Treatment-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients.

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Introduction

Impaired cognitive functioning has been recognized as a potential adverse effect of adjuvant systemic treatment in breast cancer patients. A subset of breast cancer patients (10 to 40%) experiences mild cognitive deficits in domains mainly involving memory, attention and concentration, psychomotor speed, executive functioning and multi-tasking[1]. The focus of our study is not patients with primary brain pathology or secondary (metastatic) processes, but patients without clear existence of primary or secondary (focal) brain lesions, undergoing systemic chemotherapy. The pathophysiology of this impaired cognitive functioning is still unclear. So far, evaluation of the effects of adjuvant therapy on cognitive functioning has predominantly been done using neuropsychological tests and self-rated subjective questionnaires. Only a limited number of studies have used brain imaging techniques to investigate potential physical changes in the brain, induced by the therapy. These studies suggest both functional and structural changes in the brain[2,3,4]. A potential mechanism by which systemic adjuvant treatment could impair cognitive functioning is direct neurotoxicity, causing toxic injury to brain parenchyma, producing demyelination and/or altered water content, resulting in alterations of the white matter (WM) integrity of the brain. The purpose of this diffusion tensor imaging (DTI) study is to evaluate changes in WM fractional anisotropy (FA) and mean diffusivity (MD) in a group of breast cancer patients compared to age-matched healthy controls and correlate FA with possible cognitive impairment using voxel-based analyses. We hypothesize that FA is lower and MD higher in patients relative to controls in important WM tracts that are related to cognitive functioning.

Methods and materials

Seventeen postchemotherapy (2-4 months), early-stage breast cancer patients (age 45.4 ±4.2), and 19 matched controls (age 45.2 ±3.9) were imaged on a 3T scanner (Intera, Philips, Best, the Netherlands) with an 8 channel phased array head coil. A whole brain DTI SE-EPI with 45 non-collinear directions and a b-value of 800 s/mm^2, was acquired, together with 3D-TFE, FLAIR and T2w TSE scans. The latter 3 scans were used to search for primary brain pathology as an exclusion criterion. Three subjects with excessive WM lesions and three subjects with inferior DTI image quality were excluded for further analysis, resulting in 14 patients and 16 controls included in the study. Subjects were evaluated with a comprehensive battery of cognitive tests, covering domains of attention, concentration, memory, executive functioning and psychomotor speed. Self-reported cognitive function, anxiety and depressive symptoms were assessed using the Cognitive Failure Questionnaire (CQF), the Spielberger State-Trait Anxiety Inventory and the Beck Depression Inventory. Statistically significant differences on test scores between patients and controls were assessed with two-tailed two-sample student's T-tests. Tests that showed significant difference between the groups ($p<0.05$) were subsequently selected for the voxel-based correlation analysis, namely: attention/concentration tests (Bourdon Wiersma Dot cancellation test; Test of Every Day Attention, auditory elevator with reversal (TEA_ST5)) and psychomotor/processing speed (Nine-hole Peg (9HPT); WAIS Digit Symbol; Trail Making Test A (TMTA)).

In order to correct for eddy current-induced distortions and motion artefacts, DTI images were realigned using FSL-flirt. After additional b-matrix rotation, FA and MD maps were generated and non-rigidly coregistered to a DTI atlas in ICBM81 space. FA and MD images were then smoothed with a 3D Gaussian kernel of FWHM 6mm and entered in voxel-based analysis using SPM5. A two sample T-test including age as 'covariate of no interest' was performed to assess differences in FA and/or MD values between patients and controls. Additionally, voxel-based correlation analysis was done to investigate potential correlations between FA and neuropsychological test scores.

Results

Compared to normal controls, the patient group demonstrated significantly decreased FA in frontal (superior fronto-occipital fasciculus, superior corona radiata: cluster extent 947, p_{cor} <0.001) and temporal (sagittal stratum including inferior longitudinal fasciculus, cluster extent 273, p_{cor} =0.004) WM tracts and cerebellum (inferior and middle cerebellar peduncle, cluster extent 261, p_{cor} =0.003) (Fig. 1 & 2). Additionally, a significant increase of MD in patients compared to controls was demonstrated in frontal (cluster extent = 1189, p_{cor} <0.001) and parietal (p_{cor} =0.006) subgyral WM.

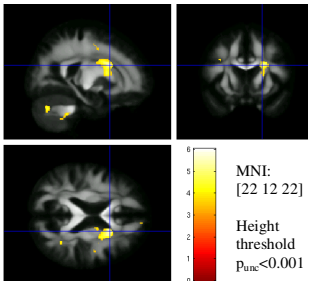

Fig 1: Regions showing significant decrease in FA in the voxel-based analysis overlaid on the mean FA map

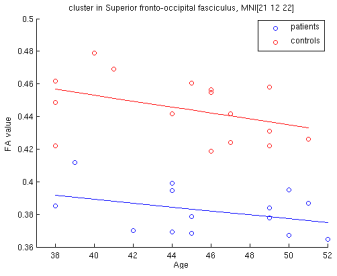

Fig 2: Scatter plot of average FA value versus age in most significant cluster including part of superior fronto-occipital fasciculus

Two-tailed t-tests comparing neuropsychological scores for patients and controls revealed differences between group means for Bourdon-Wiersma, 9HPT hole, TMTA, and TEA_ST5 ($p<0.05$). For the WAIS substitution test, difference was nearly significant ($p=0.053$).

Correlation analysis of FA with neuropsychological test scores revealed a significant correlation with attention tests in the superior longitudinal fasciculus: strong negative correlation with the Bourdon-Wiersma average time/row (cluster extent 524, p_{cor} <0.001) and positive correlation for the Every Day Attention test, TEA_ST5 (cluster extent 162, p_{cor} <0.05). Additionally, a positive correlation was found for the WAIS Digit Symbol test in the sagittal stratum including the inferior longitudinal and fronto-occipital fasciculis (cluster extent 183, p_{cor} = 0.03). No significant correlations were found for TMTA. Subjective self-reported complaints correlated negatively with FA in parietal subgyral WM. (cluster extent 192, p_{cor} =0.026).

Conclusion

In this study, we demonstrated changes in cerebral WM integrity in breast cancer patients (without primary brain lesions or metastasis) after systemic chemotherapy by means of DTI. WM tracts that are affected are the superior fronto-occipital fasciculus, inferior longitudinal fasciculus, corona radiata, and cerebellum. Several recent studies have linked these WM tracts to cognitive processing speed[5], to executive function, attention and cognition in general. These results therefore suggest a link between impaired cognition after systemic chemotherapy and WM integrity. Furthermore, significant correlations between neuropsychological tests and WM FA values seem to corroborate our findings.

References

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