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Structural and functional, empirical and modeled connectivity in the cerebral cortex of the rat

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ABSTRACT

Connectomics data from animal models provide an invaluable opportunity to reveal the complex interplay between structure and function in the mammalian brain. In this work, we investigate the relationship between structural and functional connectivity in the rat brain cortex using a directed anatomical network generated from a carefully curated meta-analysis of published tracing data, along with resting-state functional MRI data obtained from a group of 14 anesthetized Wistar rats. We found a high correspondence between the strength of functional connections, measured as blood oxygen level dependent (BOLD) signal correlations between cortical regions, and the weight of the corresponding anatomical links in the connectome graph (maximum Spearman rank-order correlation $\rho = 0.48$). At the network-level, regions belonging to the same functionally defined community tend to form more mutual weighted connections between each other compared to regions located in different communities. We further found that functional communities in resting-state networks are enriched in densely connected anatomical motifs. Importantly, these higher-order structural subgraphs cannot be explained by lower-order topological properties, suggesting that dense structural patterns support functional associations in the resting brain. Simulations of brain-wide resting-state activity based on neural mass models implemented on the empirical rat anatomical connectome demonstrated high correlation between the simulated and the measured functional connectivity (maximum Pearson correlation $\rho = 0.53$), further suggesting that the topology of structural connections plays an important role in shaping functional cortical networks.

1. Introduction

The study of brain connectivity from a network perspective (Newman, 2003; Strogatz, 2001) has become a promising framework to understand how action, perception, and cognition emerge from a dense ensemble of neural elements (Park and Friston, 2013). Leveraging advances in brain imaging and network science (Sporns, 2013; Sporns et al., 2005), recent approaches have focused on the topology and dynamics of large-scale projections linking anatomically distinct and functionally specialized brain regions (Bullmore and Bassett, 2011). The structure of these large-scale networks is thought to shape and constrain inter-regional interactions and computations.

Interactions between neuronal populations spanning brain-wide networks can be described from three different, but related, perspectives (Friston, 2011). Briefly, anatomical or structural connectivity (SC) refers to patterns of synaptic connections linking brain areas. Functional connectivity (FC) refers to statistical interdependence between activity time series recorded in different, often spatially remote, areas. Finally, effective connectivity (EC) refers to the influence that one neural system in one area exerts over another. While the interplay of these three modes of brain connectivity is not completely understood, some progress has been made combining anatomy with both resting-state and task-based functional connectivity (Hermundstad et al., 2013). Spontaneous or intrinsic neural activity (Cole et al., 2010; Fox and Raichle, 2007), as measured using fluctuations in the blood oxygen level dependent (BOLD) signals of resting-state functional MRI (rs-fMRI), has proven to be a useful technique for examining the extent to which structural patterns shape functional interactions between neural assemblies (Honey et al., 2010). Previous studies have shown that the presence of strong SC, as measured with diffusion-weighted MRI, between two areas increases the

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probability and strength of corresponding FC. Nevertheless, it has also been reported that strong FC may exist between areas with no (direct) anatomical connections, (Bowman et al., 2012; Damoiseaux and Greicius, 2009; Skudlarski et al., 2008), suggesting that indirect signaling and emergent dynamic processes make an additional strong contribution. For example, a study of SC and FC in macaque cortex supported the idea that functional interactions are strongly influenced by network-wide effects (Adachi et al., 2012).

Approaches simulating spontaneous cortical dynamics, in both humans and animal models, can yield invaluable insight into structure-function relationships by assessing the capacity of simulated dynamic patterns based on the SC scaffold to predict empirically measured BOLD signal correlations (Deco et al., 2011; Honey et al., 2007; Nakagawa et al., 2013). Connectomics data from animal models based on tract-tracing procedures allows in-depth characterization of SC networks. In contrast to MRI-based tractography, which provides coarse-grained undirected SC matrices, histological tracing technology yields highly resolved and directed connectivity information, hence providing important additional information for modelling cortical dynamics (van den Heuvel et al., 2016a). For instance, recent work relating the structural connectome of the mouse brain and the intrinsic BOLD signal dynamics within individual brain regions have shown the importance of considering both the weight and directionality of structural connections (Sethi et al., 2017). In addition, the mapping of functional connectivity networks in rodents provides an invaluable tool to understand neurological and psychiatric disorders from a more mechanistic way for translational research. (Gozzi and Schwarz, 2016; Pan et al., 2015). These experimental possibilities together with theoretical developments in network analysis are extending systems neuroscience from unimodal investigations of brain connectivity to a network-level understanding of structure-function interactions (Adachi et al., 2012; Diez et al., 2015; Goñi et al., 2014; Hsu et al., 2016; Mišić et al., 2016; Skudlarski et al., 2016; Stafford et al., 2014; Wang et al., 2015; Wirsich et al., 2016).

In this work, we examine the relationship between SC and FC in the rat cortical network. Using a detailed cortical SC matrix obtained from a carefully curated meta-analysis of published histological tracing data in rats (Bota et al., 2015), we first compare structural connections in the rat cortex with their corresponding spontaneous correlations extracted empirically from rs-fMRI data collected in a group of 14 Wistar rats. We then show the results of this comparison taking into account network-level effects by relating structural properties of brain connectivity to the functional modularity of rs-fMRI networks. Specifically, we study link reciprocity in both intra- and inter-modular connections as well as the structural motif frequency spectrum within functionally defined modules. Finally, we carry out computational simulations of neural mass models implemented on the empirical SC to generate a simulated FC matrix and compare it with the empirically measured FC. Overall, our results provide evidence on rs-fMRI BOLD signal correlations being constrained and shaped by the underlying structural connectivity patterns.

2. Materials and methods

2.1. Animals and MRI acquisition protocol

Experiments were carried out in a horizontal 7 T scanner with a 30 cm diameter bore (Biospec 70/30v, Bruker Medical, Ettlingen, Germany). The system had a 675 mT/m actively shielded gradient coil (Bruker, BGA 12-S) of 11.4 cm inner diameter. A 1H rat brain receive-only phase array coil with integrated combiner and preamplifier, no tune/no match, in combination with the actively detuned transmit-only resonator (BrukerBioSpin MRI GmbH, Germany) was employed. Data were acquired and processed with a Hewlett-Packard console running Paravision 5.1 software (Bruker Medical GmbH, Ettlingen, Germany) operating on a Linux platform.

For the rs-fMRI experiments, 14 Wistar rats were anesthetized with urethane (1.2 g/Kg). Anesthetized animals were placed in a custom-made animal holder with adjustable bite and ear bars, and positioned on the magnet bed. The animals were constantly supplied with 0.8 L/m O2 with a face mask and temperature was kept between 36.5 and 37.5 °C through a water heat-pad. The temperature, heart rate, SpO2, and breathing rate were monitored throughout the session (MouseOx, Starr Life Sciences, Oakmont, US).

T2-weighted anatomical images were collected using a rapid acquisition relaxation enhanced sequence (RARE), applying the following parameters: field of view (FOV) = 40 × 40 mm; 15 slices; slice thickness = 1 mm; matrix size = 128 × 128; effective echo time (TE_{eff}) = 56 ms, repetition time (TR) = 2 s, and a RARE factor of 8. The B0 field distribution in a large voxel (40 × 40 × 40 mm^3) containing the whole head was acquired (FieldMap). Briefly, the brain was localized with T2-weighted RARE sequence, and first- and second-order shims adjusted with MAPSHIM application in a sufficiently large voxel containing the whole brain. Functional MRI acquisition was performed using a GE-EPI sequence in 30 coronal slices applying the following parameters: FOV = 25 × 25 mm; slice thickness = 0.5 mm; matrix size = 50 × 50; segments = 1; FA = 60°; echo time (TE) = 15 ms; repetition time (TR) = 2000 ms (300 samples per run, 10 min), rendering an isotropic voxel of 0.5 × 0.5 × 0.5 mm^3. Between one and three runs were acquired from each animal. T2-weighted anatomical images with exactly the same geometry were collected using a RARE sequence using the following parameters: FOV = 25 × 25 mm; 30 slices; slice thickness = 0.5 mm; matrix size = 200 × 200; TE_{eff} = 56 ms; TR = 2 s; RARE factor = 8.

2.2. Preprocessing of MRI data

Data preprocessing within runs was carried out using FSLv5.0 (FMRIB Software Library, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (Jenkinson et al., 2012) and MATLAB 2014a (The MathWorks, Inc., Natick, MA, United States, https://www.mathworks.com/). Once images were converted to NIfTI (Neuroimaging Informatics Technology Initiative, http://nifti.nimh.nih.gov/) data format, the original voxel size, (x,y,z), was scaled up by a factor of 10. This step is very common when analyzing rodent data to accurately apply the same algorithms (largely those involving spatial transformations) as in human analyses (Kalthoff et al., 2013; Pan et al., 2015).

The very first volume of fMRI data was used as reference across runs of the same subject for head motion correction, brain segmentation and co-registration. As suggested by (Kalthoff et al., 2011), head motion correction was applied to each individual slice and restricted to (coronal) in-plane translations (x, y) and rotation (z) to reduce signal fluctuations related to respiration in anesthetized rats. After applying motion correction and brain segmentation (Smith, 2002), global intensity normalization was set to 1000 and spike detection was performed through using *DVARS* measure (Power et al., 2012). Note that *DVARS* is highly dependent on the particular dataset (Power et al., 2014); we therefore did not select an absolute threshold and instead considered as outliers those temporal points exceeding the 75th percentile + 1.5*IQR (interquartile range). None of the runs were discarded since the number of spikes was below 30 (out of 300 samples) in all cases (15 ± 4.6 spikes per run, mean ± SD), hence ensuring a minimum length of 9 min to estimate functional interactions. By using a nuisance regression model, each voxel was corrected for: (1) the three rigid body parameters (translation in x and y, and rotation in z) previously computed and their derivatives (backward difference); (2) a single regressor per spike with a "*b0, f0*" window (Satterthwaite et al., 2013) (i.e. neither preceding nor following samples were used); (3) the global signal and its derivative (backward difference); and (4) two regressors modelling the mean and a linear trend. A Band-pass filtering (nonlinear high-pass filter of $\gamma = 50$ s, and Gaussian linear low-pass filter of $\gamma = 2$ s) was applied to retain those frequencies ranging from 0.01 and at around 0.1 Hz (the resulting spectrum of this filter is shown in Supplementary Fig. 1). Spatial