Voxel-scale mapping of the mouse brain functional connectome

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Background

Resting-state functional MRI (rsfMRI) has been widely applied to study functional segregation and integration in the human brain.

Network analyses of rsfMRI connectivity – "functional connectomics" – have revealed the presence of functionally specialized sub-systems interlinked by a small number of highly-connected "hub nodes", serving as integrators of distributed neuronal activity.

Aberrations in functional connectivity have been consistently observed in several disorders of the brain; however, whether these alterations are causative or epiphenomenal to brain pathology remains to be determined.

A strong rationale exists for the **translational use** of analogous readouts in preclinical psychopharmacological studies and mouse models.

The presence of **distributed resting-state networks** in the mouse brain, identified using ICA and seed-correlation methods, has been recently reported by several research groups.

Building on previous studies (Sforazzini et al. 2014a; Sforazzini et al. 2014b; Zhan et al., 2014; Liska et al. 2015), here we have mapped whole-brain intrinsic functional connectivity (i.e. the **functional connectome**) and identified functional modules and hubs in the mouse brain at a high-resolution voxel scale.

Methods

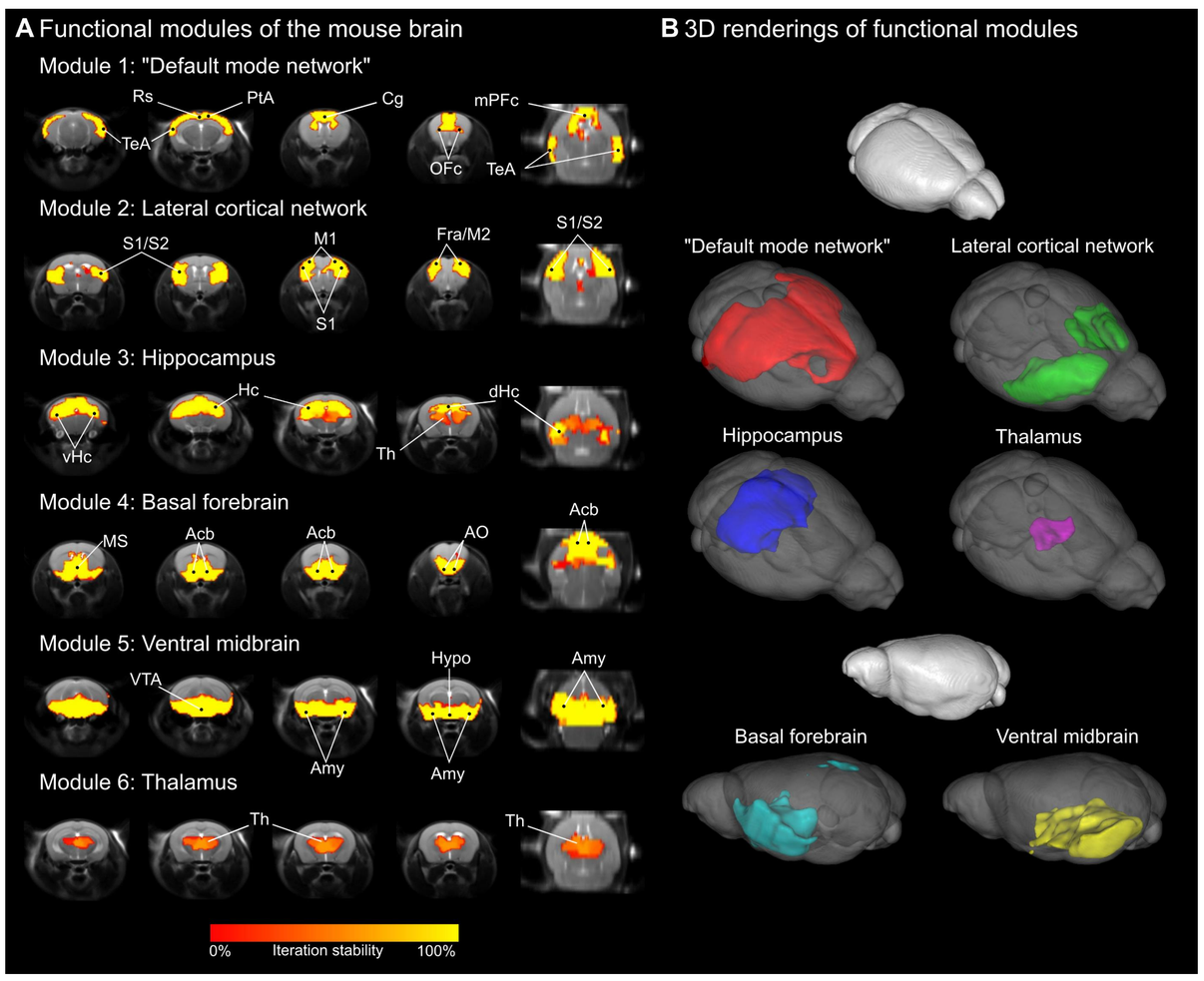
Acquisition. MRI experiments were performed on C57BL/6J mice (N=41). RsfMRI time series were acquired and preprocessed as recently described (Sforazzini et al., 2014a). Final spatial resolution: 0.2×0.2×0.5 mm^3.

Functional network. Time courses from all brain voxels were extracted and *z*-transformed correlation matrices averaged across all animals to create the final connectivity matrix, without any arbitrary thresholding and/or binarization. The network was partitioned into modules maximizing a measure of modularity incorporating both positive and negative weights.

Hub identification. We identified as *global hubs* those nodes that showed disproportionately high connection strength (i.e. a large number of connections) or connection diversity (i.e. even distribution of connections across all modules). In addition, we identified as *module hubs* those nodes that exhibited high within-module strength.

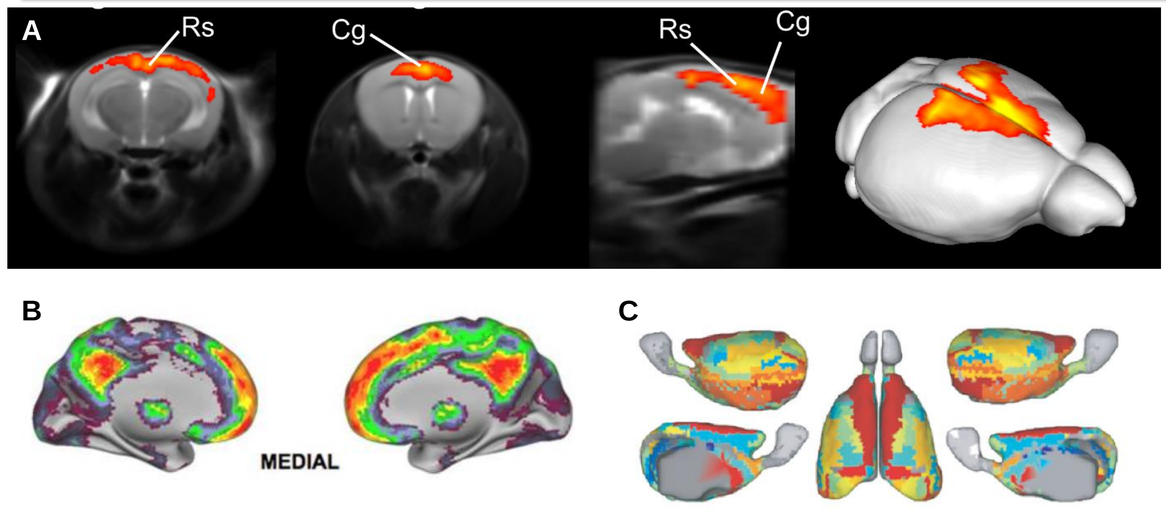
Hub interconnections. To assess whether the identified hubs are preferentially and mutually interlinked, we analysed their connectivity relationships directly by considering the network comprising only overlapping connections between the hubs. Mean hub-hub correlation values were computed and the group-level significance of each connection was assessed.

Mouse brain contains robust functional connectivity modules



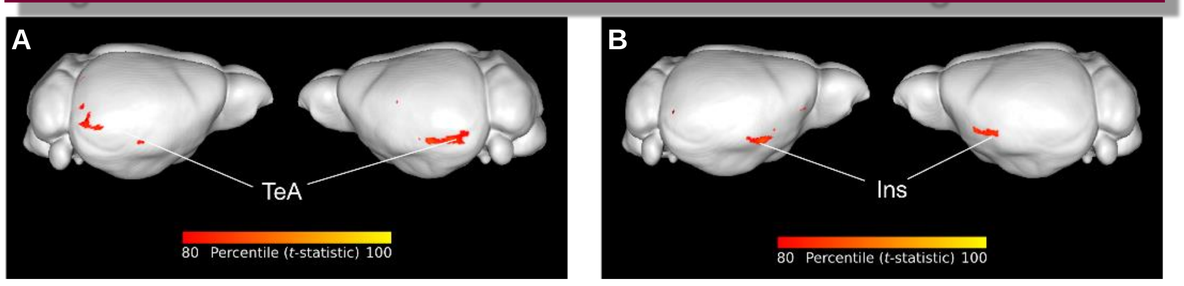
The voxel-scale mouse brain functional network was partitioned into six bilaterally symmetrical modules: a rodent homologue of the "default mode network" (DMN), a lateral cortical network (LCN), dorsal and ventral hippocampus, "basal forebrain" (striatal and septal regions, nucleus accumbens, anterior olfactory nucleus), "ventral midbrain", and thalamic areas.

High strength hubs of human and mouse brain are located in homologous areas



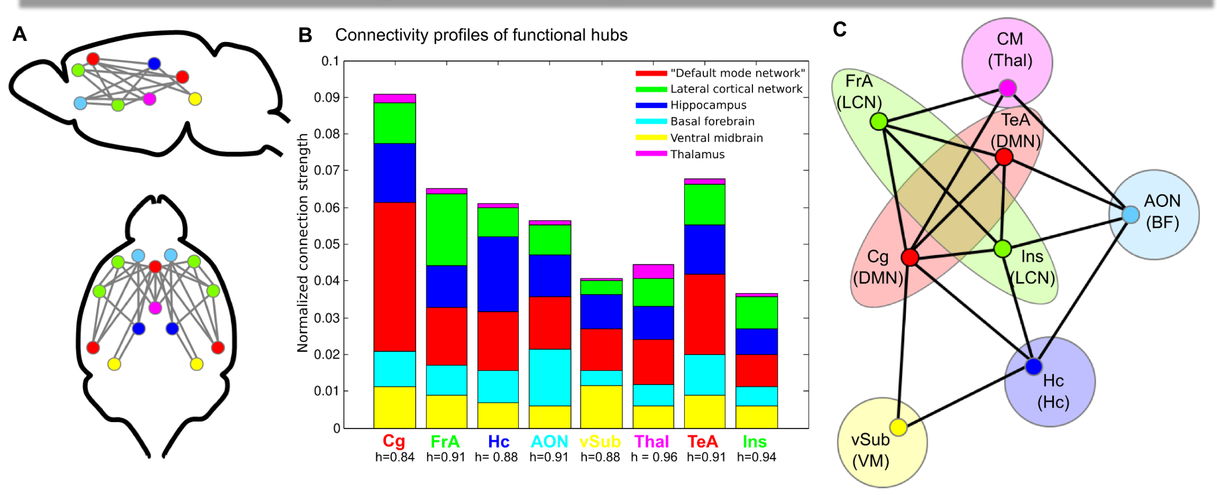
(A) Foci exhibiting the highest strength nodes were located in several sub-regions of the DMN, including prefrontal, cingulate, and parietal association cortices. (B) Regions showing high functional connectivity in the human brain. Adapted from Buckner et al., J. Neurosci. 2009. (C) Regions showing high connectivity in the mesoscale structural connectome of the mouse brain (obtained through an anterograde tracer mapping of axonal projections throughout the mouse brain). Adapted from Stafford et al., PNAS 2004.

High connection diversity hubs are located in integrative areas



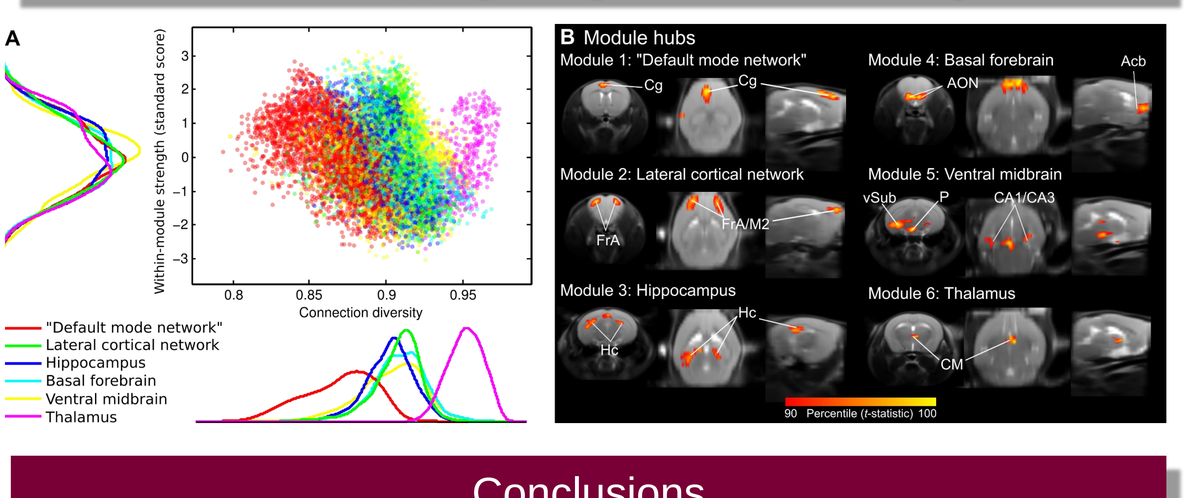
High connection diversity regions within the default-mode network (A) and lateral cortical network (B).

Connectivity relationships of the identified hubs



Connectivity relationships of candidate hubs. (A) Approximate locations of candidate hubs of the mouse brain. Connections surviving statistical thresholding are indicated by a link between nodes (B) Connectivity profiles of candidate hubs, showing the proportion of their strength across all modules. (C) Graph representation of the connections surviving statistical thresholding, with node positions determined using the GEM algorithm. (D) Average correlation matrix for all pairs of identified hubs. (E) One sample t-tests for all pairs of identified hubs; non-significant connections (after FDR correction) are shown in grey.

Intra-module mapping of high connection strength hubs



Conclusions

Network analysis used to map mouse brain **functional connectivity hubs** at voxel-scale.

Six functional modules were identified, including a **default mode network** (DMN).

Highly-connected functional hubs were identified in several regions of the DMN.

Foci of high connection diversity were mapped in associative cortical areas.

The identified hubs exhibit **mutual preferential interconnections**.

References

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