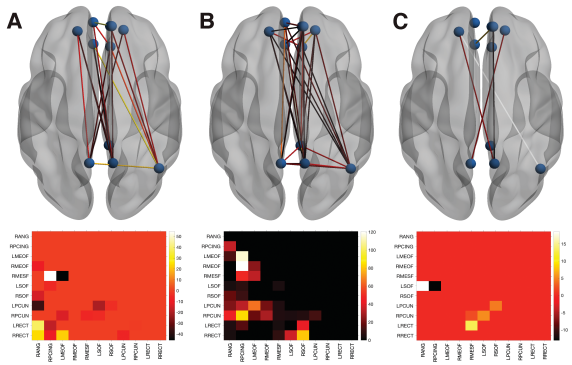
We aimed to longitudinally examine the functional and effective connectivity of the DMN in patients with breast cancer (BC) undergoing chemotherapy treatment.

Methods

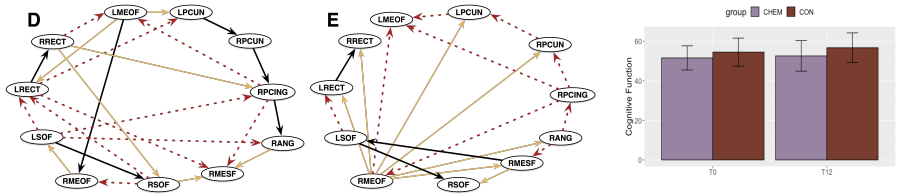
We obtained resting state fMRI and cognitive testing in 43 newly diagnosed patients with primary BC prior to and 1 year following chemotherapy [1]. We also assessed 50 healthy controls at yoked intervals who were frequency matched for age and education. Participants were age 34-65 years. Patients received an average of 7 +/- 4 chemotherapy cycles and most also received radiation and hormone therapies.



Figures and Results



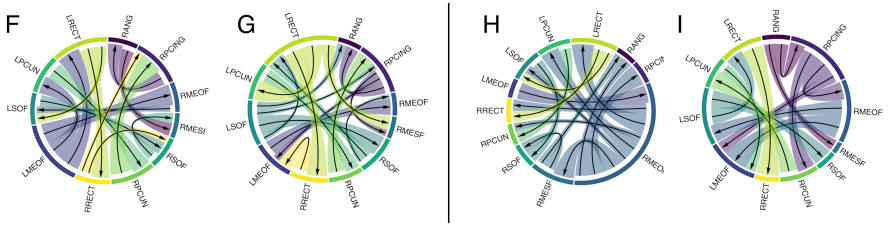
Modularity analysis [4] of 90x90 functional correlation matrices indicated 11 DMN nodes that were consistent across groups and timepoints. We defined functional connectivity as the edge betweenness centralities [5] for the resulting 11x11 DMN matrices. This was measured as the AUC across multiple network densities [6]. At Time 1 (A), the BC group showed several edges with significantly higher (negative value, darker color) or lower (positive value, lighter color) centrality compared to controls ($p < 0.013$, FDR corrected). At Time 2 (B), there were even more group differences characterized by exclusively lower centrality in the BC group ($p < 0.0001$, FDR corrected). There was a significant group by time effect (C) for several edges ($p < 0.003$, FDR corrected).



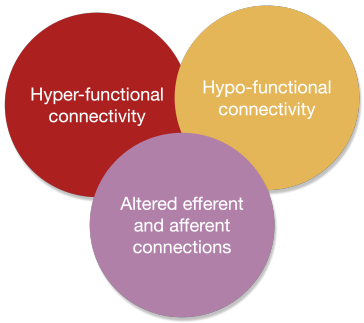
Effective connectivity was evaluated using FDR corrected, directed acyclic graphs (DAGs) learned by Bayesian network analysis [7]. At Time 1, the number of false positive and false negative DAG edges in the BC group with respect to controls was not significant (D) but was significant at Time 2 (E, false positive, $p = 0.05$, red lines; false negative, $p = 0.02$, yellow lines). DAGs for the BC group are shown in F and G for Time 1 and 2, respectively. Control DAGs are shown in H and I. Edge centrality and DAG false positive/negative comparisons were conducted with permutation testing (5000 permutations). RANG: right angular gyrus; RPCING: right posterior cingulate; L/RMEOF: left/right medial orbital frontal; RMESF: right medial superior frontal; L/RSOF: left/right superior orbital frontal; L/RPCUN: left/right precuneus; L/RRECT: left/right rectus gyrus.

Mean cognitive performance across standardized memory, attention, executive function and verbal fluency tests was significantly lower in the BC group compared to controls at both time points ($p < 0.05$) via t-test. However, linear mixed modeling indicated no significant group by time effects.

In patients, edge centralities were positively correlated with number of chemotherapy cycles ($p < 0.04$) and negatively correlated with cognitive function ($p < 0.03$).



Conclusion



Chemotherapy may be associated with complex DMN alterations including both hyper- and hypo-functional connectivity as well as reorganization of efferent and afferent pathways. Hyper-connectivity may exhaust neural resources leading to reduction in cognitive performance. The potential role of other treatments (radiation/hormone) requires further investigation.

Acknowledgements

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