Structural remodelling of contralesional and ipsilesional white matter predicts motor recovery in stroke patients

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Introduction: Restorative cell-based and pharmacological therapies show significant promise for improving functional outcome following stroke[1], but the current lack of robust biomarkers to monitor the effects of such interventions in humans limits their translation into patient care[2]. Recent research suggests that structural remodeling of both ipsilesional and contralesional white matter tracts is associated with improved motor recovery[3]. The purpose of the current study was to examine changes in fractional anisotropy (FA - a marker for neuronal integrity[4]) in recovering stroke patients, and to correlate these changes with functional outcome.

Methods: Six patients (age 53±10 y) with a non-lacunar ischemic stroke in the left middle cerebral artery territory resulting in motor impairment underwent MRI at 3 and 15 weeks after stroke onset. Diffusion tensor MR (DTI) images were acquired with a pulsed gradient spin echo EPI sequence with echo time (TE)=91ms and repetition time (TR)=8000 ms, using a 3.0 T GE TwinSpeed HDx MRI scanner. The diffusion gradient scheme included 25 gradient encoding directions with b=1000 and 3 b=0 images. The motor function of the right arm was assessed with the Fugl-Meyer (FM) scale at both visits. Seven healthy controls (age 53±7 y) were also recruited. Diffusion weighted data were corrected for eddy current distortions and the diffusion tensor was calculated on a voxelwise basis with dtifit.[5] The FA images were normalised to a standard space DTI template with FNIRT (part of the FMRIB software library http://www.fmrib.ox.ac.uk/fsl/). Permutation testing was used to investigate voxelwise differences in FA between patients and controls, changes in FA in patients between from baseline to follow-up, and correlations between FA at baseline and motor outcome.[6]

Results: All patients demonstrated a functional improvement in motor score between the baseline and follow-up visits. At baseline, patients demonstrated significantly reduced FA in the left internal capsule and corticospinal tract (Figure 1). Between the 2 visits, FA in the patients significantly decreased in the ipsilesional thalamus, corticospinal tract, and corpus callosum (Figure 2). Higher FA in the ipsilesional corticospinal tract, internal and external capsule, and lower FA in the ipsilesional thalamus and corpus callosum were associated with a higher FM score at 15 weeks (Figure 3).

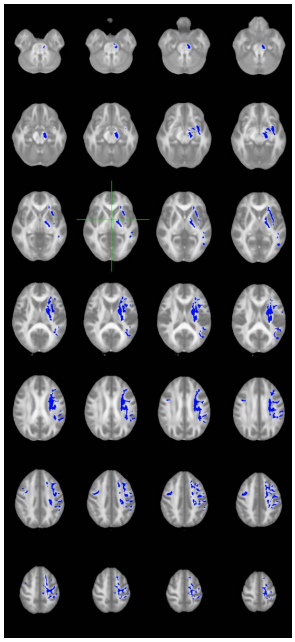

Figure 1. Significant clusters where patients show reduced FA relative to controls ($p<0.005$, corrected) at baseline.

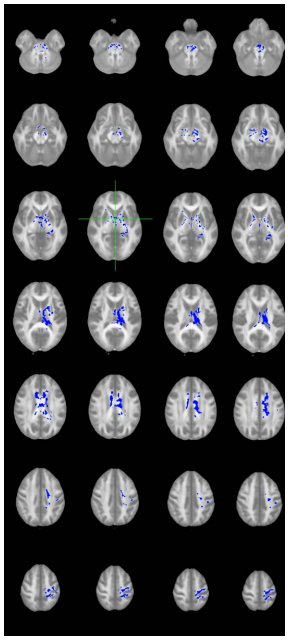

Figure 2. Significant clusters where patients show reduced FA at follow-up relative to baseline ($p<0.005$, corrected)

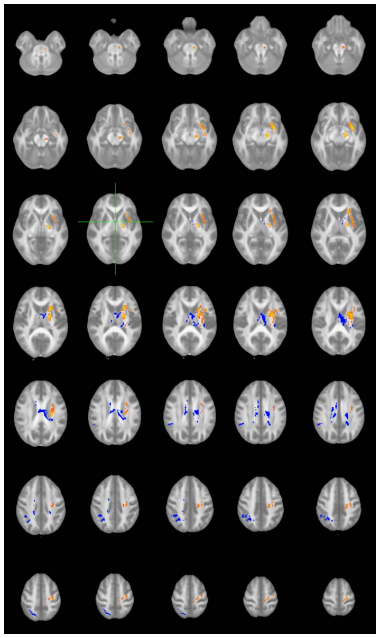

Figure 3. Correlations between baseline FA and motor outcome in patients: red clusters denote a positive correlation ($p<0.005$, corrected)

Discussion: DTI metrics like FA represent promising imaging biomarkers for stroke recovery. The positive correlation between motor outcome and baseline FA in the external and internal capsule and corticospinal tract indicates the early predictive potential of this imaging biomarker. The continued decrease in FA between 3 and 15 weeks post stroke is surprising given the functional improvement over this time, but may reflect progressive degeneration of the efferent fibre pathways from the stroke-affected areas. The negative correlation between motor outcome and baseline FA in the ipsilesional thalamus and corpus callosum may be indicative of increased recruitment of contralesional areas in patients with more severe strokes, (representing an effect rather than a cause), but further studies with larger patient cohorts will be required to elucidate these findings. However, the observed relationship between FA and motor function provides further evidence for the purported link between microstructural remodelling and recovery.

References: [1]Zhang and Chopp, Lancet Neurol 8:491-500 (2009), [2]Hachinski et al., Stroke 41:1084-99 (2010), [3]Schaechter et al., Human Brain Mapping 30:3461–3474 (2009), [4]Charlton et al. Neurology 66;217 (2006), [5]Smith et al., NeuroImage, 23(S1):208-219, 2004, [6]Suckling & Bullmore, Human brain mapping 22, 193-205 (2004)