A study on brain-behaviour functional relations in areas affected due to ischemic stroke using diffusion MRI

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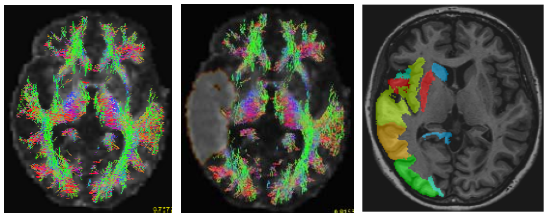
Introduction: There is growing evidence that stroke impacts not only at the focal site of lesion but also on remote brain regions and networks. Cerebral white matter, which constitutes about 50% of the human brain volume, is especially vulnerable to hypoxic-ischemic injury, resulting in white matter (WM) lesions. Knowledge of how brain networks are interrupted is critical to better understanding the nature of the clinical deficit and stroke recovery. Five functions commonly affected by stroke and important in recovery and rehabilitation include: attention; executive function; touch sensation; movement; and mood/depression. Knowledge of the impact of stroke lesions on neural networks that support these functions may be important to better inform the potential for recovery and ability to benefit from rehabilitation.

We used diffusion-weighted MRI (DWI) and probabilistic tractography to identify the common neural pathways affected in chronic stroke patients, with a view of predicting cognitive and functional deficits associated with the affected areas. Our hypothesis is that loss in connectivity in key cortical or subcortical regions exhibits a commonality and that the loss in connectivity in these common regions will correlate with the clinical measurements of cognition, sensorimotor function and disability; i.e. the fractional anisotropy (FA) values and the mean diffusivity (MD) will show negative and positive correlations respectively when regressed against clinical severity scores. To investigate these hypotheses, we used probabilistic diffusion tractography and network based statistics (NBS)[2], which is a clustering method based on generalized linear model to identify the differences in brain networks due to stroke. We then performed a linear regression analysis between the FA and MD values of the affected common regions and the clinical measures of brain-behavior functions available at the 3-months stroke stage.



(a)Whole brain tractography | (b)Tractography with exclusion ROI | (c)Loss in connectivity of the AAL regions from NBS due to stroke

Fig. 1. Examples of tractography and loss in connectivity of AAL regions from NBS. Color-code for (c): blue-no loss in connectivity, red-maximum loss in connectivity.

Method: Our study involved a cohort of 22 stroke patients (11 right-hemispheric, 11 left-hemispheric strokes) and 40 normal age matched controls. A high angular resolution diffusion imaging (HARDI) echo-planar imaging (EPI) sequence in 60 directions with b=3000s/mm^2 were acquired for both cohorts. FA and MD were generated from the EPI sequences after pre-processing[3,4] and using MRtrix[5]. 3D ROIs for the stroke lesions were manually delineated by an expert neurologist on fluid-attenuated inversion recovery (FLAIR) images and the ROIs were non-rigidly transformed to FA co-ordinates of control cohorts. The anatomical atlas labeling (AAL) with 116 regions was used for cortical/sub-cortical parcellations of grey matter areas. The clinical scores for each stroke patient were obtained by a trained therapist at 3 month post-stroke using the, Modified Rankin Scale (mRS), Montreal Cognitive Assessment (MoCA), Trail Making Test-B (TMT (B)), STROOP, Action Research Arm Test (ARAT), Stroke Impact Scale (SIS) and Tactile discrimination task (TDT) & Montgomery-Åsberg Depression Rating Scale (MADRS).

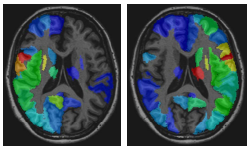


Fig. 2. Left and right images show most of the impacted areas in ipsilesional hemispheres. Color-code: blue to red denotes low to severe disconnectivity.

Whole brain probabilistic diffusion tractography using anatomically constrained tractography (ACT) with MRtrix[5,6] and with each stroke ROI (used as exclusion mask) were performed respectively for each of the 40 control data sets (Fig. 1(a) & 1(b)). The streamlines were further filtered using SIFT[7] to improve biological accuracy of streamline reconstruction. Therefore, number of streamlines connecting each pair of AAL atlas regions was used to encode the 116×116 connectivity matrices for the whole brain and exclusion ROI tractography separately. The resulting 40 connectivity matrices generated with and without the stroke ROI exclusion mask were contrasted for a pairwise permutation testing using the NBS[2]. Variable *t*-test thresholds=3 to 11, no. of permutations=5000 and a significance level of $p<0.05$ were used for the 22 patient cases in order to restrict network sizes to less than 40 nodes. NBS identifies the significant brain networks affected by stroke; therefore, the number of associations for each region may be directly interpreted as the loss in connectivity for that region (Fig. 1(c)). The loss in connectivities for the regions were totaled and the regions with high disconnectivity (more than the median disconnectivity) were identified for each set of left and right hemispheric lesions. Linear regression analysis between the FA and MD values for the sets of affected AAL regions against the respective clinical scores was then performed for the left and right hemispheric strokes separately.

Table 1 Regions with significant correlations ($p<0.05$) with FA/MD values for left hemispheric strokes

mRS	FA	Left - precentral & postcentral gyri, Rolandic operculum, occipital, inferior parietal, superior, middle and inferior temporal gyri
	MD	Left lenticular nucleus putamen
ARAT	FA	Left insula
	MD	Left thalamus
TDT	FA	Left insula
SIS	MD	Left - inferior parietal, middle temporal gyri, lenticular nucleus putamen, cerebellum

Table 2 Regions with significant correlations ($p<0.05$)with FA/MD values for right hemispheric strokes

MADRS	FA	Right - postcentral gyrus, lenticular nucleus putamen, thalamus
	MD	Right - precentral, frontal, mid-frontal, mid-occipital gyri, supplementary motor area.
MoCA	FA	Right cerebellum
	MD	Left precentral gyrus (contralesional)
TMT(B)	FA	Right - paracentral lobule, cerebellum
	MD	Right - rolandic operculum, hippocampus, mid-occipital and postcentral gyri
STROOP	FA	Left middle occipital gyrus (contralesional)
	MD	Right superior occipital gyrus
TDT	FA	Right cerebellum
	MD	Right precentral and postcentral gyri

Results: Our experiment with NBS revealed that for the patients with left or right hemisphere lesions, the disruption was primarily observed in the corresponding ipsilesional hemisphere (Fig. 2). The linear regression analysis on the FA and MD for AAL regions against the clinical scores revealed some AAL regions with significant correlations (≥ 0.6 or ≤ 0.6, $p<0.05$) (Tables 1 & 2).

Discussions: The analysis shows involvement of primary and secondary sensorimotor processsing areas in the lesioned hemisphere to be associated with the mRS, a broad disability score measuring disability impacted by impairment. More specific impairment based measures of sensorimotor function of the upper limb were associated with ipsilesional insula and thalamus for left hemispheric strokes, and with cerebellum and sensorimotor cortex for right hemispheric strokes. Associations with cognitive measures (MoCA, TMT(B), STROOP) and depression (MADRS) were only evident in patients with right hemispheric strokes and included distributed regions (ipsilesional and contralesional) involving cerebellum, precentral gyrus, postcentral gyri, frontal and occipital regions. In summary, our findings indicate that sensorimotor and disability outcomes are primarily bounded by disruption to neural pathways within the lesioned hemisphere at 3-month post-stroke. While impaired cognition and mood is associated with disruption of distributed pathways across hemispheres in stroke survivors with right hemispheric lesion.

References: **1.** Tse, T. et al. Measuring participation after stroke: A review of frequently used tools. *Arch Physical Med & Rehab*. 2013;94:177-92. **2.** Zalesky, A. et al. Network-based statistic: Identifying differences in brain networks. *NeuroImage*. 2010;53:1197-1207. **3.** Pannek, K. et al. Diffusion MRI of the neonate brain: acquisition, processing and analysis techniques. *Ped. Radiol. 2012;*42(10):1169-82. **4.** Pannek, K. et al. HOMOR: Higher order model outlier rejection for high b-value MR diffusion data. *NeuroImage.* 2012;63:835-842. **5.** Tournier, J-D. et al. MRtrix: Diffusion tractography in crossing fiber regions. *Intl J of Imag. Sys. & Tech.*. 2012;22(1):53-66. **6.** Smith, R. et al. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. *NeuroImage*. 2012;63:1924–1938. **7.** Smith, R. et al. SIFT: spherical-deconvolution informed filtering of tractograms. *NeuroImage*. 2013;67:298–312.