Voxel-scale mapping of the mouse brain functional connectome

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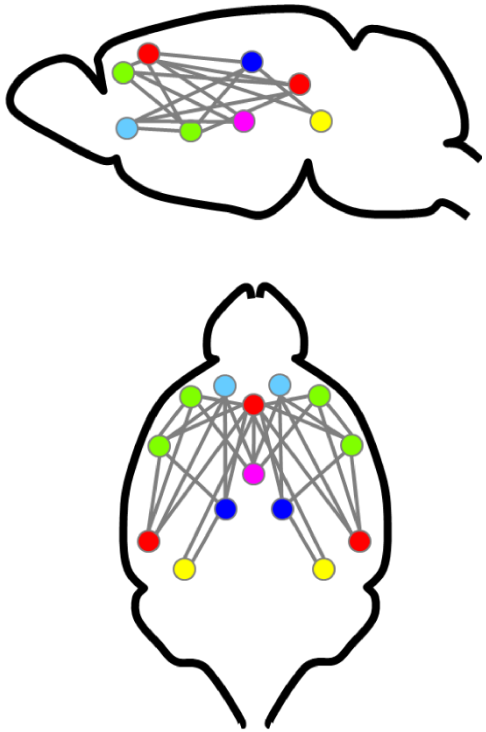

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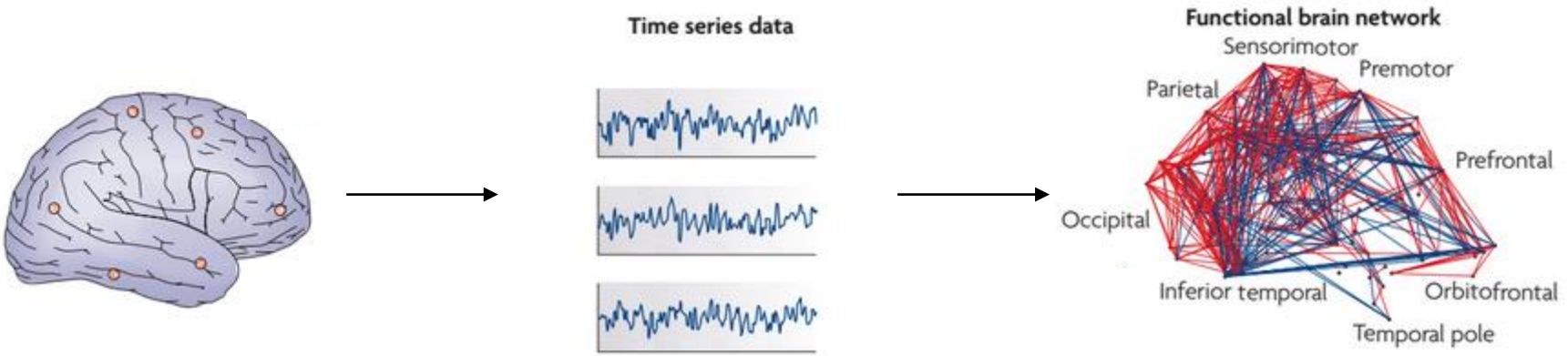
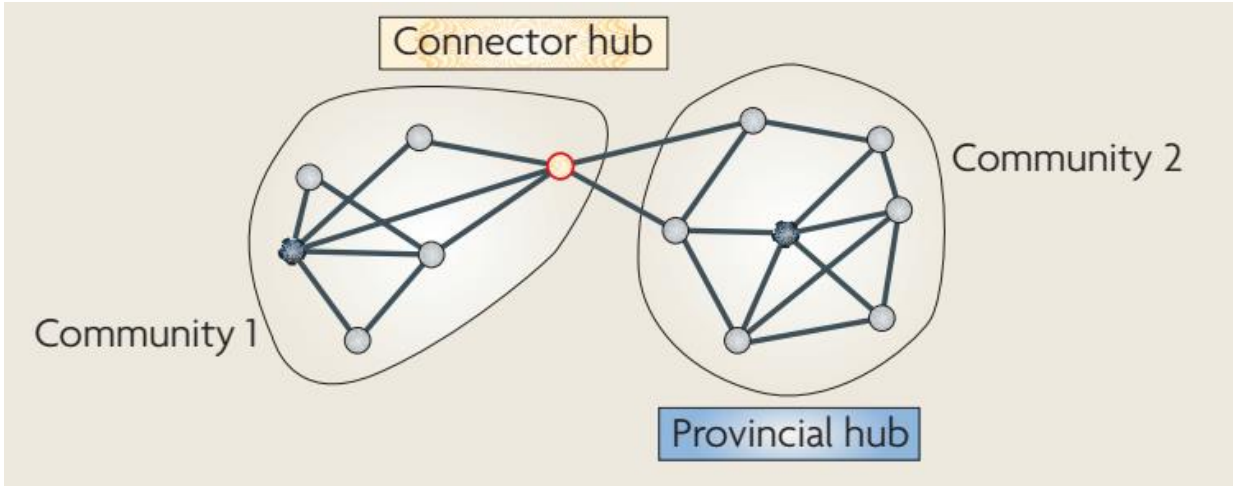
Declaration of Financial Interests or Relationships

Speaker Name: Adam Liska

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Graph representation of functional connectivity networks





Bullmore and Sporns, Nature 2009

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Open questions

- What are the neurophysiological and cellular determinants defining the topology of functional connectomes?
- What is the relation between structural and functional connectivity?
- What role do genes play in shaping these networks in health and disease?
- What is the pathophysiological significance of connectional alterations in brain disorders?
- …

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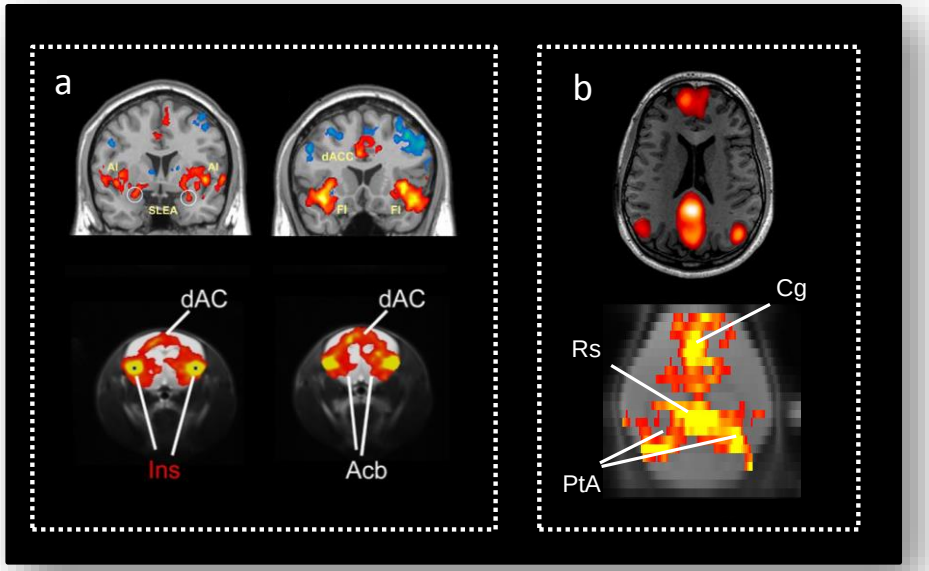
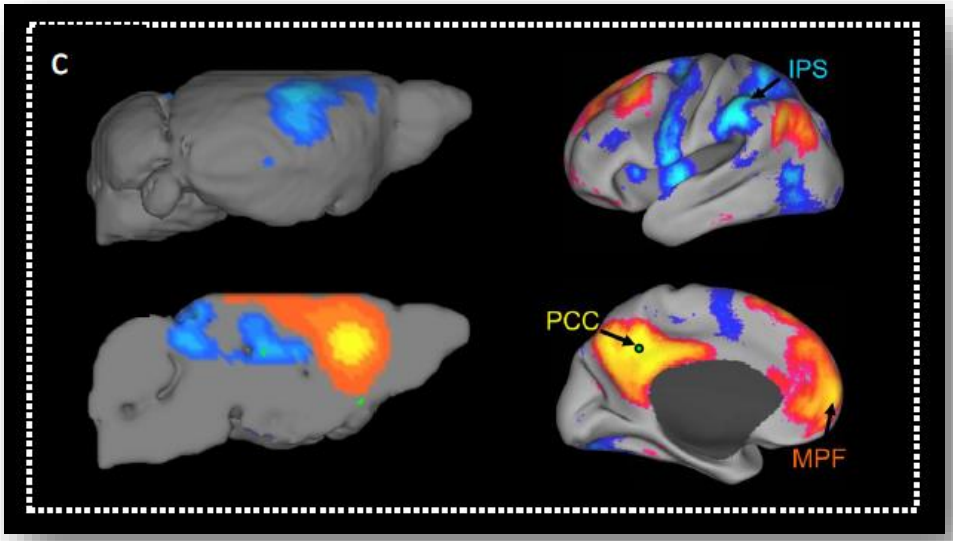
Homologous fMRI connectivity networks in mice and humans



Sforazzini et al., NeuroImage 2014



Schwarz and Gozzi, submitted

- Evidence of default-mode and “salience” networks
- Like in humans, the mouse DMN is anticorrelated to a lateral cortical “motor-sensory” network

Methods

Image data acquisition

- Adult male C57Bl6/J mice (N=41)
- Ventilated, halothane anaesthesia 0.75% maintenance (Sforazzini et al. 2014a, 2014b)
- 7T MRI scanner using a single-shot EPI sequence (TR/TE 1200/15ms, flip angle 30º, matrix 100 × 100, FOV 2 × 2 cm2, 24 coronal slices, 0.50 mm thickness, 300 volumes
- Preprocessing: motion correction, nuisance signal regression, band-pass filtering

Functional analyses

- Nodes: voxels; edges: correlations
- Connectivity matrices computed for each subject, no thresholding or binarization
- Mean connectivity matrix partitioned into modules maximizing an asymmetric measure of modularity (Rubinov & Sporns, 2011)
- Hubs identified using connection strength or diversity and the “statistical thresholding” method (Cole et al., 2010)

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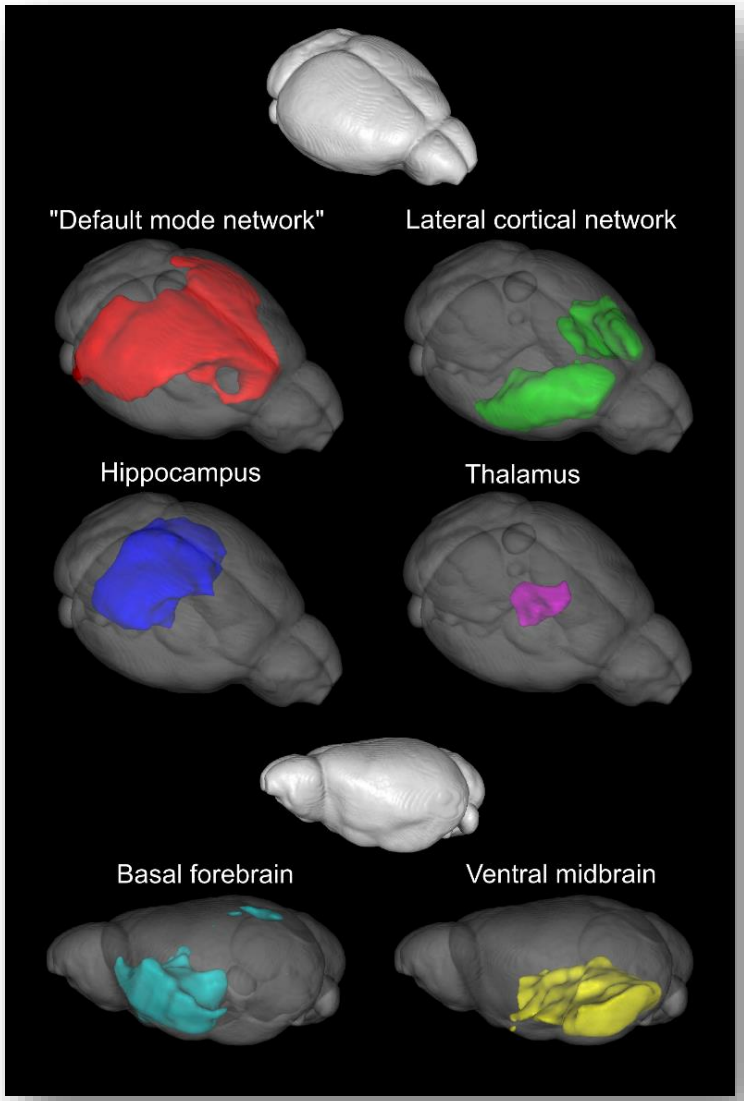
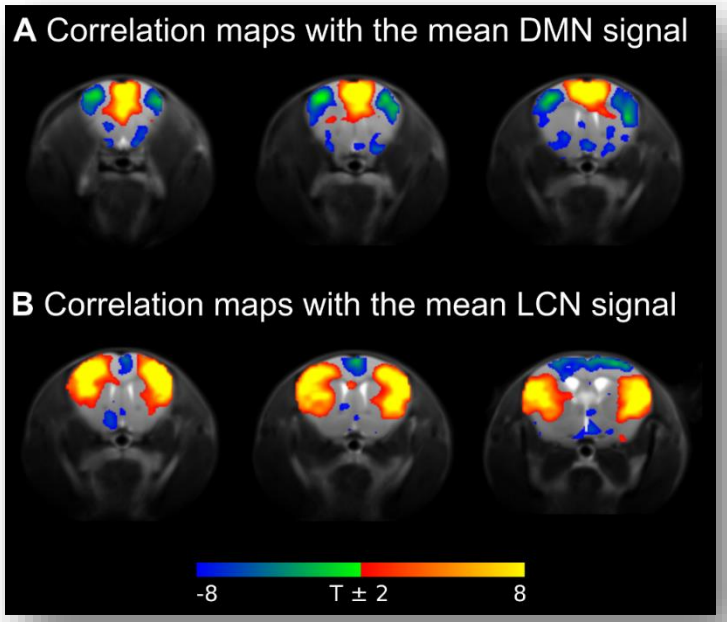
Functional modules of the mouse brain



Liska et al., NeuroImage 2015



Liska et al., NeuroImage 2015

Six neuro-anatomically plausible modules, including a default mode network

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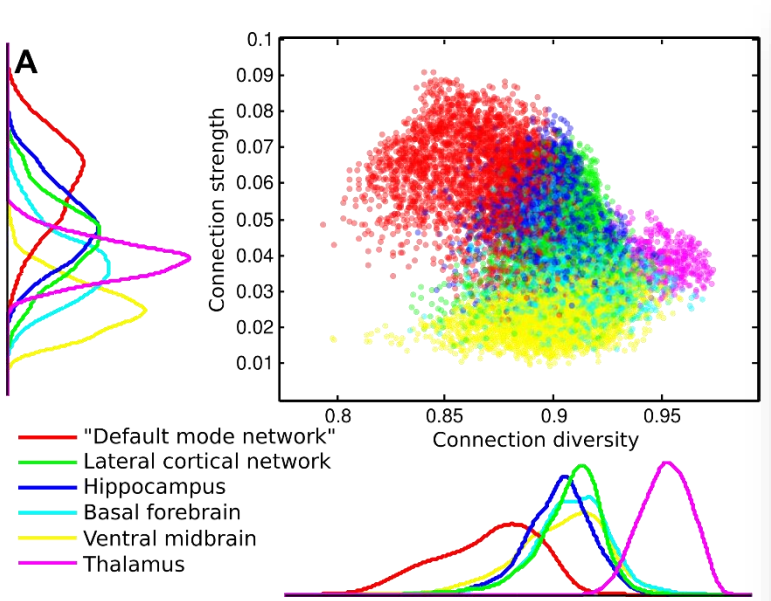
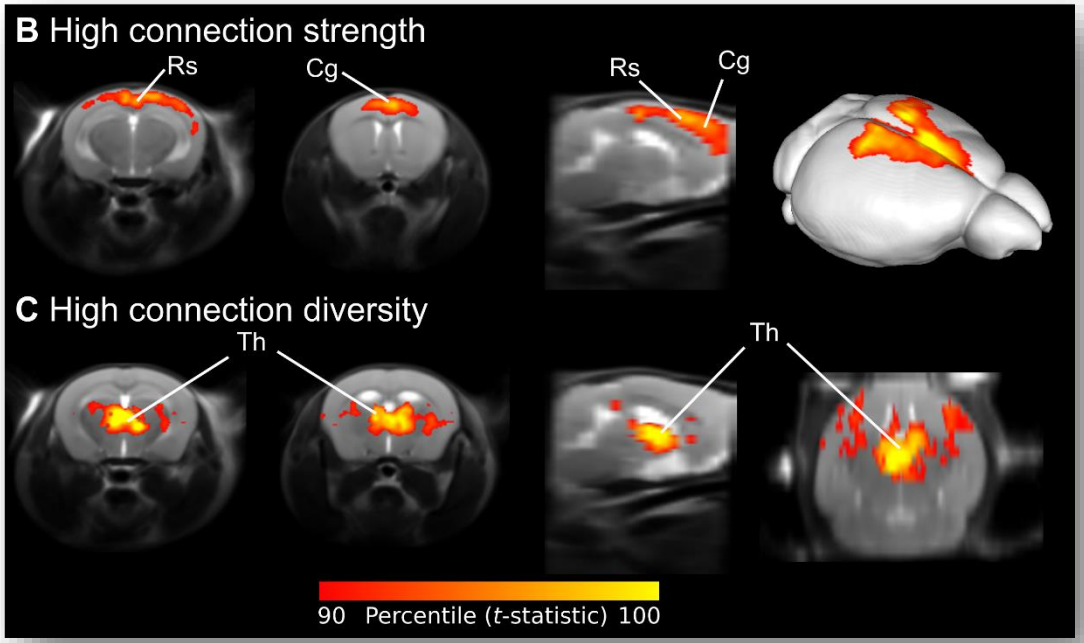
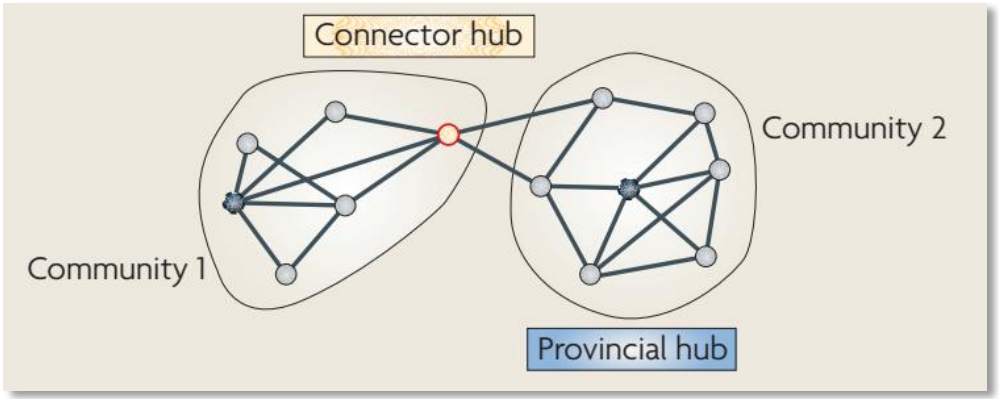
Connectivity hub mapping





Liska et al., NeuroImage 2015



Bullmore and Sporns, Nature 2009

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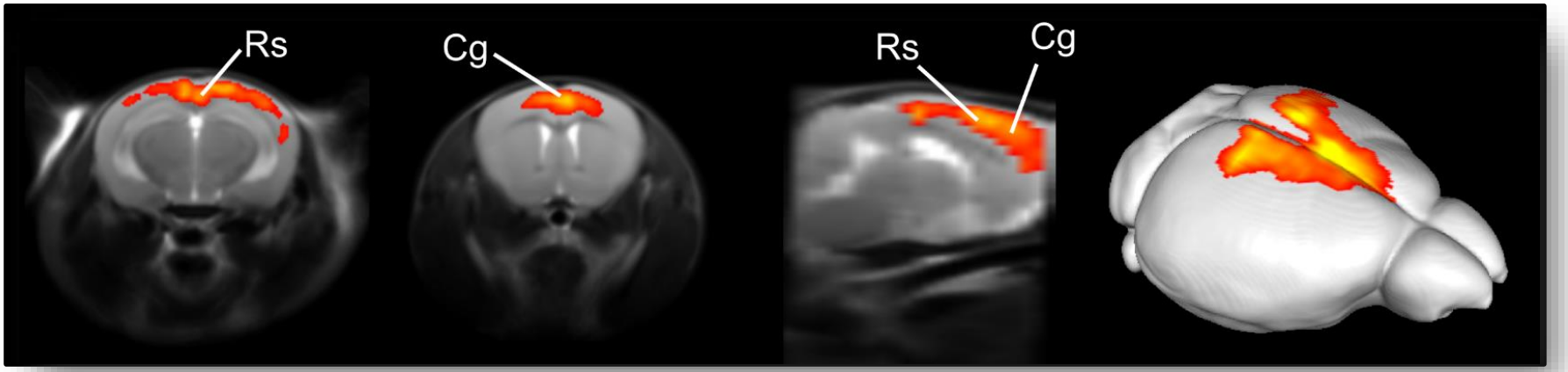
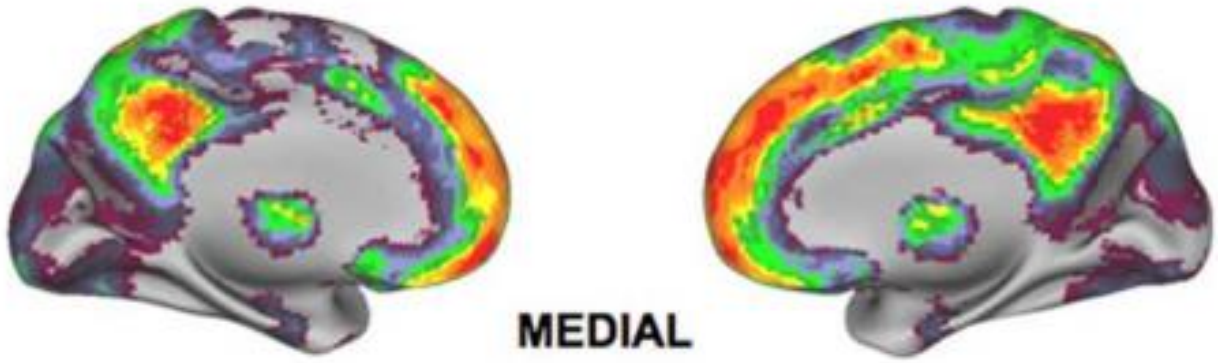
High connection strength hubs

Mouse



Liska et al., NeuroImage 2015

Human



Buckner et al, J. Neurosci. 2009

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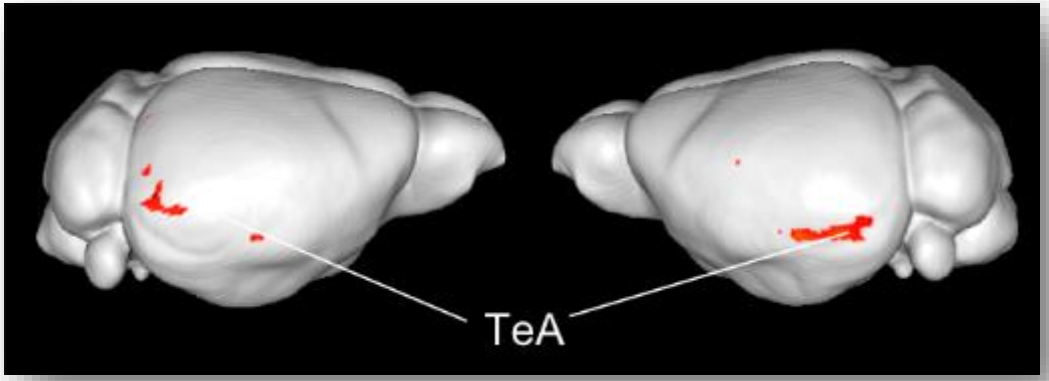
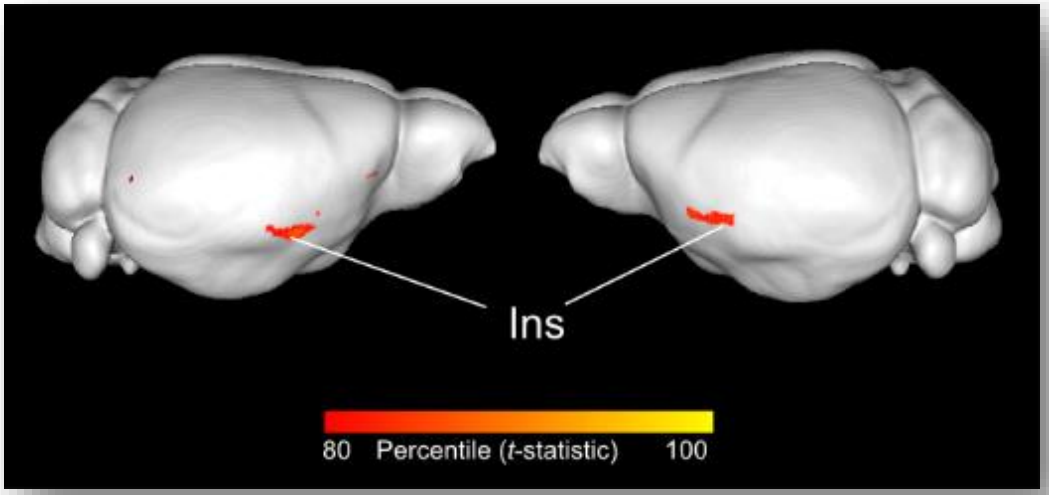
High connection diversity hubs of the cortex

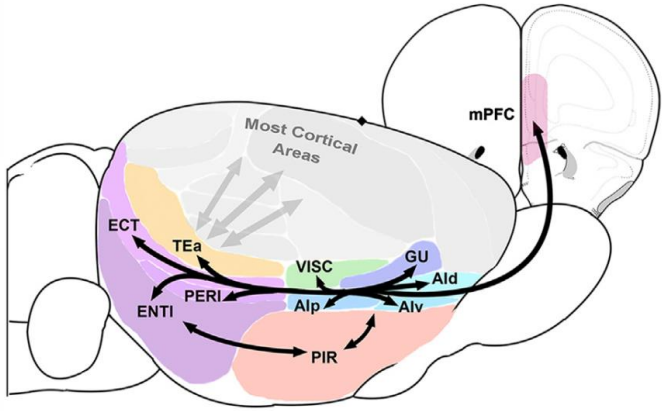
Temporal association cortices



Insular cortex



Liska et al., NeuroImage 2015



Zingg et al., Cell, 2014

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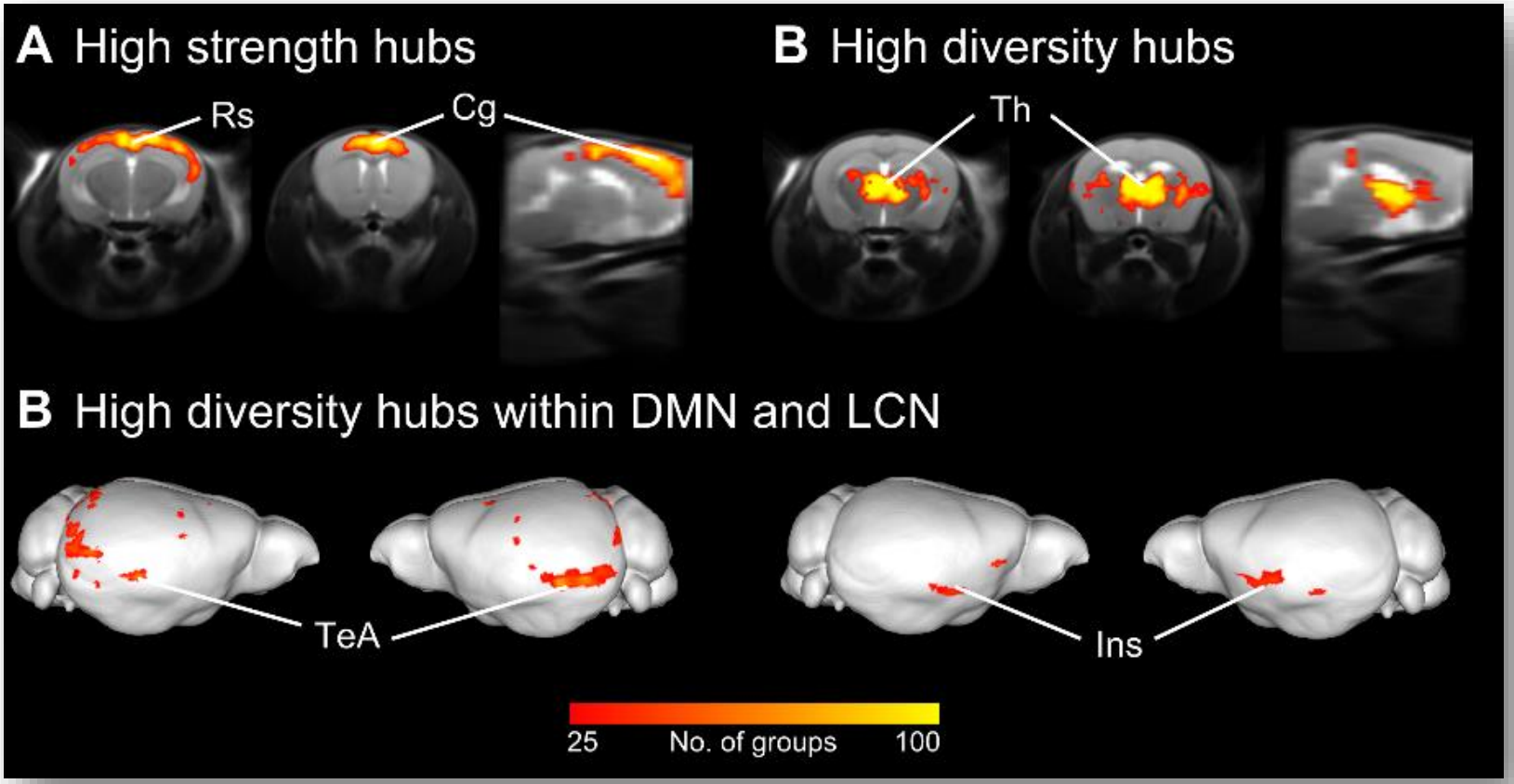
The identified hubs are reproducible in smaller cohorts



Liska et al., NeuroImage 2015

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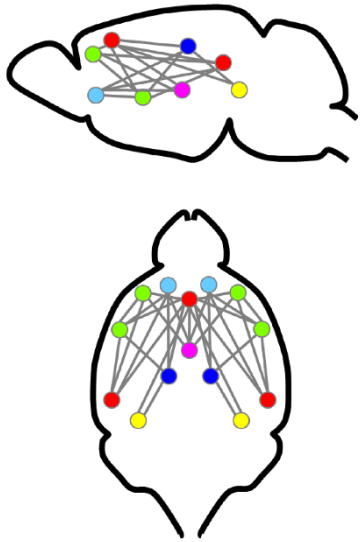
Conclusions

- **This work:**
  - Mouse resting-state fMRI connectome can be partitioned into six functional modules, including a default-mode network (DMN)
  - Like in humans:
    - Highly-connected functional hubs were identified in several sub-regions of the DMN
    - Foci of high connection diversity were mapped in associative cortical areas



- **Future directions:**
  - How are these hubs affected in mouse models of brain pathology?
  - …

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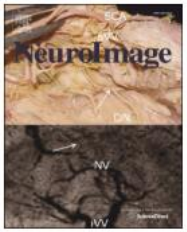

Functional connectivity hubs of the mouse brain

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ABSTRACT

Recent advances in functional connectivity methods have made it possible to identify brain hubs — a set of highly connected regions serving as integrators of distributed neuronal activity. The integrative role of hub nodes makes these areas points of high vulnerability to dysfunction in brain disorders, and abnormal hub connectivity profiles have been described for several neuropsychiatric disorders. The identification of analogous functional connectivity hubs in preclinical species like the mouse may provide critical insight into the elusive biological underpinnings of these connectional alterations. To spatially locate functional connectivity hubs in the mouse brain, here we applied a fully-weighted network analysis to map whole-brain intrinsic functional connectivity (i.e., the functional connectome) at a high-resolution voxel-scale. Analysis of a large resting-state functional magnetic resonance imaging (rsfMRI) dataset revealed the presence of six distinct functional modules related to known large-scale functional partitions of the brain, including a default-mode network (DMN). Consistent with human studies, highly-connected functional hubs were identified in several sub-regions of the DMN, including the anterior and posterior cingulate and prefrontal cortices, in the thalamus, and in small foci within well-known integrative cortical structures such as the insular and temporal association cortices. According to their integrative role, the identified hubs exhibited mutual preferential interconnections. These findings highlight the presence of evolutionarily-conserved, mutually-interconnected functional hubs in the mouse brain, and may guide future investigations of the biological foundations of aberrant rsfMRI hub connectivity associated with brain pathological states.