Partitioning functional connectivity networks using "community structure" algorithms

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Introduction: Correlation analysis of fMRI data has revealed spatially distributed patterns of functionally connected brain regions in both humans and laboratory animals under a wide range of conditions, including the "resting state" and in response to different tasks or pharmacological challenges. These observations of spatially dispersed yet correlated responses are consistent with the idea that brain function is highly integrated. FMRI data may also be represented in a very natural way as a graph or *network*, in which individual image voxels or anatomically defined structures represent the nodes and a measure of correlation between the responses in each pair determines the edges linking the nodes. This explicit network representation allows novel network-theoretic approaches to be applied to the characterization of functional connections within the brain.

Much recent research in the field of complex networks has focused on methods to identify "community structure", i.e., cohesive clusters of strongly interconnected nodes. The presence of such "communities" within fMRI data may indicate a degree of residual network modularity, a manifestation of the coexistence of segregation and integration of brain function. Here, we apply a community structure algorithm based on the maximization of a mathematical representation of "modularity" – defined by the density of links relative to that expected by chance – to partition functional connectivity (FC) networks from the rat brain under different pharmacological challenges. We examined fully-weighted networks constructed from the response to fluoxetine, *d*-amphetamine and nicotine – three canonical drugs with distinct pharmacological mechanisms. We show that this approach can identify sub-networks whose distributions indicate compelling functional subdivisions in the brain. We also discuss the biological interpretation of the modularity parameter in terms of segregation and integration of brain function.

Methods: The community structure approach was tested on previously published rat phMRI datasets obtained with three different pharmacological challenges: fluoxetine, a selective serotonin reuptake inhibitor (SSRI) [1]; *d*-amphetamine, a dopamine releaser/reuptake inhibitor [1], and the nicotinic acetylcholine receptor agonist nicotine [2]. The rat brain was anatomically parcellated into N_{region}=48 brain regions using a co-registered anatomical atlas [3]. These brain regions represent the nodes in the functional connectivity networks. PhMRI time courses were extracted from each brain region in each subject, and the post-injection response amplitude quantified, yielding a $N_{region} \times N_{subject}$ response matrix for each study. Computing the cross-correlation yielded a symmetric $N_{region} \times N_{region}$ matrix representing the strength of the correlation between each pair of nodes. These values were then normalized by Fisher's *r*-to-*z* transformation, the absolute value taken, and the diagonal set to zeros (no self-connections). This resulted in a positive-definite adjacency matrix containing the edge weights and defining a complete, weighted network. Partitioning was performed using a community structure algorithm that seeks to maximize the modularity (Q) [4], implemented in IDL. For a certain partition of the network, Q measures the difference between the weights of the edges connecting nodes within communities relative to those in a randomly connected network with the same partition. The partition of the network that maximizes Q identifies the optimal number and distribution of communities. The higher the value of Q, the stronger the community structure, i.e., the more modular the network. The maximum modularity value and the resulting partition obtained for each network was compared to a null-model derived from a random network of identical size and distribution of links, and with the partition of the corresponding vehicle group.

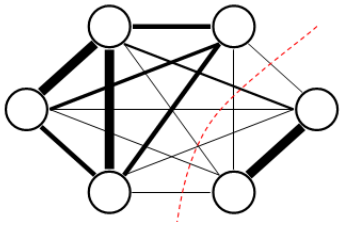

Fig. 1: *Partition of a fully-weighted network by identifying 'communities' of nodes with denser connections between their constituents than to other nodes outside the groups.*

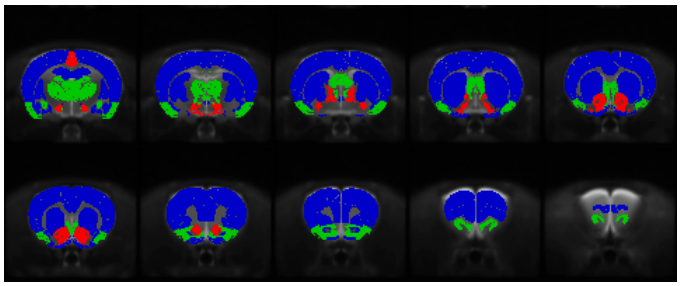

Fig. 2: *Community structure of the functional connectivity network elicited by d-amphetamine challenge. Three communities were identified, shown in red, blue and green. The red community comprises the dopamine mesolimbic system, consistent with the mechanism of action of the challenge drug.*

Results: In all three cases the maximum modularity algorithm identified drug-specific, symmetrical community structures corresponding to brain regions and neurotransmitter systems targeted by the pharmacological challenge. By way of example, in the case of *d*-amphetamine, a drug that stimulates the dopamine system, three communities were identified (Fig. 2). One community (red) included the ventral tegmental area and nucleus accumbens, key structures in the mesolimbic dopamine system. The other two communities included ventromedial and dorsolateral thalamus, amygdala and septum (green), and the Striatum and most cortical structures (blue), respectively. The maximum modularity value was about three times larger than for the vehicle group. Partition of functional connectivity networks for the other two drugs (fluoxetine and nicotine, not shown due to space limitations) resulted in three and two communities respectively, with substantially different distributions. For example, connections of the Raphe Nuclei (the source of serotonergic projections to the amygdala and to the forebrain) were captured within the same community in the fluoxetine group, consistent with its mechanism of serotonin reuptake inhibition.

Conclusion: The community structure algorithm identified functionally specific partitions of the fully-weighted FC networks derived from the response to three different pharmacological challenges. This represents a conceptually different approach to seeking structure in the patterns of functional connectivity. Such network-based methods identify clusters on the basis of topological features of the FC network, namely the density of links within vs. between communities. Importantly, we retained the full edge weight information within the networks rather than reducing them to a binary approximation [5]. Further characterisation of null models for networks derived from functional imaging data will help identify core brain structures within each community. The "communities" identified here can be readily interpreted in biological terms as a signature of functional segregation within the integrated network of brain activity. Most importantly, the maximum modularity value represents a *measure* of residual functional segregation, and may provide the basis for an operational definition of this.

References: [1] Schwarz AJ et al. (2007) NeuroImage **34** 1627 [2] Gozzi A et al. (2006) Neuropsychopharmacology **31** 1690 [3] Schwarz AJ et al. (2006) NeuroImage **32** 538 [4] Newman MEJ (2006) PNAS **103** 8577. [5] Schwarz AJ et al. (2007) arXiv:q-bio.NC/0701041v2.