Cognitive effects of breast cancer therapies: univariate and multivariate analyses of brain connectivity
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INTRODUCTION
Previous research has shown evidence of compromised cognitive function prior to adjuvant treatment (such as chemotherapy) for breast cancer1,2. These effects may increase patient reluctance to undergo therapy. Overall, the neural sequelae of cancer and its treatment remain unclear.

Resting-state MR functional connectivity has the ability to characterize healthy brain connections and pathological states, and changes in brain networks following external intervention3. Univariate and multivariate techniques can offer complementary information in these investigations.

This study investigates resting-state network correlations in women treated for breast cancer and age-matched healthy controls. Univariate changes within and between timepoints are examined. In addition, a multivariate partial-least squares analysis was performed.

METHODS

Subjects: Thirty women were enrolled, including patients with localized breast cancer undergoing treatment with either adjuvant chemotherapy (n=10) or radiotherapy (n=10) and 10 age-matched healthy controls. Subjects were scanned both at baseline (pre-adjuvant therapy, time 1) and 5 months later (time 2). For patients, time 2 corresponded to approximately 1 month after chemotherapy; and 3 months after radiotherapy.

MRI Data acquisition: BOLD functional data were acquired on a 3.0 T GE scanner. T2*-weighted data was acquired using a spiral-in sequence (TR/TE/FA/FOV=1.5s/30ms/90/24cm, 64x64 matrix, 5mm slice thickness, 25 slices). Anatomical T1 overlays matching the prescription of the functional data and whole-brain T1 SPGRs were also collected. Subjects were instructed to keep their eyes open and look at a fixation cross during the resting state acquisition (8 min duration, 240 timeframes). Respiratory and cardiac rhythms were recorded during MRI scanning.

Preprocessing: The fMRI data was preprocessed using MATLAB and SPM, including: k-space timecourse outlier removal, gridding and reconstruction, physiological noise removal using RETROICOR4, slice timing correction, and motion correction. Then, anatomical coregistration and normalization to MNI space, and spatial smoothing (4mm FWHM) were performed. Nuisance regressors (first principal component of head motion, and the global mean) were removed prior to low-pass filtering (< 0.08 Hz).

Data analysis: Average timeseries for every region of interest (ROI) in the AAL template5 were extracted and the correlation between every pair of ROI timeseries was calculated and transformed to a z-score. Paired z-score differences for each subject in each group (control, chemotherapy, radiotherapy) were formed. Univariate t-tests were used to examine significant differences versus time and group. Partial Least Squares (PLS6,7) was used to find the combination of group and time saliences (i.e., contrast weights) that explain the most variance in the data, which are called latent variables (LVs). Reliability was determined using permutation testing.

RESULTS

Changes in connectivity z-scores were observed, with significant timepoint differences in the chemotherapy and the radiation therapy group as compared to the control group (Figure 1, Table 1). Unique regional correlations were observed for each patient group (Table 1).

The multivariate PLS analysis also showed significant group interactions (p = .018; % variance explained = 40.15%). Figure 2 displays the design saliences of the principal latent variable for time 1 and time 2 for each group. This latent variable was expressed in all groups, but was accentuated for the patient groups. In particular, the chemotherapy group showed the largest difference in functional connectivity from time 1 to time 2.

DISCUSSION

Resting-state functional connectivity was used to examine pre- and post- therapy changes in subjects with breast cancer. Univariate and multivariate analyses both exhibited differential patterns of connectivity across groups and time. This may form the basis for improved diagnostic and monitoring techniques for cognitive changes associated with breast cancer and its treatment.

REFERENCES