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 cancer[1,2]. 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 intervention[3]. 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 RETROICOR[4], 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 timecourses for every region of interest (ROI) in the AAL template[5] were extracted and the correlation between every pair of ROI timecourses 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 (PLS[6,7]) 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.

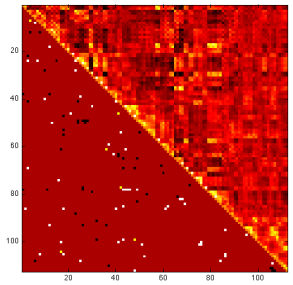

Figure 1. AAL correlation results. (Upper triangle) Average control z map, time 1 (Lower triangle) Significant time 2 – time 1 differences vs. controls for chemo (black), radiation (white), overlap(yellow) ; p<0.01

Group	Region 1	Region 2	Significance
Chemo	Thalamus_R	Frontal_Med_Orb_R	0.0005
	Frontal_Sup_Orb_R	Vermis_6	0.0005
	Heschl_L	Insula_R	0.001
	Cingulum_Ant_R	Cerebelum_6_R	0.001
Radiation	Cuneus_R	Amygdala_L	0.0003
	Thalamus_R	Calcarine_L	0.0003
	Frontal_Med_Orb_L	Vermis_6	0.0003
	Pallidum_L	Cerebelum_8_R	0.0007
	Thalamus_R	Calcarine_R	0.0008
	Temporal_Mid_R	Vermis_3	0.0008
	Thalamus_R	Cuneus_L	0.001

Table 1. Regional correlations exhibiting significant time 2-time 1 differences vs. controls for each treatment group (p <= 0.001). Anatomical labels correspond to the AAL atlas.

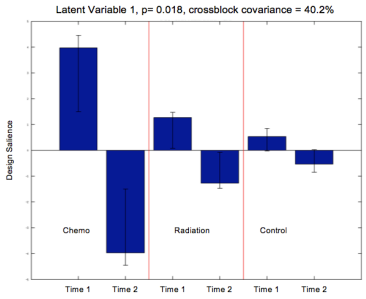

Figure 2. PLS results displaying the group by time interaction that explained the most variance between time 1 and time 2 (first latent variable).

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 time by 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.

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