Hippocampal Shape Deformity in Breast Cancer Patients With Self Reported Cognitive Concerns

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Background

Although advances in breast cancer treatments are improving health outcomes, treatment side effects can be troubling for those undergoing adjuvant chemotherapy. Up to 75% of breast cancer patients receiving chemotherapy exhibit cognitive impairment. Neuroimaging studies of this population suggest volume loss in several brain regions including parietal and occipital lobes, yet few studies have performed detailed analysis of the hippocampus, which shows volume loss in animal models of chemotherapy effects.

In this work, we used high-dimensional deformation mapping analysis to test whether hippocampal shape differs in individuals with breast cancer who received chemotherapy coupled with estrogen blockade therapy within the last 1.5 years, as compared to healthy controls. To examine whether differences in hippocampal shape were related to cognitive impairment, we tested relationships between these shape abnormalities and performance on standard neuropsychological tests.

Methods

Participants

- 16 pre-menopausal breast cancer patients and 18 healthy controls. All participants were right-handed, had no history of current or past neurological or psychiatric disorders, denied use of psychoactive drugs.
- All patients had invasive ductal carcinoma, metastatic lobular carcinoma or inflammatory breast cancer (stages I-IV, histologically confirmed). ECOG (Eastern Cooperative Oncology Group, physician rated) performances grade 0-2 (no-mild physical impairment).
- Chemotherapy interventions completed within 18 months prior to the study; receiving estrogen blockade therapy (Tamoxifen) at the time of the study.

Imaging

- 3T Siemens MPRAGE (TR = 2400 ms, TE = 3.16 ms, voxel size = 1 mm^3, FOV = 25.6 cm, flip angle = 8°, 176 sagittal slices). Automated high-dimensional deformation mapping (FS+LDDMM) was used to compare hippocampal shape differences between groups.

Analysis

- Independent sample T-tests were used to examine group differences in self report and neurocognitive performance. Repeated measures ANOVA was used to examine group and hemisphere differences with hemisphere as the repeated factor and hippocampal subfield as main effect

Cognition and Self-Report

- The NIH Toolbox Cognition Battery: measures attention, language, episodic memory, executive function, working memory and processing speed. These tasks composite fluid and crystalized intelligence estimates as well as total cognition composite.
- Neuro-QOL self-report was administered to measure anxiety, depression, fatigue, sleep disturbance, and pain levels, as well as perceived executive function and general cognitive concerns.

Table 1. Patient Demographics, Self Report and Cognition

	Oncology Group (n = 16)	Control Group (n =18)	p value (t-test)
Demographics	Mean (SD) [Range]		
Age	37.93 (5.20) [28-45]	27.17 (4.08) [21-37]	0.001*
Years of Education	16.64 (1.65) [13-20]	16.22 (1.86) [13-21]	0.431
Handedness (R/L)	100% R	100% R	—
Self Report (Neuro-QOL)	Mean T-score (SD)		
Applied Cognition - General Concerns	36.96 (5.96)	42.09 (5.58)	0.004*
Applied Cognition - Executive Function	40.55 (5.93)	43.57 (5.58)	0.144
Anxiety	53.95 (4.78)	51.37 (4.66)	0.128
Depression	48.24 (6.08)	44.77 (4.51)	0.069
Fatigue	47.86 (7.76)	46.30 (6.01)	0.520
Sleep Distrubance	50.37 (9.72)	46.50 (6.10)	0.174
Pain	47.91 (10.22)	42.71 (5.81)	0.095
NIH toolbox	Mean Standard Score (SD)		
Cognition total	120.64 (18.45)	129.43 (16.59)	0.289
Fluid Intellegence composite	96.70 (13.55)	98.30 (16.95)	0.773
Crystalized Inteligence composite	127.63 (17.29)	134.24 (17.25)	0.166

* = statistically differs between groups

Results

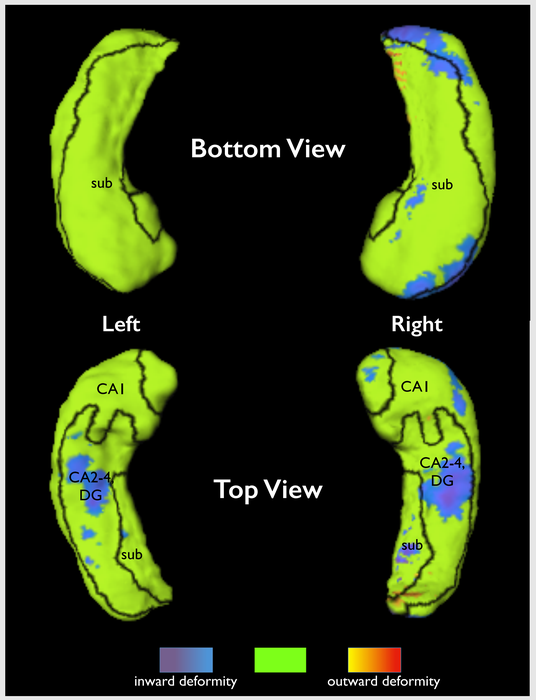

Figure 1. Hippocampal deformity between oncology patients and controls. Inward deformation (blue and purple) as calculated from t-values of a vertex-wise difference in the deformation amplitude between controls and patients (thresholded at p=0.05, uncorrected).

Demographics, Self-Report and Cognition

- Significant age difference between patients and controls (mean age = 37.9 and 27.2 years, respectively). No significant difference in years of education.
- Patients self-reported a greater level of general cognitive concern when compared to controls (p = 0.004). No differences between groups for perceived executive function, anxiety, depression, fatigue, sleep disturbance or pain.
- Patients did not differ from controls in composite measures of objective cognitive function obtained with the NIH Toolbox Cognition Battery. No significant difference in composite fluid cognition [t(30)=0.291, *p*=0.773], composite crystallized cognition [t(30)=1.080, *p*=0.286], nor in the overall composite score [t(30)=1.419, *p*=0.166].

Imaging

- Significant hippocampal surface deformation [F(1,31)=6.558, p=0.016] after controlling for age [F(1,31)=1.865, p=0.182] in patients compared with controls. Patients showed greater inward deformity.
- No significant difference in shape deformity between hemispheres.
- Post-hoc analysis of subfields revealed significant difference in deformity in the subiculum [F(1,32)=5.669, p=0.023].
- Overall volume for left and right combined hippocampi was greater in controls (mean = 2247.35 mm^3, std=173.09) compared to patients (mean = 2102.37 mm^3, std = 192.63) [F(1,31)=6.902, p=0.013].
- No significant difference in volume between left and right hemispheres.

Correlations between Deformation and Self report/Cognitive Measures

- No significant correlations were found between self reported cognitive concerns and deformation.
- No significant correlations were found between deformity and NIH toolbox measures of fluid, crystalized nor overall cognition.

Table 2. Hippocampal Shape Deformations in mm^3

	Oncology Group (n = 16)	Control Group (n =18)	p value
	Mean (SD) [Range]		
Hippocampal			
Combined	-0.068 (0.13)	0.026 (0.12)	0.016*
Right	-0.083 (0.13)	0.032 (0.13)	0.016*
Left	-0.053 (0.18)	0.020 (0.11)	0.163
CA1 Deformation			
Combined	-0.100 (0.26)	0.076 (0.24)	0.224
Right	-0.147 (.21)	0.023 (0.25)	0.042*
Left	-0.053 (.0.39)	-0.008 (0.25)	0.684
CA2-4, Dentate Gyrus			
Combined	-0.025 (0.14)	0.040 (0.073)	0.097
Right	0.005 (0.15)	0.029 (0.11)	0.608
Left	-0.056 (0.17)	0.052 (0.10)	0.027*
Subiculum Deformation			
Combined	-0.060 (0.17)	0.033 (0.10)	0.023*
Right	-0.069 (0.14)	0.038 (0.12)	0.022*
Left	-0.050 (0.14)	0.028 (0.10)	0.060

* = statistically differs between groups

Conclusions

- Cancer patients receiving adjuvant chemotherapy and estrogen blockade therapy exhibit inward deformation of the hippocampus, predominantly in the bilateral subiculum compared with controls.

Research Implications

- Animal studies indicate that adjuvant chemotherapy and hormone depletion inhibit neurogenesis of the hippocampus, alter blood supply through vessel damage, and may cause white matter damage.
- Consistent with these previous results, chemotherapy patients had smaller total hippocampal volume than controls.
- High-dimensional deformation mapping localized volume change to specific sub-regions of the hippocampus, indicating that the subiculum may particularly vulnerable to the cytotoxic effects of chemotherapy or estrogen blockade therapy.

Clinical Implications

- Although patients report more general cognitive concerns, their performance on neuropsychological measures of cognitive function are no different from controls.
- Given the morphological changes in hippocampal structure and this self reported cognitive difficulties, it is possible that these neuropsychological measures are not sensitive enough to detect deficits.

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