TRANSFER FUNCTION OF THE RESTING STATE: A NOVEL APPROACH TO ASSESS OPTIC NEURITIS

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INTRODUCTION: Optic Neuritis (ON) is an inflammatory disease of optic nerve which causes partial or complete vision loss, pain on eye movement and subtle color washout of the affected eye (1). ON presents good early symptoms for Multiple Sclerosis (MS) (2) which is an acute autoimmune neurological disease. Reliable imaging biomarkers can be developed using ON as a system model which are essential for advanced treatment and pathology of MS (3). Consequently the study of the connectivity change of brain regions associated with ON has become an imperative field of research. Recent studies have revealed that resting-state functional magnetic resonance imaging (rs-fMRI) exhibits temporal correlation between brain regions (4). Rombouts *et al.* (5) found abnormal pattern of brain activities within visual areas in ON patients. We propose an approach of differentiating healthy persons from ON patients by transfer function analysis between brain regions that are correlated in optical activity during resting state for both eyes closed and open conditions. We provide Receiver Operator Characteristic (ROC) analysis results on various transfer function metrics and compare the results with existing outcomes.

METHOD: Data was collected from 21 consecutively enrolled patients (mean age 33.8 years) and 12 age-matched healthy volunteers following ethics clearance procedure at the Neuro-Ophthalmology Clinic in the University of Calgary. Images were obtained using T2*-weighted Echo Planar Imaging (EPI) sequence by a 3T MRI scanner with imaging parameters: TR = 1500 ms, TE =30 ms, FOV = 240x240 mm, slice thickness = 5mm and slice number = 30. Image processing steps include brain extraction, interleaved slice timing correction, motion correction and drift removal by temporal high-pass filtering (>0.01Hz). Six regions of interests were traced from activation maps showing differences between patients and control subjects both in eyes closed and open conditions in resting state: Lateral Geniculate Nuclei (LGN) of both hemispheres, Primary Visual Cortex (V1), right and left Lateral Occipital Cortex (LOC1 and LOC2) and right and left Superior Parietal Areas (SPA1 and SPA2). After obtaining signals from each region, we removed the DC components and windowed the signals using Tukey temporal filter. We then computed the transfer functions, which assess how signals transfer between different brain regions, assuming feed-forward propagation of visual information in the cortex (Fig. A). The transfer function (TF) from region X to region Y is defined as, $TF_{X\to Y} = DFT(Y)/DFT(X)$, where *DFT(.)* indicates discrete Fourier transform. The transfer function power spectrum was computed subsequently. In order to compute the decision metrics, total power in the bands P_1=0-0.1 Hz, P_2 = 0.1-0.2 Hz, P_3 = 0.2-0.3 Hz were considered since total power in the transfer functions are distributed in these bands. The ratios of power of a particular band to total power, P_i / P_{TOTAL}, and ratios of power between band i to band j, P_i / P_j were determined (i =1,2,3). ROC curves were then generated for each of the metrics. The area under the ROC curve, A_z, was used as a preliminary identifier for the optimal transfer function metric. Since the transfer function involves division, a comparatively small value in *DFT(X)* may produce an extraneous high peak in the transfer function power spectrum in spite of small *DFT(Y)* value (Fig. B). This problem was overcome by applying different threshold values for the normalized *DFT(X)* signal of the transfer function. ROC analysis was performed for different thresholds to observe the effect of thresholds on signal propagation behavior.

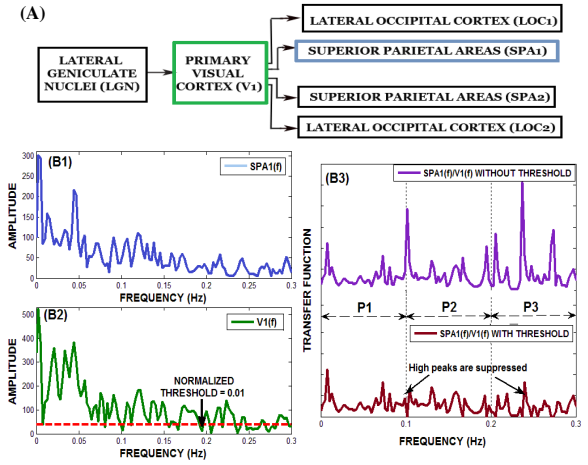

Figure: (A) Feed-forward model for propagation of visual information in the cortex; Amplitude spectrum for (B1) SPA1 and (B2) V1 for a patient sample; (B3) Transfer function spectrum for V1 to SPA1 signal propagation without (upper curve) and with (lower curve) threshold. Note that in the absence of threshold, minute V1 value (*e.g.* near 0.1 Hz) results in high peak in the transfer function nevertheless SPA1 is low; The extraneous peaks are removed from the transfer function by applying threshold in the spectrum of V1.

Table 1: Area Under Curve for (A_z) for different decision metrics with changing thresholds for LGN to V1 and V1 to SPA1 propagation in resting state eyes closed condition. Higher values (shown in bold) indicate better test performance.

	Decision Metric	Threshold					
		No threshold	0.02	0.04	0.06	0.08	0.1
LGN to V1	P_1/P_{TOTAL}	**0.75**	0.54	0.55	0.49	0.40	0.48
	P_2/P_{TOTAL}	0.65	0.44	0.30	0.39	0.37	0.48
	P_3/P_{TOTAL}	0.66	0.60	0.49	0.45	0.41	0.54
	P_1/P_2	0.68	-	-	-	-	-
	P_1/P_3	0.69	0.40	-	-	-	-
	P_2/P_3	0.56	0.31	-	-	-	-
V1 to SPA1	P_1/P_{TOTAL}	0.61	**0.74**	**0.76**	0.63	0.60	0.54
	P_2/P_{TOTAL}	0.56	**0.75**	**0.70**	0.53	0.53	0.44
	P_3/P_{TOTAL}	0.59	0.60	0.73	0.67	0.57	0.60
	P_1/P_2	0.44	0.75	-	-	-	-
	P_1/P_3	0.40	0.65	-	-	-	-
	P_2/P_3	0.44	0.57	-	-	-	-

RESULTS: Table 1 shows higher A_z values of the parameter P_1/P_{TOTAL} for LGN to V1 signal propagation in resting state eyes closed condition indicating significant difference between subject groups in signal transfer from LGN to V1for power transfer in 0-0.1Hz. If threshold is increased then test performance for LGN to V1 signal propagation degrades but for higher order propagation, i.e. V1 to SPA1 performance improves with changing threshold. Power transfer in 0-0.1Hz (P_1) band provides better differentiation between subject groups (typically for normalized threshold = 0.04) for V1 to SPA1 propagation. No significant differences are found between subject groups for V1 to LOC propagation and for resting state eyes open condition. Zayed et al. (6) performed transfer function analysis by comparing proportion of total power and median power of each of the three frequency bands: 0-0.1Hz, 0.1-0.2Hz and 0.2-0.3Hz using t-test and obtained differences between subject groups in visual information propagation from LGN to V1 only. Our analysis suggests that with proper choice of threshold and decision metrics we can better differentiate subject groups for both lower and higher order visual information propagation.

CONCLUSION: Preliminary results suggest that the proposed transfer function analysis with threshold has potential in identifying ON presence. However, additional sample data along with the consideration of signal feedback and reliability measurements are required to boost the accuracy of the transfer function metrics.

References: (1) Boomer J.A. et al., Sem Ophthalmol, #18, 174-180, 2003, (2) Gilbert M. et al., Ophthalmol, #52, 529-534, 2007, (3) Kaur P. et al., Int Rev Neurobiol, 633-663, 2007, (4) Biswal et al., NMR Biomed, 165-170, 1997,(5) Rombouts et al., Neurology, #50, 1896-1899,1998, (6) Zayed, N. et al., 32nd CMBE, 2009.
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