Stimulus-independent functional connectivity in the rat brain

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Introduction: Functional connectivity derived from neuroimaging data is a measure of correlation, or covariance, between spatially remote neurofunctional events. However, it is still unclear to what extent these interregional correlations reflect the dynamical features of the brain functional processes, or structural constraints of the underlying neuronal substrate. To address this question, we have mapped functional connectivity in the rat brain under various pharmacological treatments, to discriminate between connectivity patterns that are stimulus-specific, and those *independent* of the brain neurochemical state induced by the drug, thus likely to reflect general features of the brain organization.

Methods: All experiments were carried out in accordance with Italian regulations governing animal welfare and protection. Protocols were also reviewed and consented to by a local animal care committee, in accordance with the guidelines of the Principles of Laboratory Animal Care (NIH publication 86-23, revised 1985). Animal preparation and fMRI protocols are described in detail in [1]. In short, male Sprague-Dawley rats were scanned on a 4.7T Bruker Biospec MRI system under halothane anesthesia, neuromuscular blockade and mechanical ventilation. MRI time series data were acquired using a T_2-weighted RARE sequence (RARE factor 32, matrix 128x128, FOV 40mm, slice thickness 1mm, 16 contiguous coronal slices, TR_{eff} = 2700 ms, TE_{eff} = 100 ms) in the presence of a blood-pool contrast agent (Endorem, Guerbet, France) in order to sensitise signal changes to alterations in relative Cerebral Blood Volume (rCBV). Pharmacological MRI (phMRI) datasets were obtained with three different pharmacological challenges: fluoxetine (N=7), a selective serotonin reuptake inhibitor (SSRI); D-amphetamine (N=17), a dopamine releaser/reuptake inhibitor, and the nicotinic acetylcholine receptor agonist nicotine (N=9). Functional connectivity was calculated from the amplitude response vectors across subjects, and represented as a network of nodes and links, with the image voxels representing the nodes, and interregional correlations determining the edges of the links between nodes. A community structure algorithm was applied to a binarized version of the networks to identify clusters of tightly coupled nodes whose within-group links were denser than links between groups [2]. The use of community structure approaches to partitioning functional connectivity networks was recently demonstrated in rodents [2] and humans [3].

Results and discussion:
Two communities of nodes were identified in all three phMRI networks. Common features across pharmacological conditions revealed two groups of tightly coupled brain structures that responded as functional units independent of the drug (Fig.1). One group was dominated by voxels in cortical sensorimotor regions (Fig1A) – while the other identified connectivity structure that included the prefrontal cortex and sub-cortical regions extending from the striatum to the amygdala (Fig.1B), consistent with the strong underlying structural connectivity between these brain structures. It is important to emphasize that this division was obtained from a network representation based on image pixels with no imposition of symmetry nor any prior anatomical constraints.

Conclusion:
Complex network analysis of phMRI identified two groups of tightly connected nodes in the rat brain that were independent of the specific neurotransmitter system engaged by the drug. This suggests that these patterns of functional connectivity reflect general features of the brain organization, consistent with the intrinsic neuronal connectivity in these networks.

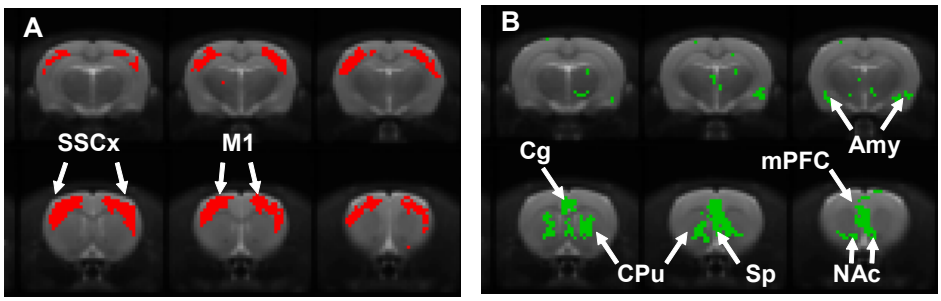

Figure 1: Voxels assigned to the same community in all three drug-challenge phMRI networks. (a) A set of cortical voxels comprising motor, somatosensory and parietal cortices. (b) A set of voxels in regions including cingulate and medial prefrontal cortices, parts of the caudate putamen and accumbens, septum/BNST, hypothalamus and amygdala.

References: [1] A.J. Schwarz, A.Gozzi, and A.Bifone, Community structure and modularity in networks of correlated brain activity, Magn Reson. Imaging 26 (2008) 914-920. [2] A.J. Schwarz, A.Gozzi, and A.Bifone, Community structure in networks of functional connectivity: resolving functional organization in the rat brain with pharmacological MRI, Neuroimage. 47 (2009) 302-311. [3] D. Meunier, S.Achard, A.Morcom, and E.Bullmore, Age-related changes in modular organization of human brain functional networks, Neuroimage. 44 (2009) 715-723.