Automated detection of brain regions associated with post-stroke depression: A hypothesis

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Introduction: Post-stroke (PSD) depression is a common neuro-psychiatric complication of stroke. Approximately 20% of patients, who sustain a stroke, meet the criteria for major depressive disorder in the post-stroke period while another 20% meet the criteria for minor depression following stroke[1]. Several studies have found a significant association between lesion location and the development of PSD, particularly during the first few months following stroke[2]. Lesions in the subcortical white matter, thalamus, basal ganglia, and brain stem show strong association with PSD with cognitive disturbance[3]. However, little is known regarding the impact of stroke lesions on neural networks that are associated with PSD.

In this study we used diffusion-weighted MRI (DWI) and probabilistic tractography to measure the connectivity of WM networks in chronic stroke patients, with a view of developing a model to predict which stroke patients will go onto develop PSD. Our hypothesis was that loss in connectivity[4] in key cortical or subcortical regions due to stroke lesions would positively correlate with the PSD scores, i.e. higher loss in connectivity within certain regions leads to severe PSD. To our knowledge this is the first attempt to use diffusion tractography to identify the brain networks associated with PSD.

Using this approach, we performed a groupwise linear regression analysis between the loss in connectivity at each automated anatomical labeling (AAL) atlas region, and the PSD scores available for the stroke cohort at the chronic 3-month stage. Prior to the regression analysis probabilistic diffusion tractography[5] and network based statistics (NBS)[6], which is a clustering method based on generalized linear model are applied to identify the differences in brain networks.

Method: Our study involved a cohort of 14 stroke patients and 41 normal age matched controls. A high angular resolution diffusion imaging (HARDI) echo-planar imaging (EPI) sequence in 60 directions with B=3000 were acquired for the control and stroke cohorts. Fractional anisotropy (FA) maps were generated from the EPI sequences after pre-processing[7,8] and using MRtrix[5]. 3D ROIs for the stroke lesions were manually delineated by an expert neurologist on fluid-attenuated inversion recovery (FLAIR) images. Intra-patient affine registrations were performed to transform the ROIs from FLAIR to FA co-ordinates. Non-rigid registrations were performed between the FA maps of each stroke patient and each control participant to transform the ROIs into control co-ordinates. The depression scores for each stroke patient had been analyzed by a neuro-psychiatrist at 3 month chronic stage using the Montgomery-Åsberg depression scale (MADRS).

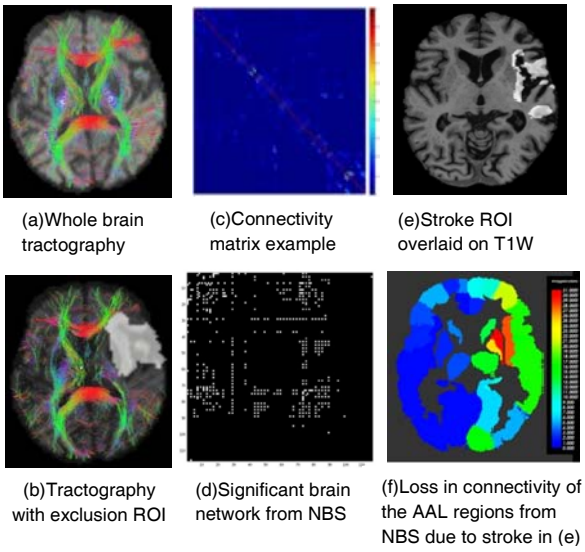

Fig.1 Examples of tractography, connectivity matrix, brain network from NBS and loss in connectivity of AAL regions. Color-code for (f): blue-no loss in connectivity, red-maximum loss in connectivity.

Whole brain probabilistic diffusion tractography[5] and with each stroke ROI (used as exclusion mask) were performed respectively for each of the 41 control data sets (Fig.1(a) & 1(b)). The numbers of white-matter fiber tracts connecting each of the AAL atlas regions were used to compute the 116×116 connectivity matrices for the whole brain and exclusion ROI tractography separately (Fig. 1(c)). The connectivity matrices were symmetric with unit diagonal and normalized by dividing the row elements by the respective row sums. The resulting 41 connectivity matrices generated with and without the stroke ROI exclusion mask were contrasted for a pairwise permutation testing using the NBS[6]. A t-test threshold of 2.0, number of permutations=5000 and a significance level of $p<0.05$ were selected for all patient cases. In this case, the NBS identifies the significant brain networks affected by the stroke (Fig. 1(d)). The number of associations for each region may be directly interpreted as the loss in connectivity for that region (Fig. 1(f)). A groupwise linear regression analysis between the loss in connections at each of the AAL regions with the respective MADRS scores for the stroke cohort was then performed.

Results: The groupwise linear regression analysis revealed 8 AAL regions to be affected by PSD at the chronic 3-month stage with $p<0.05$. The correlations obtained were all positive this signifies that higher loss in connectivity can be interpreted as severe PSD. Table 1 shows the correlation and p-values (uncorrected for multiple correction) for the respective AAL regions found to be significantly associated with PSD. Fig.2 shows the axial and sagittal views of the AAL regions associated with PSD overlaid on a T1W AIBL atlas.

Table 1: AAL regions associated with PSD with their respective correlation values.

AAL region	*Posterior_cingulate_gyrus_Right*	*Cuneus_Right*	*Superior_occipital_gyrus_Right*	*Thalamus_left*	*Thalamus_right*	*Temporal_pole_middle_temporal_gyrus_Right*	*Vermis_7*	*Vermis_9*
Correlation	0.559	0.559	0.559	0.563	0.710	0.559	0.559	0.559
p-value	0.037	0.037	0.037	0.036	0.004	0.037	0.037	0.037

Discussions: From our analysis, we could automatically identify the sub-cortical/cortical regions that were most likely associated with depression at 3 months post-stroke stage. Our hypothesis that the loss in fiber-tract connections due to stroke is directly correlated with depression, was successful in identifying sub-cortical regions that overlap with those reported in literature[2,3], especially the thalamus and the cingulate gyrus. This study highlights that structural connectivity analyses can be used to identify neural circuits associated with PSD. Furthermore, such an approach has the potential to identify stroke patients at high risk of developing PSD.

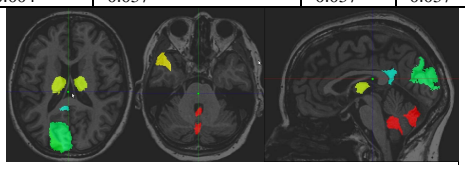

Fig.2 AAL regions associated with PSD. Regions associated are shown in axial and sagittal views.

References: **1.** Huffman J.C, Stern T.H. Poststroke neuropsychiatric symptoms and pseudoseizures: A discussion. *Primary Care Companion J Clin Psychiatr.* 2003;5(2):85–88. **2.** Bhogal S.K., et al. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. *Stroke.* 2004;35:794-802. **3.** Bogousslavsky J. William Feinberg Lecture 2002: Emotions, mood, and behavior after stroke. *Stroke.* 2003;34:1046-1050. **4.** Kuceyeski A, et al. Linking white matter integrity loss to associated cortical regions using structural connectivity information in Alzheimer's disease and fronto-temporal dementia; the Loss in Connectivity (LoCo) score. *NeuroImage*. 2012;61:1311-1323. **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.** Zalesky A, et al. Network-based statistic: Identifying differences in brain networks. *NeuroImage.* 2010;53:1197-1207. **7.** Pannek K, et al. Diffusion MRI of the neonate brain: acquisition, processing and analysis techniques. *Ped. Radiol. 2012;*42(10):1169-82. **8.** Pannek K, et al. HOMOR: Higher order model outlier rejection for high b-value MR diffusion data. *NeuroImage.* 2012;63:835-842.