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Directed Transfer Function Analysis of fMRI Data to Investigate Network Dynamics

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Abstract— **In this work, we have adapted the directed transfer function (DTF) to fMRI for the analysis of cortical network dynamics. While modern fMRI sequences are capable of sampling at second or sub-second rates, the underlying hemodynamic response limits the true temporal resolution to the order of 6-12 seconds. Therefore, DTF analysis of fMRI is appropriate for characterizing dynamics in brain response which evolves more slowly than the fMRI response, such as those during learning, fatigue and habituation. In such cases, the response to repeated trials will change with time and a summary measure from each trial can be used as input to the DTF analysis because these summary measures are of appropriate sampling rates and are not affected by the sluggishness of the hemodynamic response. As an example, we investigated the dynamic effects of muscle fatigue on the motor network. Specifically, DTF was used as a multivariate measure of the strength and direction of information flow between the various nodes of the network. We found that the primary motor area had a causal influence on the supplementary motor area, pre-motor area and cerebellum, and this influence initially increased with time and diminished towards the end of the experiment, probably as a result of fatigue.**

I. Introduction

IT is increasingly being recognized that many brain functions are carried out by networks rather than individual areas [1,2]. Therefore it is important to study neural networks in the brain and the interaction between areas. In fMRI literature, networks in the brain are primarily studied in terms of functional connectivity (defined as temporal correlations between remote neurophysiologic events). In addition to functional connectivity, effective connectivity (defined as the causal influence one neuronal system exerts over another) is also important [3] since it reveals the strength and direction of the flow of information between the areas that are functionally related. Various methods including structural equation modeling [4], graphical modeling [5], Bayesian approaches [6], Kalman filtering [7] and information theoretic models [8] have been used in the fMRI literature to infer effective connectivity. Even though these techniques are multivariate, they rely on the statistical covariance structure of the data [4,6], multivariate probability distributions [8] and regression [7] and hence do not incorporate temporal precedence information which is important in investigating causal influences between multiple areas. Directed transfer function (DTF) was recently introduced as an alternate method for inferring multivariate causal influences between multiple channels of EEG [9]. Not only does this technique rely on Granger causality [10] and hence incorporate temporal precedence information, it also has been shown to be superior in performance to all other contemporary spectral measures of directed information flow [9]. Therefore, DTF seems to be a good choice for investigating cortical network dynamics and directional information flow.

There are many challenges involved in using the temporal precedence information to derive causality in fMRI data. Even though typical fMRI sampling rates are at the second or sub-second level, the true temporal resolution is limited to 6-12 seconds by the underlying hemodynamic response. Therefore, temporal precedence information can only be used to derive long term causal influences underlying neurophysiological processes such as learning, fatigue and habituation. In this study, we demonstrate the utility of DTF with fatigue as an example.

Muscle fatigue has been extensively studied both in basic and clinical science. However, its effects on the brain have not been fully understood [11]. It is extremely important to understand the cortical effects of muscular fatigue considering the fact that muscle fatigue is a characteristic of many neurological disorders [12,13]. Hence an understanding of the cortical effects of muscular fatigue would pave the way for better management and more efficient strategies in rehabilitation medicine [12].

With the advent of non-invasive neuroimaging techniques including functional magnetic resonance imaging (fMRI), there have been some recent studies which have addressed the issue of cortical effects of peripheral fatigue. The prevalent hypothesis supports the notion that muscle fatigue creates conditions of 'temporary pathology' in the cortex. It is supported by studies showing reduced low frequency functional connectivity [14] and decreased excitability of cortical neurons [15,16,17] due to fatigue. Researchers have also attempted to characterize cortical effects of fatigue by changes in fMRI signal intensity [18] and alterations in activation area and functional connectivity [19]. In this work, the network dynamics during fatigue is investigated

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using DTF.

II. Materials and Methods

A. MRI Data Acquisition

Ten healthy right-handed male subjects were scanned in a 3T Siemens Trio scanner. Soft padding was used to immobilize the subject's head to reduce motion artifacts. The task involved repetitive right-hand grips at 50% maximal voluntary contraction (MVC) level by gripping a bottle-like device [20]. Handgrip force was measured online by a pressure transducer connected to the device through a nylon tube filled with distilled water. The target level (50% MVC) was calculated based on the maximal grip force measured at the beginning of the experiment. Subjects performed the contractions by following visual cues generated by a waveform generator projected onto the screen above the subject's eye in the magnet. Each visual cue was a rectangular pulse, whose profile matched the amplitude and duration of the handgrip contraction. The duration of each contraction was 3.5 seconds, followed by a 6.5-s inter-trial interval (ITI). The fatigue task lasted 20 minutes, with a total of 120 contractions performed by each subject.

Immediately after the completion of 120 contractions, the MVC handgrip force was measured again to determine the level of muscle fatigue. The 50% MVC level was chosen to fatigue the muscles within the 10-min time frame with the given length of contraction (3.5 s) and ITI (6.5 s). The 6.5-s ITI was necessary to allow the fMRI haemodynamic response to return to baseline after each muscle contraction. Subjects were scanned during the fatigue task using an echo planar imaging (EPI) sequence [21]. The scan parameters for the fatigue task were as follows: 30 slices covering from the top of the cerebrum to the bottom of the cerebellum, 600 volumes, repetition time (TR) = 2 s, echo time (TE) = 30 ms and flip angle (FA) = 90° with a slice thickness and spacing of 4 mm and an in plane resolution of 3.44×3.44 mm^2.

B. Data Pre-processing

The preliminary data analysis was carried out using Brainvoyager™ 2000 (Ver 4.9 © Rainer Goebel and Max Planck Society, www.brainvoyager.com). Motion correction was performed on all subjects and two subjects were excluded from analysis due gross head motion of more than half a voxel. Slice scan time correction and further analysis were applied to the data of the remaining eight subjects. Activation maps were generated by cross-correlating a reference waveform with each of the voxel time series as shown in Fig.1. A sample activation map is shown in Fig.2.

Four regions of interest (ROI) - primary motor (M), supplementary motor (SMA), pre-motor (PM) and cerebellum (C) - were identified from the activation maps and the mean time course of all voxels in each ROI was calculated. To investigate the long term causal influences, a summary measure, the area under each epoch of 10 s, was calculated. A time series consisting of the areas of epochs was formed for each ROI. Subsets of time series (40 points) were used as inputs to the DTF analysis to characterize brain dynamics due to fatigue. Note that these time series evolve more slowly than the fMRI hemodynamic response.

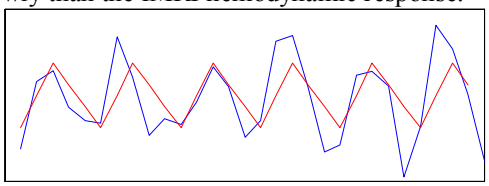

Fig 1. Red- Reference waveform. Blue- Actual voxel time series

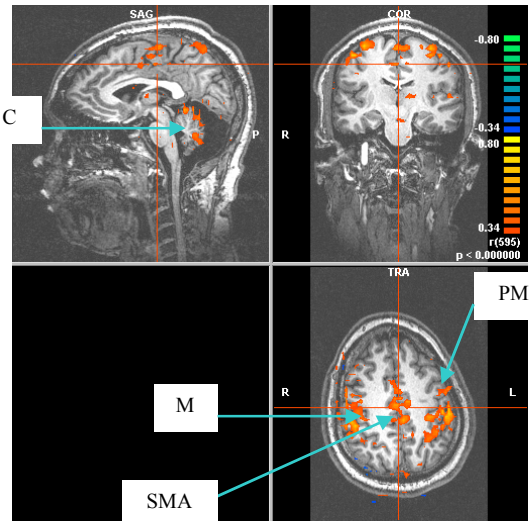

Fig 2. Sample activation map showing M, PM, SMA and C.

C. Mathematical Data Analysis

The aim of the mathematical analysis (implemented in MATLAB) was to uncover directional flow of information between the identified ROIs. As outlined in the introduction, DTF offers many advantages over other competing methods and hence was employed in this work.

The first step was to form a multivariate autoregressive (MVAR) model from the time series obtained from the ROIs. Let $\mathbf{X}(t)=(X_1(t),X_2(t),\ldots\ X_k(t))$ be the data vector wherein X_k is the time series corresponding to the k^{th} ROI. Then the MVAR with model parameters A(i) of order p is given by

$$X(t)=\sum_{i=1}^{p}A(i)X(t-i)+E(t) \tag{1}$$

where E(t) is the vector corresponding to white noise process. The model order was determined using the Akaike information criterion [22]. Transforming Eq.1 to the frequency domain, we obtain

$$X(f)=A^{-1}(f)E(f)=H(f)E(f) \tag{2}$$

All the information regarding the spectral properties and relationships between channels is contained in H(*f*), the transfer matrix of the model, which when normalized w.r.t to the inflows into ROI *i*, yields DTF as given by

$$DTF_{ij}^2(f) = \frac{|H_{ij}(f)|^2}{\sum_{m=1}^{k} |H_{im}(f)|^2} \quad (3)$$

DTF given by Eq. 3 was averaged over all frequencies and a single value of DTF was obtained for each connection between ROIs *i* and *j*. A DTF value of 1 between a pair of ROIs signified maximum direct causal relation and a value of 0, an absence of it. The analysis was applied to 11 overlapping windows that span the total number of epochs.

III. Results and Discussion

A network was constructed involving all possible connections between the four ROIs. The resulting network dynamics is shown in Fig. 3. The networks for the first, middle and last time windows are shown in Fig. 4 where the width of the arrow indicates the strength of the connection.

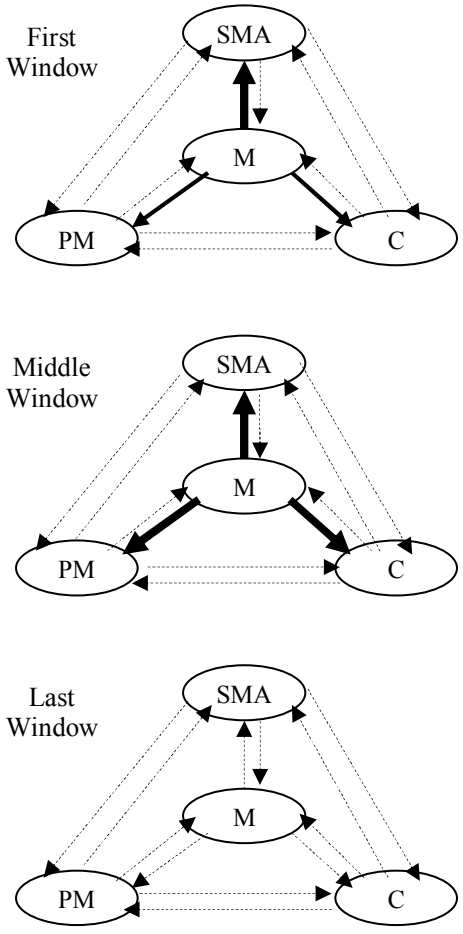

Fig 4. Cortical network dynamics during muscle fatigue. Top, middle and bottom correspond to the network during first, middle and last respectively.

TABLE I
DTF VALUES OF THE CONNECTIONS SHOWN IN FIG.4

	Stage	M→	SMA→	PM→	C→
	1		0.09±.02	0.15±.05	0.14±.04
→M	2	-	0.06±.03	0.13±.04	0.06±.02
	3		0.08±.02	0.22±.05	0.13±.03
	1	0.42±.07		0.16±.03	0.13±.03
→SMA	2	0.50±.08	-	0.16±.04	0.09±.03
	3	0.25±.06		0.21±.04	0.19±.04
	1	0.31±.06	0.11±.03		0.15±.05
→PM	2	0.40±.06	0.06±.02	-	0.08±.02
	3	0.16±.05	0.08±.01		0.15±.03
	1	0.37±.06	0.07±.02	0.13±.04	
→C	2	0.47±.06	0.11±.04	0.17±.04	-
	3	0.15±.05	0.08±.02	0.24±.05	

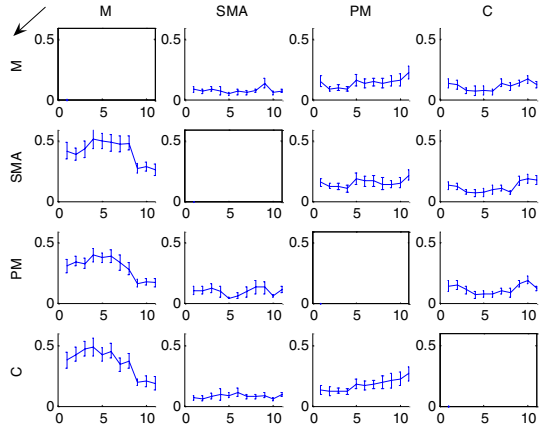

Fig 3. Network dynamics using overlapping windows. x-axis: overlapping window number, y-axis: mean DTF value over all subjects. Error bars indicate standard deviation

The corresponding DTF values for Fig.4 are given in Table.1. Several interesting observations can be made from these results. Interestingly, in Fig. 3, C seems to complement the dynamics of M so that when M is driving, C tends to be suppressed and when M gets suppressed, the drive due to C increases. In the first time window of Fig. 4 and Table 1, we note that, significant information flows from M to SMA, PM and C. Based on current neuroscientific understanding, the role of PM is to select and initiate movement based on a cue (visual cue in our experiment) while the SMA, which receives anatomical projections from M, mediates the input-output coupling and helps in planning the execution of movement [23]. C has been shown to have a crucial role in scheduling a sequence of ordered responses [24]. In our experiment, the subjects needed to schedule a sequence of movements in response to the visual cue. M receives projections from the spinal cord through the lower and upper motor neurons and hence is directly involved in execution of movement [25]. Information flow from M to SMA, PM and C may reflect epoch-to-epoch adjustment and coordination between these areas. In the middle time window, the demands on movement execution increased considerably and hence the bulk of the information received at PM, SMA and C was from M. Also, from Table.1, it can be seen that the strength of information flow increased from the first to middle window. However in the last time window, the

strength of information flow was generally much lower.

During the fatigue task, it has been reported that fMRI signals show nonlinear modulation [18] where the signal intensity increases in the beginning to support the increasing demands of the motor task and then decreases in response to inhibitory re-afferent feedback. Since the re-afferent feedback projects onto M, it suppresses all the outgoing connections from M, which may be reflected in our DTF-based network connections in the middle time window. There can be several plausible mechanisms for the perceived inhibition. One possible mechanism is that the fatigue-induced inhibition of alpha motor neurons in the spinal cord [26,27,28] may project onto the cortical neurons through ascending pathways. Another possible reason may be the neuronal adaptation due to unabating stimulation [29,30].

Interestingly, a recent study reported that the cortical effects of peripheral fatigue manifest as continually increasing activation area and continually decreasing functional connectivity [19]. The monotonic nature of the results reported may be because of the insensitivity of the bivariate methods employed in that study. Our results seem to agree more with reports of nonlinear modulation of fMRI signal intensity during fatigue [18].

IV. Conclusion

In this study, we have demonstrated the utility of DTF in uncovering cortical network dynamics and information flow in the human brain using fMRI, with specific application to cerebral effects of peripheral muscle fatigue. We found that the causal influence of the primary motor area over other motor areas initially increased, likely as a result of increasing motor demands, but subsequent fatigue markedly decreased the information flow in the entire network.

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