

Accounting for Arterial Transit Delays is Crucial for Identifying Functional Connectivity Networks: a Resting-State fMRI Study of the Default Mode Network in Moyamoya Disease Patients

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Purpose: Resting state fMRI (rs-fMRI) has been increasingly used to explore the brain's functional organization and to probe its alterations in neurological or psychiatric diseases¹. In rs-fMRI, functional networks are assessed utilizing the temporal correlation between spontaneous BOLD signal fluctuations of spatially remote areas of the brain. Thus, rs-fMRI results can be sensitive to regional differences in arterial transit time. In neurological diseases where there are significant delays in different areas of the brain, standard rs-fMRI analysis, both seed-based and using independent component analysis (ICA), may lead to erroneous identification of functional connectivity networks or result in them not being detected. Moyamoya is an example of such a neurological disease and is characterized by a chronic steno-occlusive vasculopathy affecting the terminal internal carotid arteries that causes considerably increased arterial transit delays. In an effort to investigate the effects of these transit delays on rs-fMRI, we studied the default mode network (DMN) in a group of Moyamoya patients and compared it with normal healthy volunteers. We also propose a functional connectivity analysis method that accounts for transit delay.

Methods: Fifteen Moyamoya patients (45±9 years; range 31-61) and ten healthy volunteers (30±6 years; range 24-45) were included in this study. Subjects were scanned at 3T (GE MR750) using an 8-channel head coil. For all subjects, rs-fMRI data was collected using a 2D gradient echo EPI sequence (FOV=22 cm, matrix= 64×64, slice thickness=3.5 mm, number of slices=35, TR/TE=2 s/25 ms, scan time=6 min). For Moyamoya patients we also collected gadolinium-based DSC images and calculated Tmax maps using RAPID software². EPI images were preprocessed using FSL, including removal of first 6 volumes, motion correction, spatial smoothing (Gaussian kernel of 6mm FWHM), and normalization to MNI atlas space. Subsequent data preprocessing included removal of linear trends, band-pass filtering (0.01-0.1 Hz), and removing movement parameter time-courses from the data by linear regression. The DMN was probed using a seed-based functional connectivity analysis as well as ICA. ICA analysis was carried out using FSL's MELODIC and the DMN was defined by manually inspection of 30 independent components. For the seed-based method, the DMN seed ROI was defined as a ~10 mm-radius sphere centered at (0,-56,28) mm in the precuneus/PCC in the MNI space. The DMN reference time course was generated by extracting the mean time series within the seed ROI and was correlated against all brain voxels to obtain the "In-phase" functional connectivity map. We also shifted the reference time course by values ranging from -5 TR to +5 TR and for each shift, derived the corresponding "delayed" functional connectivity maps. We then combined all connectivity maps (10 delayed and 1 In-phase) voxel-wise by choosing the maximum positive correlation for each voxel and formed "combined shifted seed-based" map. A mask for DMN was also created from the healthy subjects using group ICA analysis³.

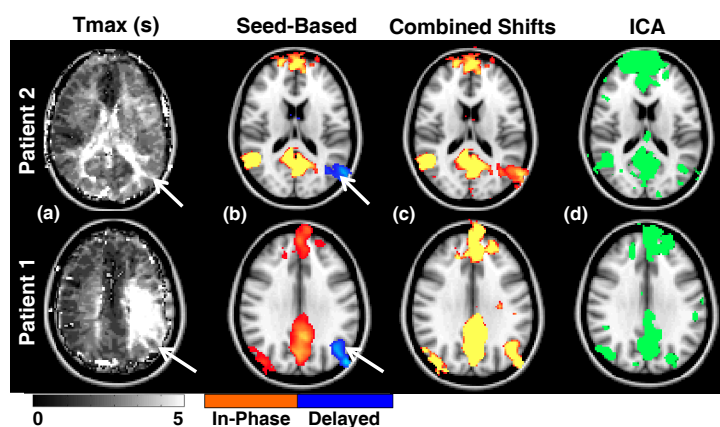


Figure 1. Tmax map (a) along with the corresponding DMN maps identified using (b): standard seed base with in phase and delayed reference signals, (c): combined shifted seed-based, and (d): ICA for two representative Moyamoya patients.

delays in the reference signal (Fig 1c and blue areas in Fig 1b). The shift that provided the highest average Z-score within the DMN mask was recorded for each subject. Fig 2 shows the histogram of these shifts in healthy and Moyamoya cohorts, as well as the average Tmax values within the DMN mask for Moyamoya patients. The relationship between these two histograms (b and c) strongly suggests that transit delays are the cause of the spread in the DMN optimum shift of the rs-fMRI analysis in the Moyamoya patients.

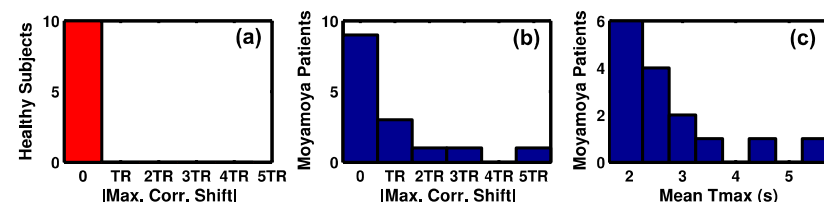


Figure 2. Histogram of absolute shift values that provided the highest correlation in DMN (Max. Corr. Shift) for: (a) healthy subjects (N=10) and (b) Moyamoya patients (N=15). (c): Histogram of Tmax values in the DMN for Moyamoya patients (N=15).

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References: [1] Vargas et al. J Affect Disord 3:727-35 2013. [2] Straka et al. JMIR 32:1024-37 2010. [3] Shirer et al, Cerebral Cortex 22:158-165 2012.

Results: Resting-state connectivity analyses in 2 Moyamoya patients with increased transit delays are presented in Fig 1. In both of them the standard seed-based approach and ICA could not detect the connectivity of the inferior parietal lobule (IPL) ipsilateral to the long delay area defined by Tmax map (arrows). These "missing" nodes were identified by accounting for the

shift that provided the highest average Z-score within the DMN mask was recorded for each subject. Fig 2 shows the histogram of these shifts in healthy and Moyamoya cohorts, as well as the average Tmax values within the DMN mask for Moyamoya patients. The relationship between these two histograms (b and c) strongly suggests that transit delays are the cause of the spread in the DMN optimum shift of the rs-fMRI analysis in the Moyamoya patients.

Discussion: Our results indicate that accounting for transit delays is crucial for analyzing the rs-fMRI data in Moyamoya patients. Here we have presented the results for the DMN. However, we have also found similar effects on other functional networks, such as language and auditory networks. We showed that using the proposed method (combined shifted seed-based), it is possible to solve this problem, where ICA and standard seed-based analyses failed. We expect similar effects in other neurological diseases with regional transit delays, including stroke, carotid occlusion, and even perhaps, normal aging.