Recovery of consciousness in brain injury: insights from the structural and functional connectome

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Target audience Clinicians and researchers alike will benefit from the information gained in this study.

Purpose Functional connectivity (FC) and structural connectivity (SC) brain networks derived from neuroimaging are proposed to measure the primary substrates upon which the brain functions. Subjects with severe brain injury suffer widespread deafferentation and connectivity loss across brain regions, at times resulting in disorders of consciousness. Recovery from such injuries can occur over months or years post-injury, but the process and mechanisms are poorly understood. It is increasingly becoming clear that recovery is largely dependent on recruitable cerebral reserve[1]. Neuroimaging methods offer the ability to calculate inferred SC and FC in the brain; analysis of these networks may allow insight into the mechanisms behind disorders of and recovery of consciousness[2]. Here, we use a mathematical model linking functional and structural brain networks in healthy and severely brain injured subjects to draw mechanistic inferences. We test if model parameters relate to level of consciousness in patients with severe brain injury.

Methods *Subjects and Data* Resting-state fMRI (single-shot EPI, 5mm slice thickness, 180 time points), dMRI (55 directions, b = 1000) and T1 scans (axial 3D-IRFSPGR, 1.2 mm slice thickness) were collected from 12 normal controls (9 male, 34.8 ± 11.6 years) and 18 subjects (10 male, age: 40.2 ± 14.3 years, time since injury: 7.1 ± 7.6 years). Ten out of the 12 healthy controls and 18/26 patients had both fMRI and dMRI. Subjects' level of consciousness response was assessed via the Coma Recovery Scale – Revised (CSR-R) scores.

Network Construction Structural images were segmented into white matter, gray matter and CSF; gray matter was further parcellated into 116 cortical and subcortical regions. Functional connectivity networks were constructed by taking the Pearson correlation of the average fMRI activation in each GM region pair. Structural connectivity networks were constructed by counting the number of fibers connecting each region pair after performing tractography using the diffusion MRI. FC networks were normalized by the mean of the non-zero entries and SC networks were normalized by the total number of fibers in each individual.

Graph diffusion model The model for predicting FC from SC, presented in[3], is based on the assumption that FC can be described as the diffusion of neuronal activity within the SC network. The model assumes that the diffusing quantity representing functional activation undergoes a random walk on a graph representing the structural connections. Thus, the rate of change of activation at any node i, denoted x_i, is related to the difference between the level of activation at that node and its connected neighbors, relative to the sum of outgoing SC of each node. That is, $d\boldsymbol{x}(t)/dt = -\beta\mathcal{L}\boldsymbol{x}(t)$, where $\mathcal{L}$ is the network Laplacian of the SC matrix. This equation has the explicit solution $\boldsymbol{x}(t) = \exp(-\beta\mathcal{L}t)\boldsymbol{x_0}$ for a given initial configuration, or activation pattern, $\boldsymbol{x_0}$. Let A be the true FC matrix and $\hat{\mathrm{A}}$ be the predicted FC matrix. It was hypothesized that the estimated FC of region i with all other regions at time t is the evolution on the graph of an initial configuration involving only region i, i.e. $\hat{a}_i(t) = \exp(-\beta\mathcal{L}t)\mathrm{e}_i$ where e_i is the unit vector in the i^{th} direction. If we collect all regions/unit vectors together, we obtain $\langle\hat{a}_1(t)|\cdots|\hat{a}_1(t)\rangle = \exp(-\beta\mathcal{L}t)\langle\mathrm{e}_1|\cdots|\mathrm{e}_N\rangle$, or $\hat{\mathrm{A}}(t) = \exp(-\beta\mathcal{L}t)$ which gives the prediction for the true FC matrix A. The value of t at which the model was evaluated, t_m, was taken to be the time at which maximal correlation with the true FC was achieved. That is, $t_m = \max_{0\le t\le 10} c(t)$, where $c(t)$ is the Pearson correlation of the actual versus predicted FC at each time point. Group-wise differences in global SC and FC network measures and the two model parameters, maximal correlation $c(t_m)$ and time at maximal correlation t_m, were assessed with t-tests. Partial Pearson's correlation, accounting for duration of injury, was calculated between the two model parameters and a measure of consciousness, the CRS-R score. P-values for all hypothesis tests were adjusted for multiple comparisons using FDR correction.

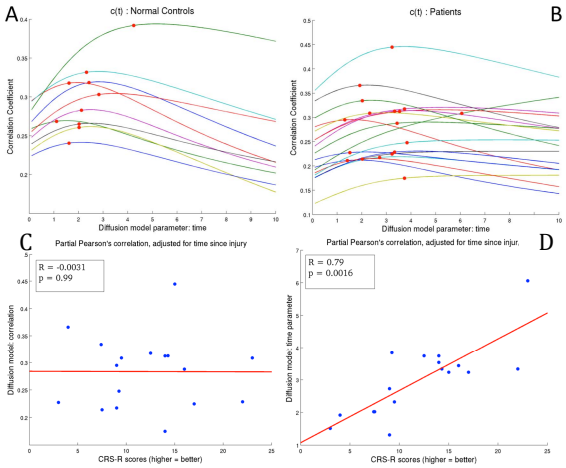

Figure 1: Panels A and B show the correlation of the true and predicted functional connectivity as the graph diffusion model evolves over time, with the normal controls on the left and the severe brain injury subjects on the right. Panels C and D show the correlation of the two diffusion model parameters (maximal correlation with true functional connectivity on the left and graph diffusion time on the right).

Results The curves $c(t)$ are displayed in Figure 1, with panel A showing the normal controls and panel B showing the patients. The red points indicate the location of t_m. For one subject, $c'(t) > 0.005$ for $0 \le t \le 10$; therefore, a threshold of $a = 0.01$ was imposed instead. Interestingly, this subject was the one with the largest CRS-R score. Model correspondence of true versus predicted FC, $c(t_m)$, was higher in normal controls than in patients, but the effect was not significant (t = 0.77, p = 0.44). The time of modeled graph diffusion t_m was higher in patients than in normal controls, but, again, the effect was not significant (t = -1.65, p = 0.10). Model correspondence of true versus predicted FC, $c(t_m)$, was not correlated with CRS-R scores (r = -0.003, p = 0.99). On the other hand, correlation between the time of modeled graph diffusion, t_m, and CRS-R scores was high and significant (r = 0.79, p = 0.0016). Scatter plots with the line of best fit are given in Figure 1 (panels C and D). The subject with a slightly higher threshold and highest CRS-R score can be seen in the upper right corner of Figure 1D. We wanted to test that this subject was not driving the correlation. Therefore we calculated the correlation between t_m and CRS-R with this point removed and found that this result was indeed robust (r = 0.71, p = 0.003).

Discussion The varying and at times divergent findings in the existing literature in patients with disorders of consciousness are most likely a result of the heterogeneity of the populations utilized, noise in the imaging data and complexity of the relationship between the brain's networks and consciousness. Here, we present the first study that investigates the relationship between recovery of consciousness after severe brain injury using a mechanistic model that relates structural and functional networks. We observe a strong positive relationship between level of consciousness and t_m, the parameter that describes the amount of time that the predicted FC is allowed to diffuse along the SC network before achieving maximal correlation with true FC. Larger values of t_m, which corresponded to higher levels of consciousness response, indicate that these brains require a longer time for putative brain activity to propagate on the SC network in order to recapitulate their observed FC. A parsimonious explanation of this finding is that a patient's consciousness as inferred from behavioral measurements may be related to the ability of the brain to establish previously non-existent functional connections using synaptic remodeling of shorter-range structural connections.

Conclusions If the mechanism for recovery of consciousness after severe brain injury proposed in this work were indeed true, it raises important questions about how alternate structural pathways are used to reestablish functional links between regions with impaired structural connections due to injury. Additionally, the reestablishment of particular linkages may have a causal role in consciousness; this possibility could be investigated at an individual level. Transcranial magnetic or direct current stimulation could be investigated as a tool to help reshape these compensatory pathways in order to encourage restoration of functional connections and possibly recovery of consciousness.

References 1. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends Neurosci*. 2010;33(1):1–9. 2. Kinnunen KM, Greenwood R, Powell JH, et al. White matter damage and cognitive impairment after traumatic brain injury. *Brain*. 2011;134(Pt 2):449–63. 3. Abdelnour F, Voss HU, Raj A. Network diffusion accurately models the relationship between structural and functional brain connectivity networks. *Neuroimage*. 2014;90:335–47.