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The application of a mathematical model linking structural and functional connectomes in severe brain injury

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ABSTRACT

Following severe injuries that result in disorders of consciousness, recovery can occur over many months or years post-injury. While post-injury synaptogenesis, axonal sprouting and functional reorganization are known to occur, the network-level processes underlying recovery are poorly understood. Here, we test a network-level functional rerouting hypothesis in recovery of patients with disorders of consciousness following severe brain injury. This hypothesis states that the brain recovers from injury by restoring normal functional connections via alternate structural pathways that circumvent impaired white matter connections. The so-called network diffusion model, which relates an individual's structural and functional connectomes by assuming that functional activation diffuses along structural pathways, is used here to capture this functional rerouting. We jointly examined functional and structural connectomes extracted from MRIs of 12 healthy and 16 brain-injured subjects. Connectome properties were quantified via graph theoretic measures and network diffusion model parameters. While a few graph metrics showed groupwise differences, they did not correlate with patients' level of consciousness as measured by the Coma Recovery Scale — Revised. There was, however, a strong and significant partial Pearson's correlation (accounting for age and years post-injury) between level of consciousness and network diffusion model propagation time ($r = 0.76$, $p < 0.05$, corrected), i.e. the time functional activation spends traversing the structural network. We concluded that functional rerouting via alternate (and less efficient) pathways leads to increases in network diffusion model propagation time. Simulations of injury and recovery in healthy connectomes confirmed these results. This work establishes the feasibility for using the network diffusion model to capture network-level mechanisms in recovery of consciousness after severe brain injury.

1. Introduction

Subjects with severe brain injury suffer widespread connectivity loss between brain regions, at times resulting in disorders of consciousness (DOC). Recovery from DOC can occur over many months or years post-injury (Lammi et al., 2005; Sidaros et al., 2008; Voss et al., 2006) in a variety of etiologies (Estraneo et al., 2010; Luauté et al., 2010; Nakase-Richardson et al., 2012), but the process and mechanisms of this process are poorly understood. It is, however, increasingly becoming clear that recovery is largely dependent on recruitable cerebral reserve (Schiff, 2010). One interpretation of cerebral reserve could be in the reorganization of neuronal connections via synaptogenesis and axonal sprouting (Bütefisch, 2006; Frost et al., 2003; Nudo, 2006; Wang et al., 2010) that is known to occur in post-injury recovery. One interpretation of cerebral reserve is the concept of cerebral reorganization or plasticity, i.e. changes in the brain's functional connections/activation patterns in response to changes in the environment or damage/disease, which has been proposed in various forms by previous work (Moretti et al., 2012; Nithianantharajah and Hannan, 2009; Schoonheim et al., 2015). However, details of how the brain performs network-level reorganization in recovery from injury remain unknown. Here, we consider the implications of functional reorganization in the context of structural and functional connectomes, or whole-brain networks. Neuroimaging methods offer the ability to measure the brain's structural and functional connectivity networks, i.e. connectomes, which in turn allows insight into network-level changes underlying disorders of and recovery of consciousness.

Studies using diffusion (dMRI) and/or functional (fMRI) imaging modalities (Cabral et al., 2013; Damoiseaux and Greicius, 2009; Fox and

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Raichle, 2007) have allowed investigation of the brain's structural connectivity (SC) and functional connectivity (FC) networks (Bullmore and Sporns, 2009; Sporns et al., 2004) and their sensitivity to clinical state, disease and behavioral variability (Calhoun et al., 2011; Cocchi et al., 2014; Griffa et al., 2013; Lo et al., 2010). In patients with DOC, numerous studies have used fMRI to provide evidence of language and cognitive abilities and establish functional network reserve (Laureys and Schiff, 2012). Resting state fMRI analyses in DOC patients have shown functional disconnections within the default mode network that appear to correlate with clinical severity (Boly et al., 2012; Soddu et al., 2011). Many times DOCs result from traumatic brain injury (TBI), which has been studied extensively using network approaches; see Sharp et al. (2014) for a review. Using a graph theory approach, TBI has been shown to impair small-world topology (Pandit et al., 2013) normally associated with healthy brain networks (Bassett and Bullmore, 2006; Watts and Strogatz, 1998). Differences between SC and FC graph network metrics between TBI and controls and correlations between network metrics with cognitive abilities have been shown (Caeyenberghs et al., 2013, Caeyenberghs et al., 2012; Castellanos et al., 2011). In addition, the location of injury in TBI with respect to influence on the SC network metrics has been related to cognitive impairment (Kuceyeski et al., 2011), while recovery from TBI has been shown to correlate with a gradual return to normal FC network metrics (Nakamura et al., 2009).

One important question that is only beginning to be addressed is whether and how the structural and functional networks are related in both health and pathology. Recent work has focused on predicting FC networks from SC networks and vice-versa in normal subjects in order to better understand their relationship (Cabral et al., 2011; Das et al., 2014; Deco et al., 2012; Fernández Galán, 2008; Honey et al., 2009; Messé et al., 2014; Woolrich and Stephan, 2013). One of the most recent developments in this area (Abdelnour et al., 2014) presented a connectome-based mathematical model that assumes functional activation spreads along structural connections like a diffusive agent, similar to the model presented in Fernández Galán (2008). The main difference between the two is that the former uses the Laplacian of the structural connectivity network, while the latter uses the structural connectivity network directly. Abdelnour et al. (2014) showed that this simple linear model resulted in predictions of FC from the SC networks that were comparable to or better than predictions from both the model in Fernández Galán (2008) and more complicated non-linear models. The model detailed in Abdelnour et al. (2014)) enables novel quantification of the relationship between structural and functional connectomes, which may relate more to an individual's behavior than individual analysis of either connectome.

In this work, we conjecture that recovery from brain injury could entail re-establishment of normal FC without requiring a concurrent change in the SC network. A few reports of positive changes in SC related to recovery from brain injury exist (Fernández-Espejo et al., 2011; Sidaros et al., 2008; Voss et al., 2006), however one recent study showed long-term impairment of WM structures 5 years after severe brain injury even in the presence of recovery (Dinkel et al., 2014). FC network improvements are more widely reported in the context of recovery after brain injury (Demertzi et al., 2014; Laureys and Schiff, 2012; Sharp et al., 2011; Soddu et al., 2011; Vanhaudenhuyse et al., 2010). In a study of chronic TBI patients, Palacios and co-authors found increases in FC in frontal areas compared to healthy controls that was positively associated with better cognitive outcomes and negatively associated with a measure of SC (Palacios et al., 2013). They concluded that altered SC between brain regions could be in part compensated for by increases of FC. Along this line of reasoning, we further speculate that this return to normal/above-normal levels of FC, made possible by the plasticity of the brain's functional connections, may be performed within the confines of a possibly further degenerating post-injury SC network. Specifically, we propose a network-level "functional rerouting" hypothesis that states recovery from injury depends on the brain's ability to reestablish FC by circumventing impaired SC via alternate intact white matter pathways (see Fig. 1). It is important to note that functional rerouting via alternate white matter pathways only requires synaptic switching at the local circuit level; no physical changes to extant white matter projections are required. Furthermore, we hypothesized that the connectome-based network diffusion model in Abdelnour et al. (2014)) could be used to capture and quantify this network-level functional rerouting mechanism. While the network diffusion model was used in a previous study to predict FC from SC, we instead apply it here to obtain a measure of the relationship between the FC and SC. This measure, which we refer to as *model propagation time*, represents the amount of SC that is used to recapitulate the observed FC, i.e. "network depth". We expected that our proposed functional rerouting mechanism that utilizes alternate, and presumably less efficient, structural pathways would increase propagation time. Higher propagation time in this context means the existence of intact SC routes whose recruitment by the brain would result in more accurate recapitulation of the observed FC. It follows that longer propagation times should be positively correlated with better recovery measures.

To test this hypothesis, we applied the network diffusion model to both severe brain injury patient connectomes and simulated injury and recovery networks derived from healthy connectomes. We compared the strength of the relationships between the network diffusion model's propagation time with those of standard graph theoretical measures of the FC and SC networks. Next we investigated the functional rerouting hypothesis at a region-pair level, i.e. at the level of connectivity between pairs of regions. If region-pair functional rerouting were true, more normal FC between pairs of regions with impaired SC should correspond to better recovery. Therefore, we identified region-pairs with significantly impaired SC in our severe brain injury cohort and tested for correlations between measures of recovery and the amount of FC, compared to control FC, between these regions.

2. Materials and methods

2.1. Data

The Institutional Review Board of Weill Cornell Medical College approved all experiments (IRB # 0309006330A028 and IRB # 0903010274). Written informed consent was obtained from the healthy control volunteers and the legally authorized representatives of the subjects with severe brain injury. Data was collected from 12 normal controls (9 male, 34.8 ± 11.6 years) and 29 subjects (22 male, 37.6 ± 13.5 years). Some patients had data collected at multiple time points; in total there were 37 sets of data. Some patients were excluded on the basis of imaging artifacts or failures in post-processing; 21 sets of scans from 16 subjects were used in the final analysis (10 males, age: 39.9 ± 14.1 years, time since injury: 7.8 ± 8.1 years), see Table 1 for details. Consciousness level was assessed with the Coma Recovery Scale — Revised test that measures operationally-defined behavioral responses, including auditory, visual, motor, oromotor, communication and arousal (Giacino et al., 2004). No subjects that had CRS-R scores were known to have locked-in syndrome, which can result in an underestimation of level of consciousness due to an inability to respond to motor commands. Resting-state fMRI, dMRI and anatomical MRI scans were collected at the same time as the CRS-R test was administered.

2.1.1. General Electric MRI acquisition

All but one of the scans were acquired on a 3.0 Tesla General Electric Signa Excite HDx (Waukesha, WI) clinical MRI system with an eight-channel head receive-only coil. FMRI pulse sequences consisted of an echo-planar gradient-echo sequence with repetition time TR = 2 s, echo time TE = 30 ms, flip angle = 70°, axial field of view 24 cm, slice thickness = 5 mm, matrix size = 64 × 64 × 28, 180 time samples. DMRI scans were obtained using a spin-echo diffusion tensor pulse sequence with one T2-weighted image, 55 diffusion-weighted images evenly distributed on a sphere with b = 1000 s/mm^2, minimum TE,