Modular organization of mouse brain functional connectivity

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Introduction: Resting state fMRI (rsfMRI) has been widely employed to investigate the intrinsic organizational structure of the brain. A strong rationale exists for the translational implementation of analogous measurements in small laboratory animals, such as the laboratory mouse. We recently described the presence of robust distributed resting-state fMRI networks in the mouse brain displaying striking analogy with those observed in humans and primates, comprising plausible homologues for the salience and default-mode network (*1*). Here we capitalised on this recent work to investigate the topological architecture of mouse brain rsfMRI networks. Specifically, we used graph theoretical analysis to investigate the modular organisation of mouse brain functional connectivity networks (*2, 3*). To this purpose, rsfMRI signals were parcellated into anatomical clusters to cover the entire brain, and the corresponding correlation matrix partitioned into functional connectivity communities (i.e., cohesive clusters of strongly interconnected nodes) using an algorithm that relies on the optimization of the mathematical representation of "modularity" – defined by the density of links relative to that expected by chance. We show that this approach can identify sub-networks whose distributions indicate compelling functional subdivisions in the mouse brain that can be related to known partitions of the brain.

Methods: All experiments were carried out in accordance with Italian regulations governing animal welfare and protection. **Animals:** MRI experiments were performed on male C57Bl6/J mice (n=40). **Animal preparation**: The procedure employed for rsfMRI has been recently described (*1, 4*). Briefly, mice were anaesthetized with isoflurane (5%), intubated, and artificially ventilated. rsfMRI timeseries were acquired using controlled halothane anesthesia (0.7%). **rsfMRI:** All experiments were performed using a 7.0 Tesla MRI scanner using a single-shot EPI sequence with TR/TE 1000/15 ms, matrix 100 × 87, field of view 2.3 × 2 cm2, 16 coronal slices, slice thickness 0.75 mm an NT=360. **rsfMRI data analysis:** rsfMRI time series were pre-processed (registered, motion regressed band-pass filtered; 0.1-0.01 Hz and smoothed) as recently described (*1*). ROI masks corresponding to 52 cortical were extracted from a brain atlas *(1),* and mean pair-wise correlation coefficients (r-z Fisher transformed) were computed from the rsfMRI time-series for each pair of VOIs. A mean weighted graph representing the interregional correlations across the whole cohort of subjects was built using the ROIs as nodes, and pairwise (r-z Fisher transformed) correlations as links. The graph was then thresholded over a range of r ($0.05< |r| < 0.6$) to retain only the strongest links. A community structure analysis was performed (2, 3) using the Louvain method (5), an approach previously applied to human and rodent data (*2, 3, 6*). The number of communities was computed as a function of r threshold.

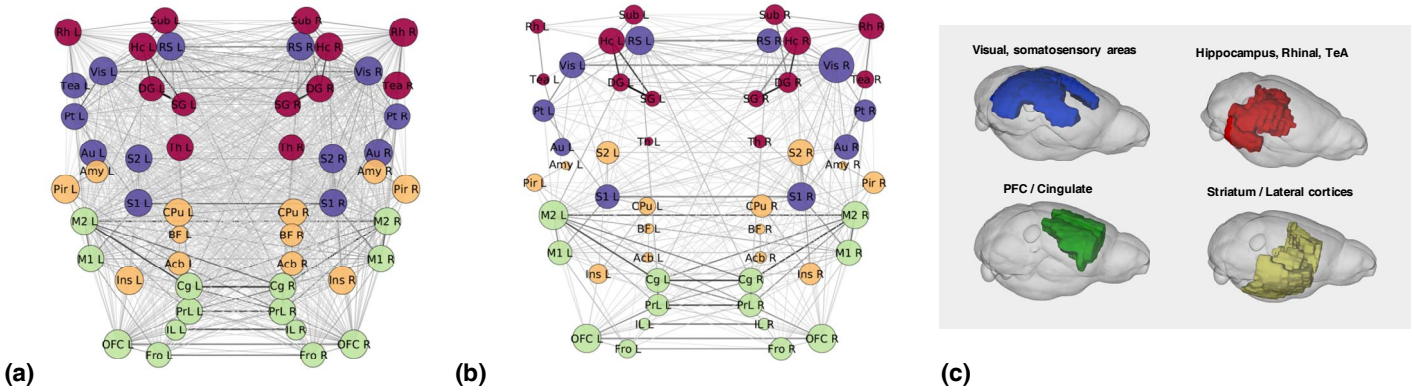

Figure 1: Graph-representation of the regions assigned to the four modules identified by the community structure algorithm. The nodes have been arranged according to their approximate location over a horizontal section of the mouse brain (top – caudal areas, bottom – rostral areas). Result are shown at two representative low **(a)** ad high **(b)** r thresholds (a, $|r|$=0.10, 1152 links, b, $|r|$=0.28, 319 links). The area of the circles is proportional to the degree (i.e. nr.. of links) of the node, and link thickness to the strength of connection. **(c)** Three dimensional representation of the communities described in graph **(b)** [Tea: temporal association areas, abbreviations in networks (**a**) and (**b**) are described in (*1*)]

Results and discussion

The community detection algorithm employed produced a stable number of inter-hemispheric communities (N=3-4) over a wide range of r correlation thresholds (0.10-0.30). Higher thresholding produced a monotonically increasing number of communities, reflecting the increasing incidence of disconnected or weakly connected nodes. Over the threshold range $0.10< r <0.30$, four distributed communities were consistently identified as being stably bilateral and with a considerable antero-posterior extension (Figure 1). These included pre-frontal and cingulate, hippocampal and peri-hippocampal cortices, parietal (somatosensory) areas and ventro-striatal latero-cortical structures. Each of these networks is associated to known brain processes and can be related to well-characterized functional network modules of the human brain (default-mode, visual – hippocampal, sensory-motor, and basal ganglia, respectively, (*7*)). Within the same threshold range, network partitioning into three communities consistently resulted in the fusion of dorsal cortical areas to produce a large antero-distributed community ranging from prefrontal to retrosplenial and visual cortices.

Conclusions

To the best of our knowledge, this is the first graph-based study to describe topological features of mouse brain resting-state rsfMRI networks. These results provide initial evidence that the mouse brain conserves fundamental topological properties that have been observed in higher species, including primates and humans (*6,7*). The use of threshold-independent (*8*) and voxelwise partitioning (*9*) approaches, together with the characterisation of null models for networks derived from rsfMRI data will help identify core topological features of the resting mouse brain.

References: **[1]** Sforazzini et al., *NeuroImage* In press, (2013) **[2]** Schwarz, et al., *MRI* 26, 914 (2008) **[3]** Schwarz et al., *Neuroimage.* 47, 302 (2009) **[4]** Dodero *et al.*, *PLoS ONE* 8, e76655 (2013) **[5]** Blondel et al., *J. Stat. Mech. Theory* E 10, P10008 (2013) **[6]** Meunier et al., *Frontiers in Neuroinformatics* 3, (2009) **[7]** Moussa et al., *PLoS ONE* 7, e44428 (2012) **[8]** Rubinov et al., *NeuroImage* 56, 2068 (2011) **[9]** Wu et al., *PLoS ONE* 8, e73670 (2013).