Use of a neural mass model to investigate the disruption of functional brain networks by simulated focal lesions

Xiaoyun Liang[1], Alan Connelly[1,2], and Fernando Calamante[1,2]

[1]*Brain Research Institute, Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia,* [2]*Department of Medicine, Austin Health and Northern Health, University of Melbourne, Melbourne, VIC, Australia*

Introduction: With advances in brain imaging and complex networks methods, the way we consider models of brain plasticity and degeneration has changed, with increasing emphasis on brain networks [1]. It has been widely accepted that focal brain damage can have a widespread non-local brain network disruption when there is damage to brain regions that are important for global information communication. Computation models provide a viable approach to systematically investigate how lesions disrupt brain networks. With a neural mass model (NMM), neural activity has been simulated based on structural connectivity, and by including local polymorphic delta activity (PDA) combined with weakening of lesioned structural connections [2]. However, no BOLD fMRI signal has been simulated in that study. While neural activity and BOLD signal are believed to be closely correlated in normal brain, it remains to be investigated whether the disrupted networks of abnormal brain can be convergently predicted by the simulated data at two different levels, i.e., mesoscale and macroscale. Moreover, it has been shown that focal lesions to critical brain regions lead to greater disruption of brain networks [3]. While this has been partly supported by in vivo results, it is rather difficult to systematically investigate with in vivo data. In this study, we employ an established NMM to simulate neural activity and BOLD signal with lesion effects. Disrupted network efficiencies (global and local) are first predicted by simulating each brain region (one at a time) as a lesioned area. We seek to investigate the relationship between disrupted network efficiency and network metrics, such as degree, betweenness centrality (BC), etc.

Methods: In the NMM, each neural mass represents a local ensemble of neurons (in our case, a brain region). ***Simulation:*** Despite the known limitations of tensor based tractography [4], for consistency with previous studies, a published structural connectivity matrix (with 78 brain regions) [5] was used to model the structural connections of the network. NMM simulations are based on the Morris-Lecar model [6]. The regional neural masses are coupled based on the structural connectivity matrix [5]. Excitatory coupling strength between cortical regions is controlled by parameter c. Three dynamic variables (mean membrane potential of pyramidal cells, V, and inhibitory interneurons, Z, and the average number of 'open' potassium ion neurons, W) can be obtained by solving ordinary differential equations. To simulate the BOLD signal for each neural mass, a Balloon-Windkessel hemodynamic model was employed with the absolute values of the dV/dt as an input to generate BOLD data within each brain region [7]. For normal brain regions, a uniform coupling strength c=0.1 was chosen [7]. The simulation (time resolution=0.2ms) was implemented in Matlab *R2013b*. An initial 2-min transient was discarded, and the next 10-min data were retained, which were then downsampled to 1ms time resolution. The procedure was repeated twice with random initial conditions to simulate 2 datasets (2 runs) for each lesioned brain area [7]. Notably, to simulate a lesioned region, the corresponding row and column of the lesioned region is *not* simply removed from the connectivity matrix. Instead, lesions were simulated in each region (one at a time, i.e. generating 78 different lesioned brain models) as follows [2, 8]: (*i*) by adjusting the relevant parameters to generate V data, hereafter called neural signal, of lesioned brain regions similar to delta waves (relatively lower frequency) [2]; and (*ii*) by reducing the coupling strength of all connections to the lesioned brain region (c=0.01) [2]. ***Data analysis:*** For each lesioned region, the 2 runs were concatenated to estimate the functional connectivity matrix for either neural or BOLD data. Pearson correlation was employed to generate connectivity matrices. Constant threshold was used for both V and BOLD data, which was determined such that the total number of connections for estimated normal networks (from neural and BOLD data) is equivalent to that of the structural network. All connectivity matrices were then subject to network analysis. As a result, lesioned-region-wise global and local efficiencies were obtained for both neural and BOLD data. The relationships between *lesioned* network efficiencies (global and local) and *normal* network metrics (degree, BC and vulnerability calculated from the structural connectivity matrix) were assessed.

Results: The connectivity matrices in Fig. 1 show that equivalent normal networks can be estimated from both simulated neural (left) and BOLD data (middle), of which the 78 brain regions are coupled (c=0.1) based on the structural connectivity matrix (right). As expected [2, 7], the two networks have well matched the underlying structural connectivity matrix by setting appropriate thresholds. Fig. 2 (top) demonstrates that lesioned-region-wise global efficiency (GE) from neural data is correlated with underlying (normal) structural network metrics degree, betweenness centrality and vulnerability (Note: each point in the plot corresponds to a different lesioned brain model). For BOLD data (see Fig. 2, bottom), while correlations are not as strong as for neural data, similar trends have been detected. In contrast, no similar trends were detected between local efficiency (LE) and the 3 network metrics (data not shown).

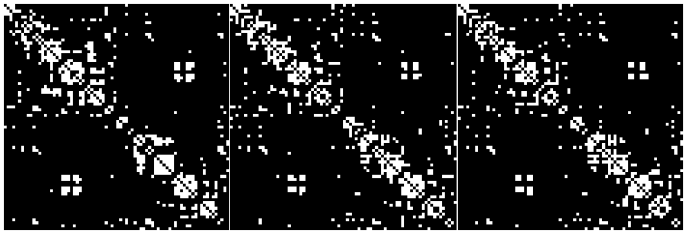

Figure 1

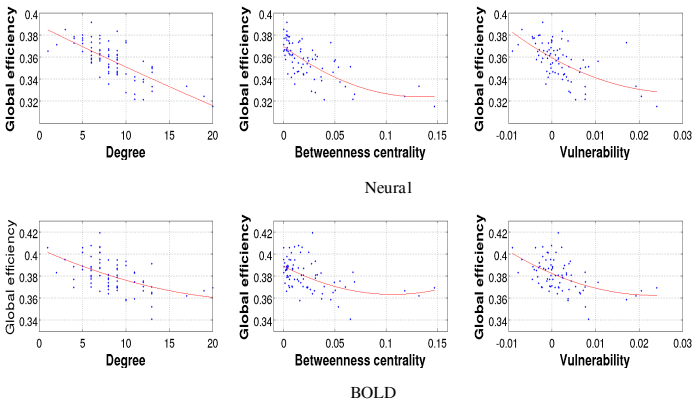

Figure 2

Discussion: In this study, the NMM has been employed to simulate brain activity at two different levels: mesoscale (mean membrane potential, V) and macroscale (BOLD). Using graph theory, disrupted network efficiencies (GE and LE) have been systematically investigated by simulating each lesioned brain region separately. Furthermore, the relationships between disrupted network efficiencies and degree, betweenness centrality and vulnerability have been studied. Our simulated results indicate that damage to 'hub' regions (e.g. brain regions with large degree, and betweenness centrality) lead to lower GE, but not LE. While neural and BOLD data predict similar trends between GE and network metrics, fitting outcomes from BOLD data are, as expected, not as reliable as from V data. It could be expected, however, that more repetitions of simulated data should improve the fitting outcomes (albeit at an increased computational load). Overall, our simulated results show that the NMM predicts disrupted network efficiencies, and can be used to show their relationships with network metrics. This provides a useful framework to investigate brain activity, especially abnormal brain activity, as well as to study how specific abnormalities to brain regions can disrupt brain networks in disease.

References: [1] Sporns O et al., *Plos CB*. 2005; 4: 0245-51; [2] van Dellen E et al., *NeuroImage* 2013; 83:524-32; [3] Gratton C et al., *JoCN* 2012; 24 (6): 1275-85; [4] S.Farquharson et al, *J Neurosurg.* 2013, 118, 1367-1377; [5] Gong G et al., *Cerebral Cortex* 2009; 19: 524-36; [6] Morris C et al., *Biophys J*. 1981, 35 (1):193–213; [7] Honey C et al., *PNAS* 2009; 106(6): 2035-40; [8] Larter R et al., *Chaos* 1999; 9(3): 795-804.