Investigating the long-term effects of systemic chemotherapy on brain white matter using multi-shell diffusion MRI and myelin water imaging

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Target audience: Basic scientists and clinicians with an interest in diffusion MRI, neuroscience, neuroimaging and oncology.

Purpose: Systemic chemotherapy treatment for breast cancer has been associated with cognitive dysfunction [1]. Furthermore, the dysfunction has been shown to correlate with decreased fractional anisotropy (FA) and mean diffusivity (MD) in white matter [2]. The underlying pathology and evolution of systemic chemotherapy-related neurobiological effects is unknown. The purpose of this follow-up study is to investigate brain microstructural changes three years post-chemotherapy using multi-shell diffusion MRI and myelin water imaging.

Methods: **Subjects**: Recovering female breast cancer patients who received chemotherapy (C+, n=25) or did not receive chemotherapy (C-, n=14) and healthy controls (HC, n=12). **Imaging**: DWIs were acquired (3T Philips Achieva) with b-values 700, 1000 and 2800 s/mm² along 25, 40 and 75 directions, respectively. Multicomponent T2-relaxation data were acquired using a modified GraSE sequence [3]. **Measures**: Conventional diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) parameters were estimated using ExploreDTI [4]. The fraction of isotropic fluid (FISO), the neurite density index (NDI) and the orientation dispersion index (ODI) were calculated using the NODDI toolbox [5]. Relaxometry data yielded the myelin water fraction (MWF), the intra- and extracellular water fraction (IEWF), geometric mean T2 time of the general T2 distribution (G-gmT2) and the IE water (IEW-gmT2) and the width of the IEW-peak (IEW-pw) [6]. A population-based FA-template was constructed [7], to which all parameter maps were registered. Fiber orientation distribution profiles (FODs) were calculated using MRtrix [8], and reoriented to the FA-template [9]. Tracts previously associated with chemotherapy-related changes were delineated using constrained spherical deconvolution (CSD) [10]: cingulum, forceps minor, forceps major and the superior longitudinal fasciculus (SLF). Parameter values of each subject were calculated in the tract masks in template space. **Statistical analysis**: Whole tract: one-way ANOVA was used to investigate the main effect of group membership. Local difference: the group:position interaction term in a 2-way ANOVA was used. A permutation method was applied to correct significant ($p<0.05$) findings for multiple comparisons [11]. To identify which groups or positions caused significant differences in these F-tests, post-hoc t-tests were performed and corrected using Tukey's honestly significant difference criterion.

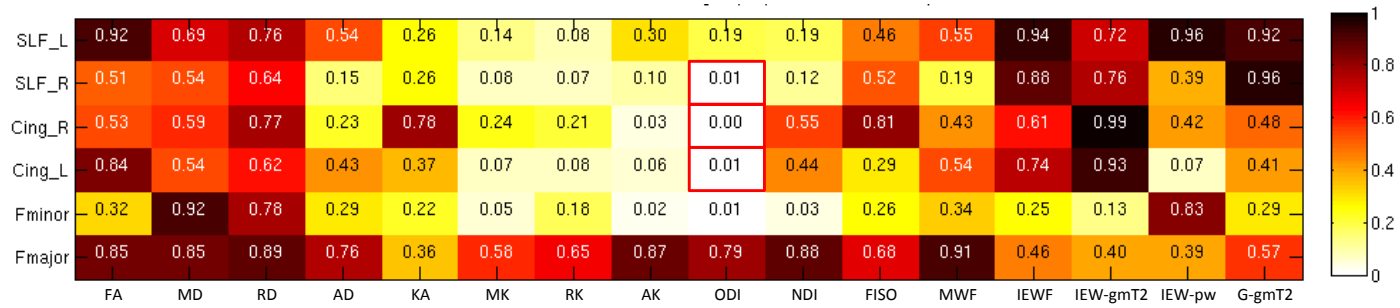

Figure 1. P-values for each tract/parameter combination. Squares with a red border indicate significance after correction for multiple comparisons.

Results: Figure 1 illustrates the resulting p-values. The only parameter that significantly differed after correction for multiple comparisons was the orientation dispersion index (ODI). ODI significantly increased in the right SLF ($p=0.008$) of the C+ group compared to HC. Both C+ and C- groups had increased ODI in both left ($p=0.008$) and right ($p=0.0001$) cinguli, compared to HC, with additional local variations in the right cingulum. Furthermore, a trend is visible towards whole tract differences of AK along the Fminor and right cingulum. However, these differences do not remain significant after correcting for multiple comparisons. Figure 2 illustrates the significant tract/parameter combinations.

Discussion & conclusion: Three years after chemotherapy, no remaining alterations were found in mean DTI metrics along the main tracts of interest. However, kurtosis and NODDI parameters did yield whole tract differences between subject groups. This may reflect an increased sensitivity of more advanced multi-shell based models for detecting latent microstructural damage and ongoing recovery in this population.

Localized differences were limited to the right cingulum suggesting a possible vulnerability in this tract or, that in general, chemotherapy-related damage may be diffuse rather than local.

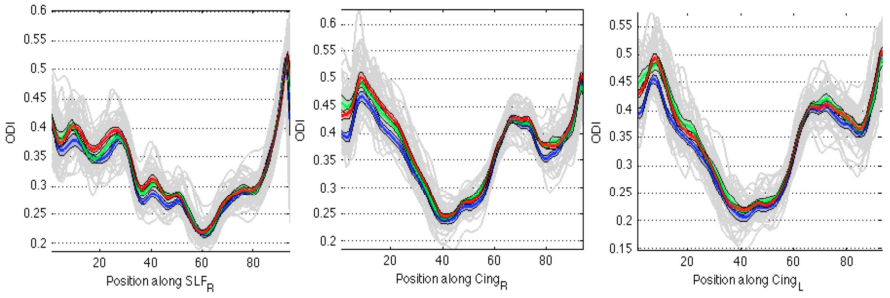

Figure 2. Change in ODI across the length of the right SLF and bilateral cinguli, illustrating whole tract and locally significant differences between groups. (red = C+, green = C-, blue = HC)

The lack of findings from MWI parameters was consistent with the lack of findings from NDI. These parameters are concerned with the composition of tissue, while ODI reveals organizational changes, adding a unique dimension to the analysis.

Of all the parameters investigated, ODI appeared to be most sensitive for detecting long-term microstructural change following systemic chemotherapy.

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