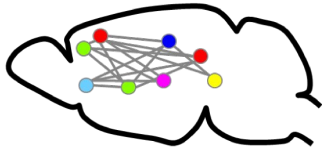
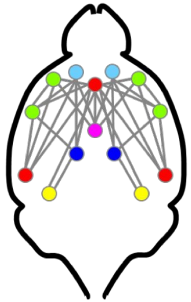
Functional connectivity hubs of the mouse brain and their impairment in autism models

Adam Liška
Advisor: Alessandro Gozzi

Tuesday, February 28, 2017
Cambridge Connectome Consortium





CIMeC
Center for Mind/Brain Sciences

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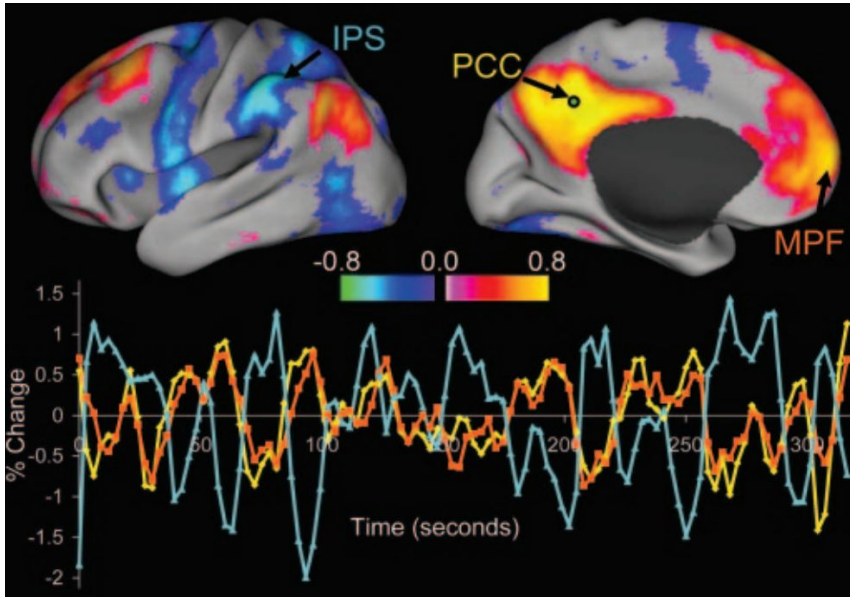
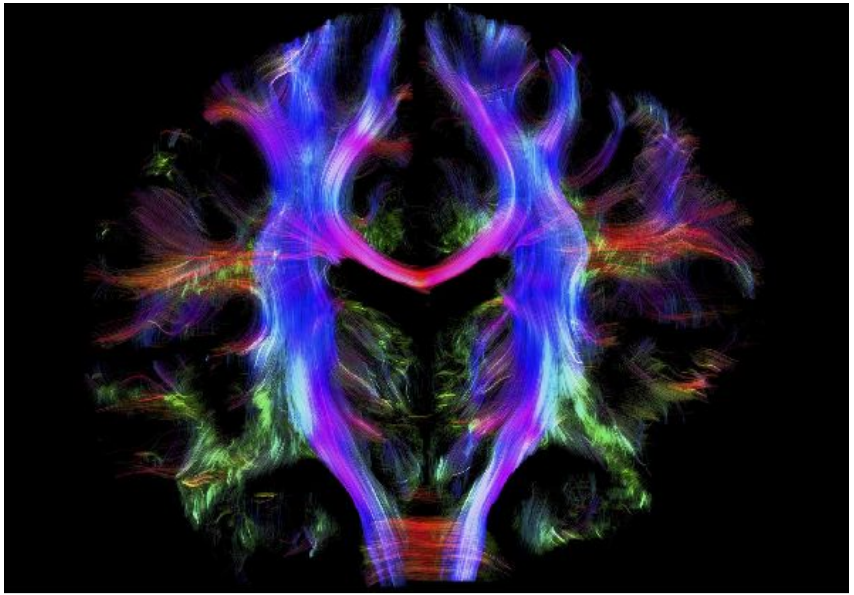
DI TECNOLOGIA

Brain connectivity and its applications



Fox et al. Proc. Natl. Acad. Sci. 2005



Alfred Anwander, Wellcome Image Awards

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Special Issue: The Connectome

Fledgling pathoconnectomics of psychiatric disorders

Mikail Rubinov[1,2,3] and Ed Bullmore[1,2,4]

Open questions and challenges

What is the significance of connectional alterations in brain disorders?

What are the neurobiological mechanisms that underpin brain connectivity in health and disease?

Are functional disruptions mediated via structural disruptions?

What is the relation between structural and functional connectivity?

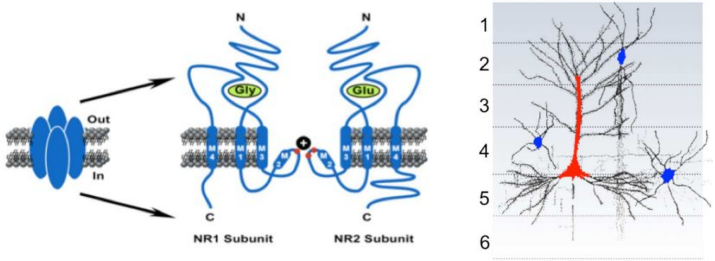
Brain connectivity alterations: state effects or illness pathophysiology?

"[We] believe the evidence that these "findings" are reflections of changes in the brain related to pathogenesis is inconclusive at best and potentially represents artifacts or epiphenomena of dubious value."

Weinberger and Radulescu. Am J. Psychiatry. 2016

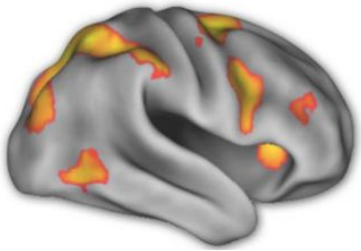
Potential of animal models in brain imaging

Cellular biology/Physiology



Explanatory gap

Neural Systems



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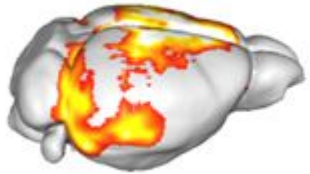
Mouse Neural Systems



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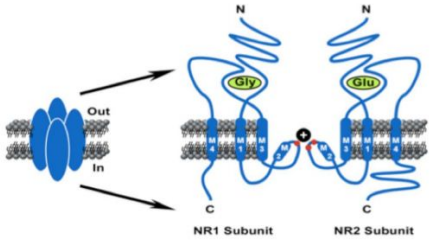

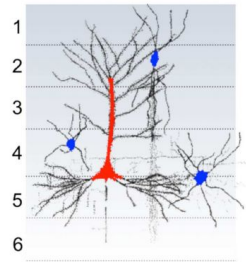

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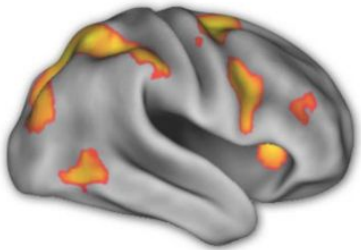

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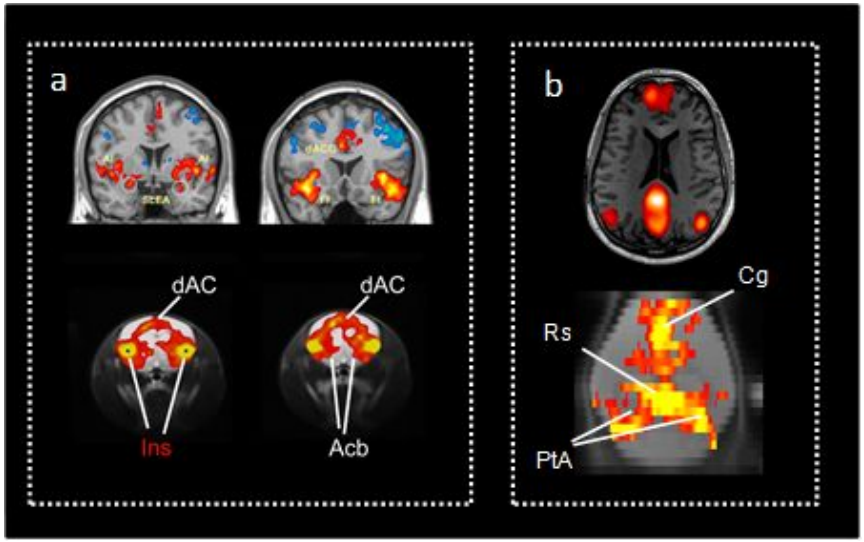
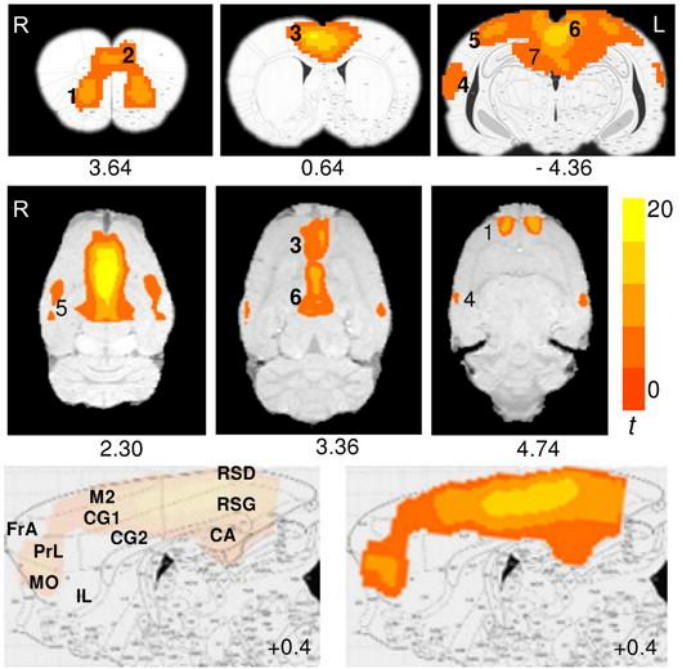
Functional connectivity in the rodent brain

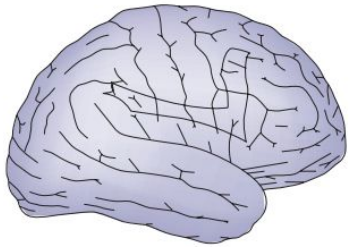


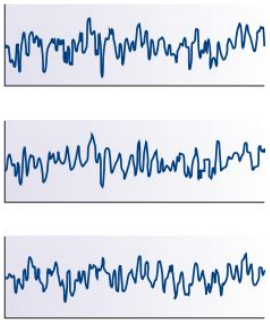
Sforazzini et al. NeuroImage. 2013

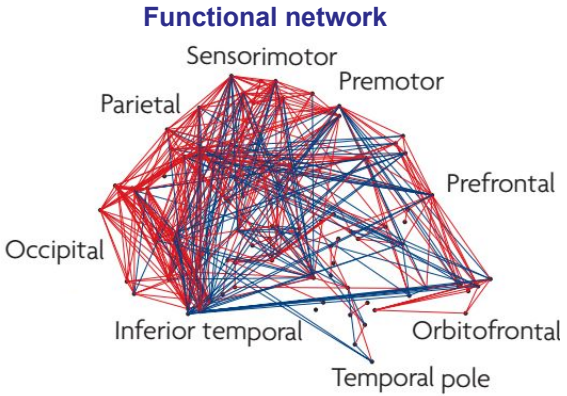


Lu et al. Proc Natl Acad Sci. 2012

Functional network organization of the human brain







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Nat. Rev. Neurosci. 2009

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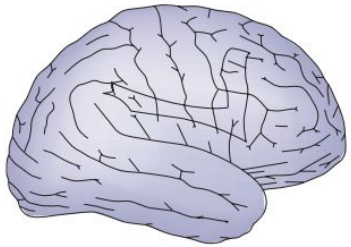

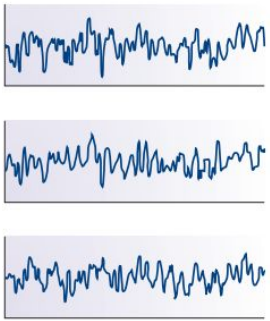

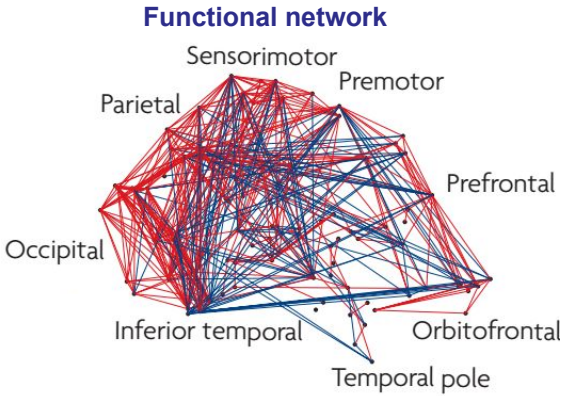

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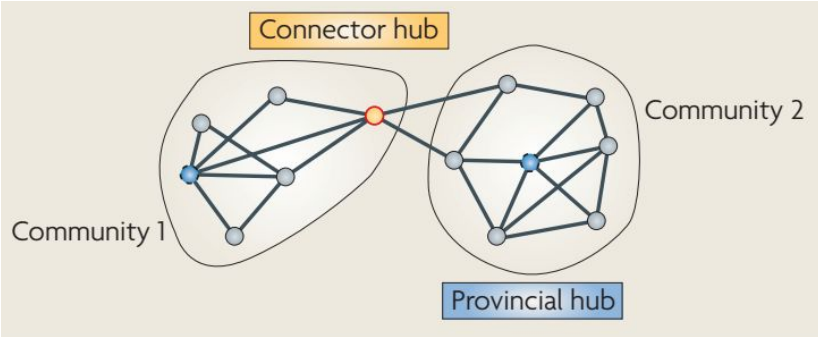

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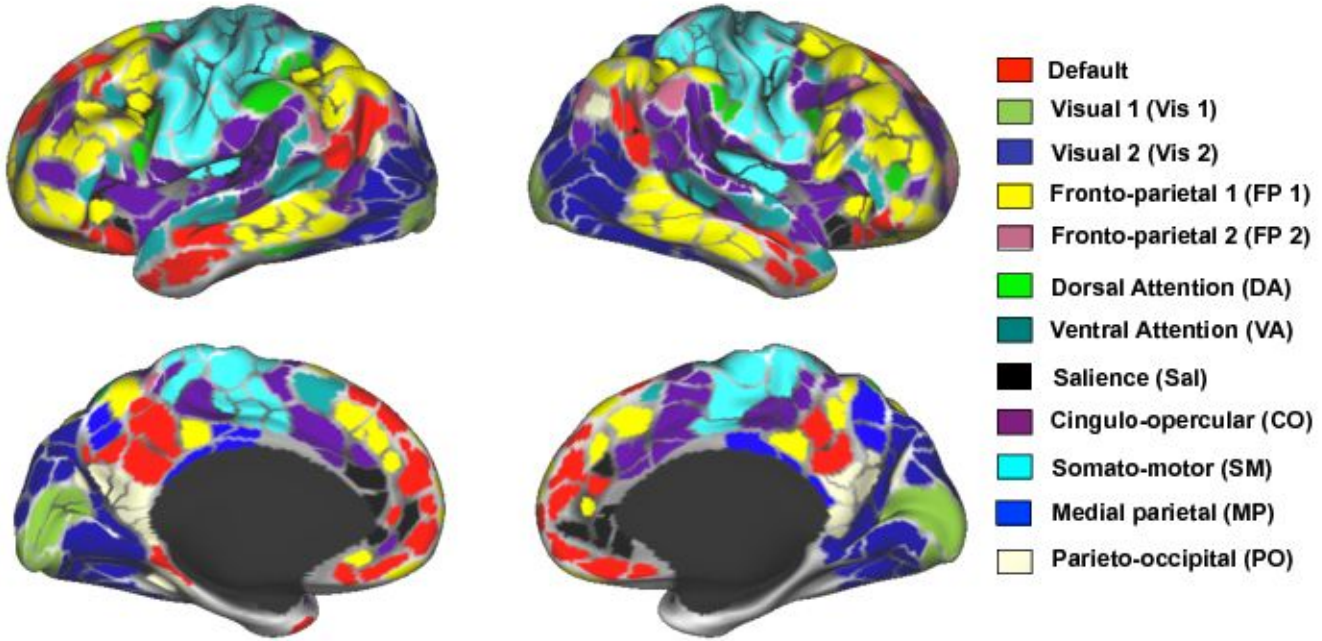
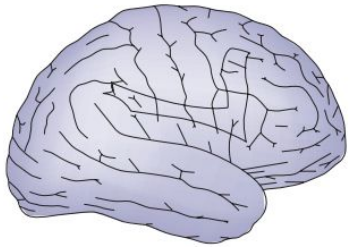
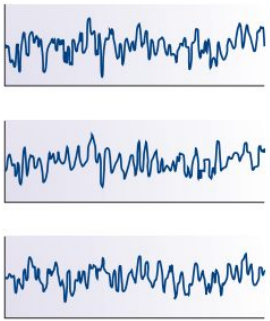
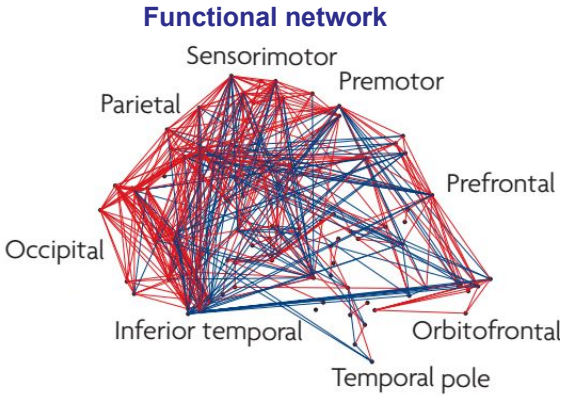


Laumann et al. Neuron. 2015

What is the functional network organization of the mouse brain?







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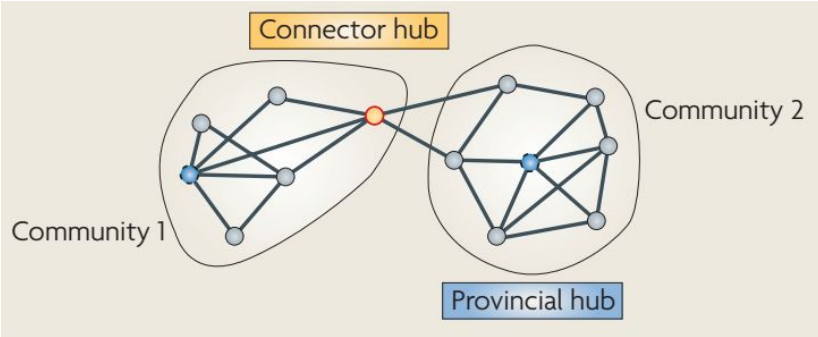

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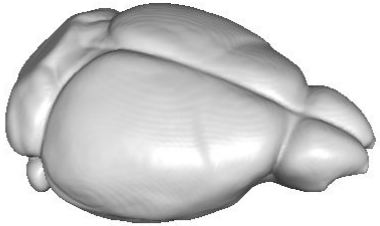

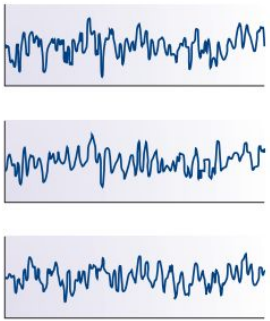

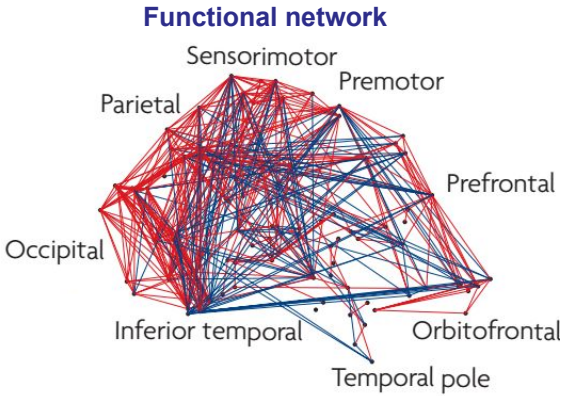

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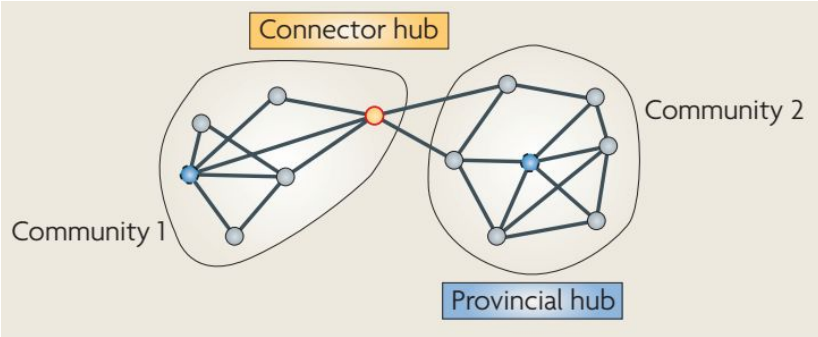

Methods

Image acquisition

- **Adult male C57Bl6/J mice** (N = 41)
- Ventilated under **halothane anaesthesia** at 0.75% maintenance
- 7T MRI scanner using a single-shot EPI sequence:
  - TR/TE 1200/15ms, flip angle 30º, matrix 100×100, FOV 2×2 cm^2,
  - 24 coronal slices, 0.50 mm thickness
  - 300 volumes, total time 6 min
- Preprocessing: motion correction, nuisance signal regression, band-pass filtering

Functional analyses

- Nodes and edges: **voxels and 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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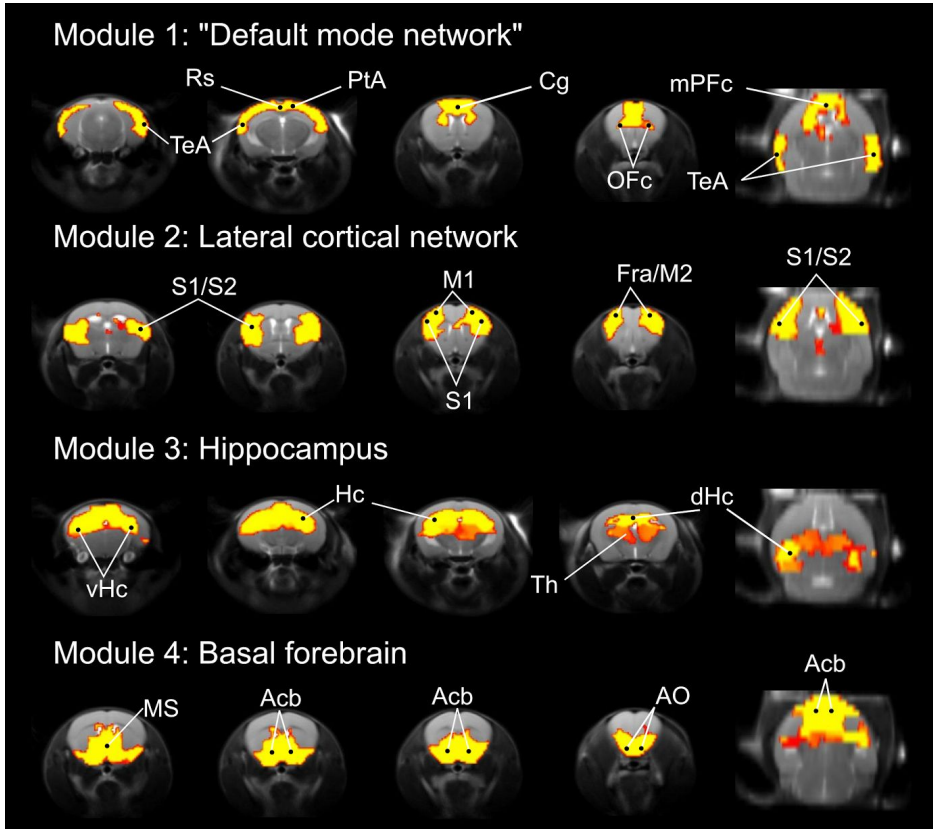
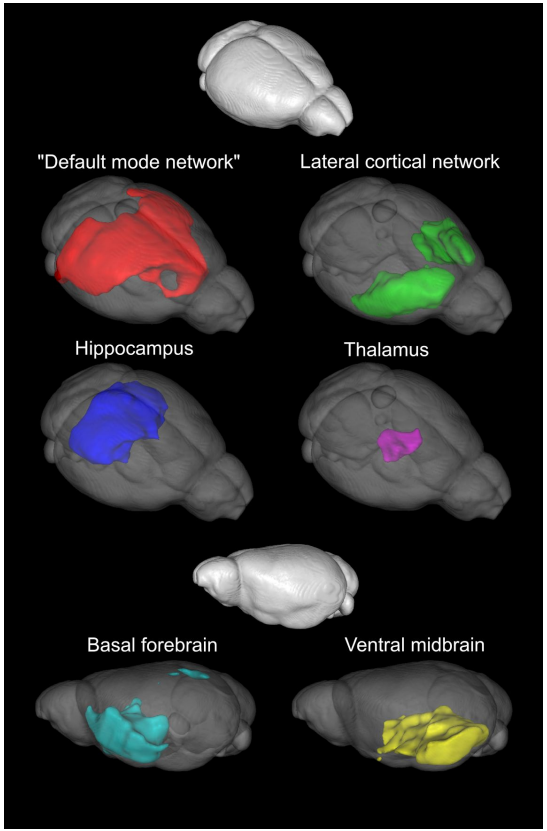
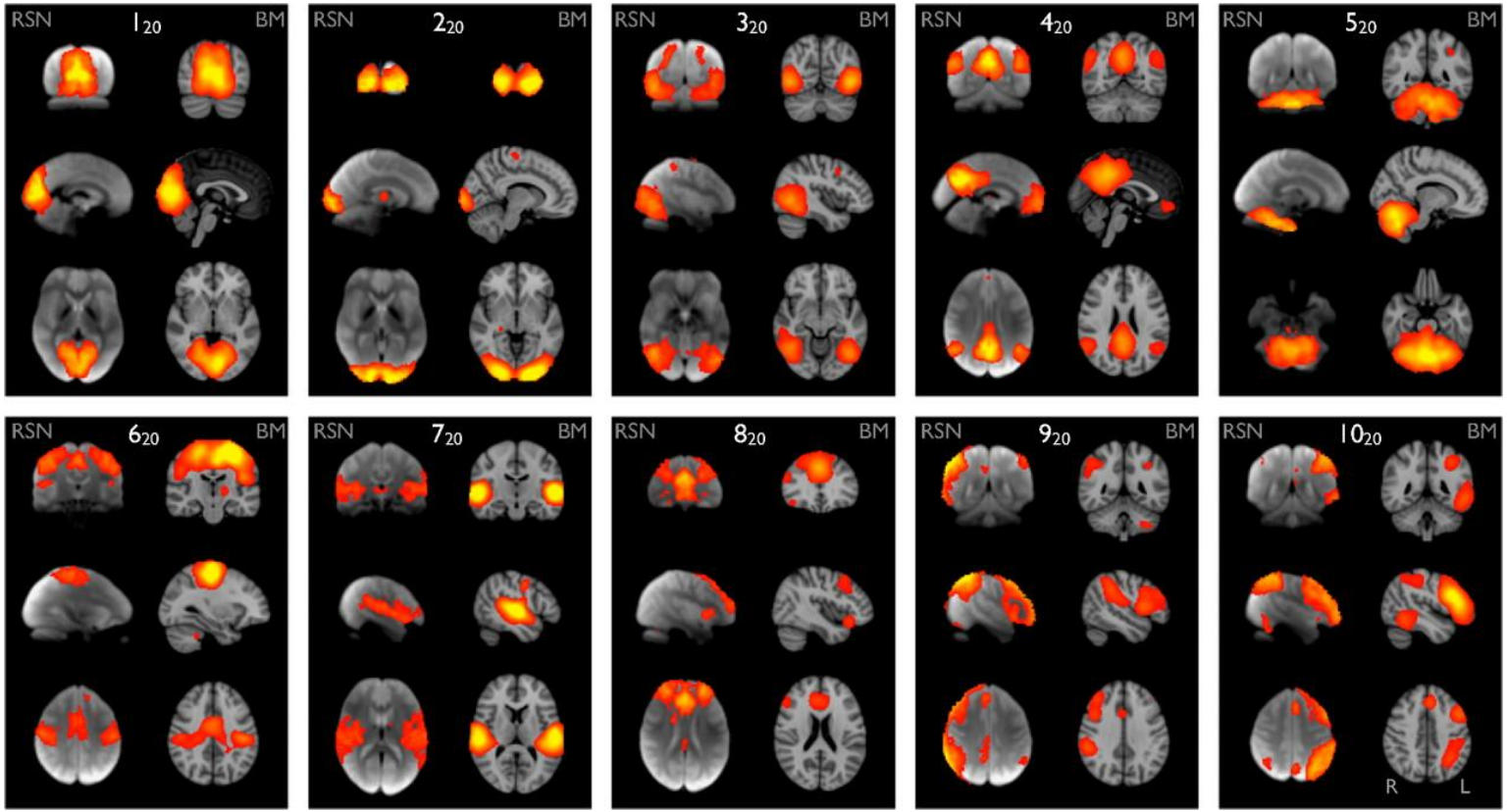




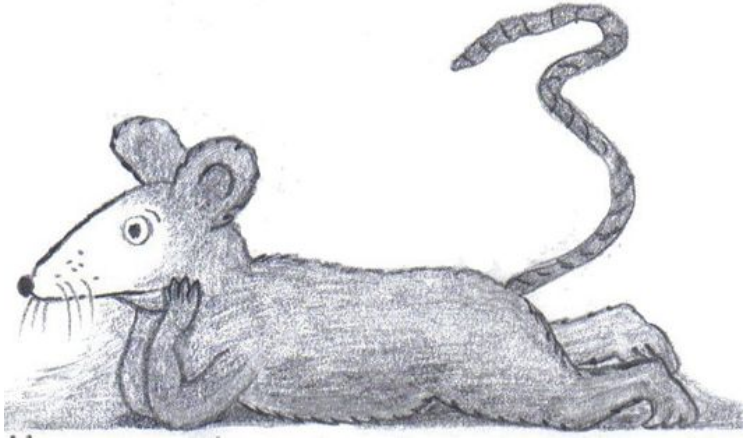
Liska et al. NeuroImage. 2015

Correspondence of the brain's functional architecture during activation and rest



Smith et al. Proc Natl Acad Sci. 2009

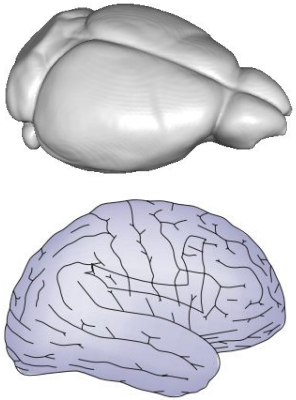
Functional homology between mouse and human brain modules?

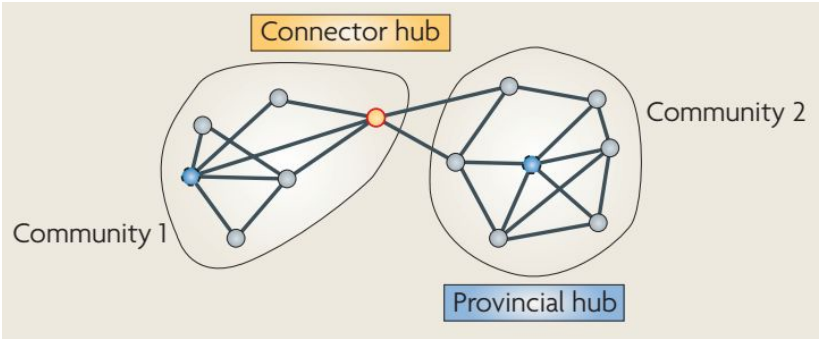


For example, is the mouse DMN deactivated by high-demand cognitive tasks?

We don’t know, yet.

Shared topological properties of mouse and human brain functional networks

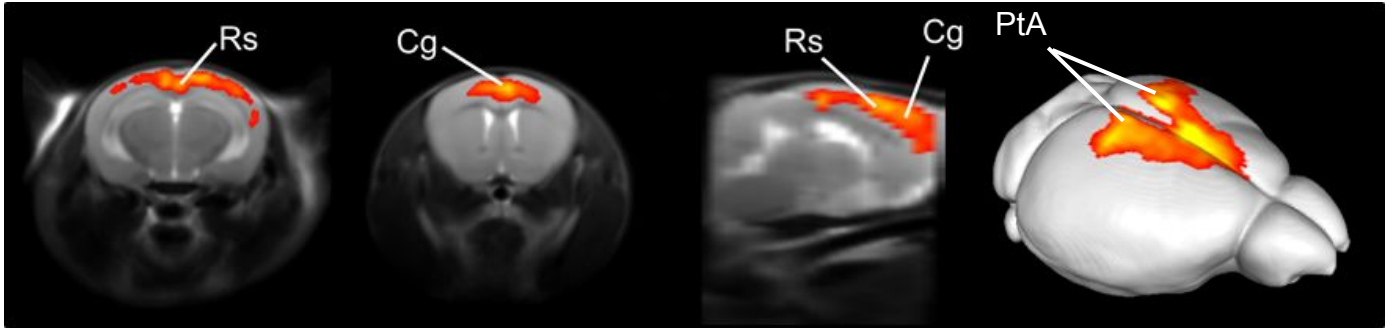




Adapted from Bullmore & Sporns
Nat. Rev. Neurosci. 2009

High connection strength hubs are located within the DMN

Mouse



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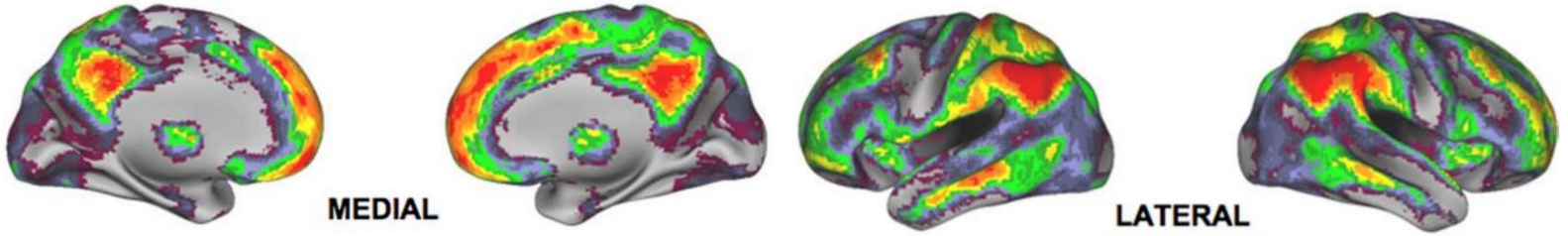
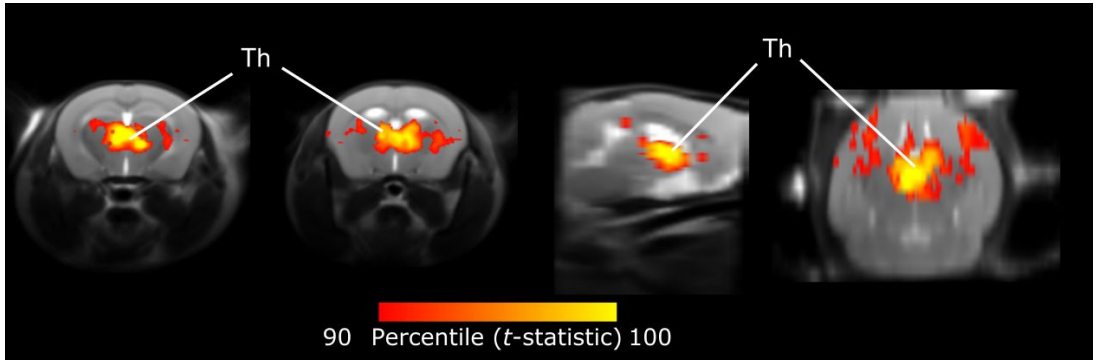


Buckner et al. J Neurosci. 2009

High connection diversity hubs within the thalamus

Mouse



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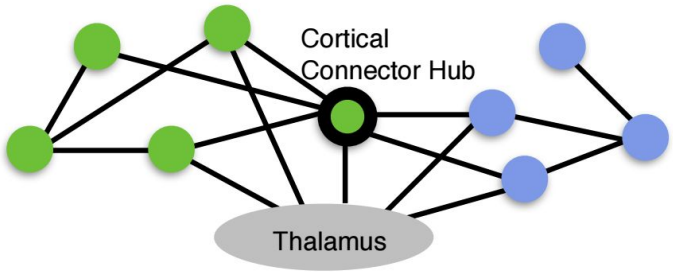
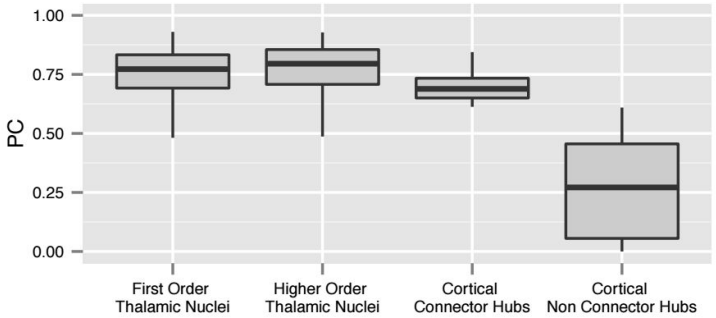
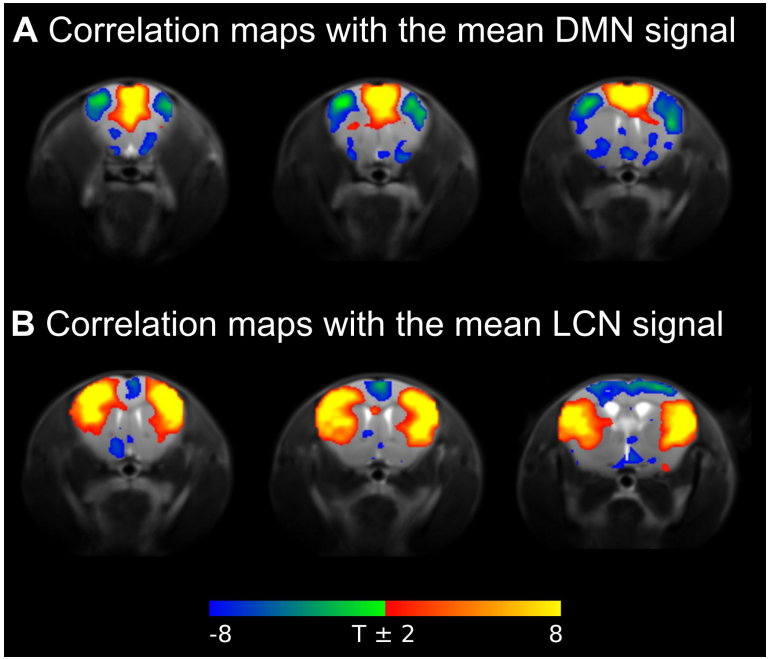




Hwang et al. bioRxiv. 2016

Presence of negatively correlated networks

Mouse



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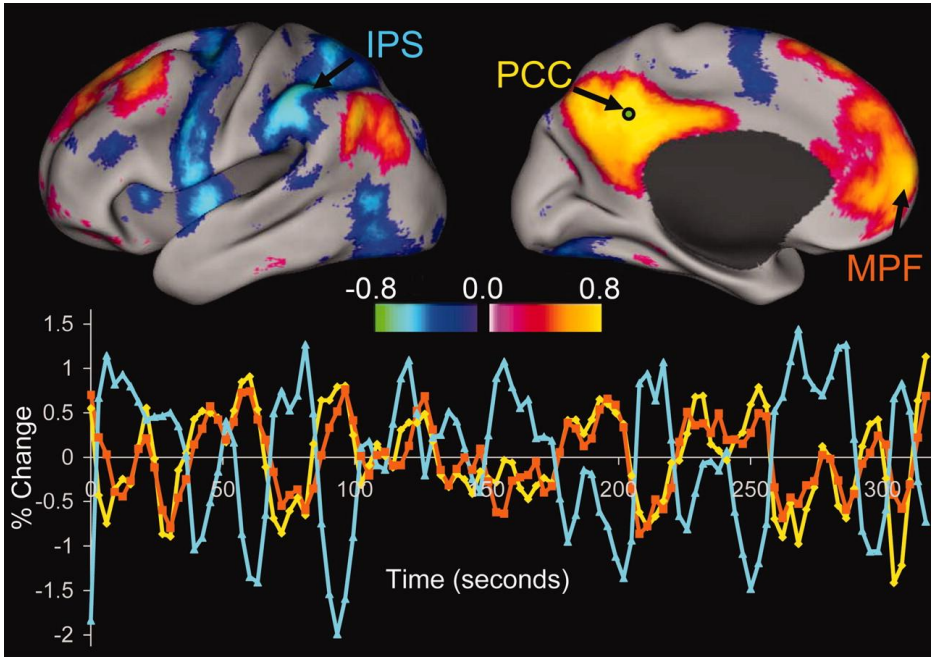

Fox et al. Proc Natl Acad Sci. 2005

Functional networks in the mouse brain

Evidence of distributed and homotopic resting-state functional networks in the mouse brain

High connection strength hubs are located within the DMN regions, while high connection diversity hubs are located within the thalamic nuclei

Network-based analyses showed correspondences between the mouse and human brain functional networks

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Special Issue: The Connectome

Fledgling pathoconnectomics of psychiatric disorders

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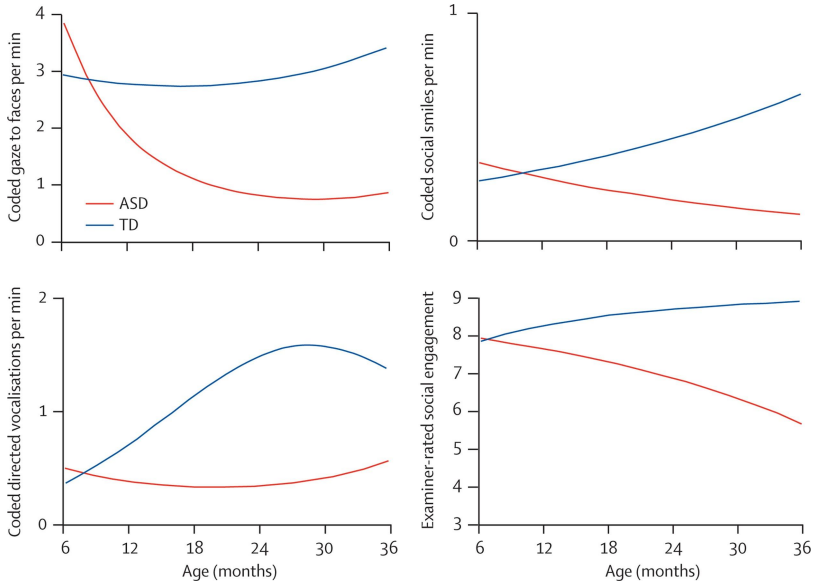
Autism Spectrum Disorders (ASD)

A set of heterogeneous neurodevelopmental conditions with:

- deficits in social communication and interaction,
- repetitive behaviours and restricted interests.

Highly heritable, yet of remarkable genetic heterogeneity.

Trajectories for social communication behaviours in children with ASD



Constantino & Charman. Lancet. 2016

Functional connectivity studies in ASD

Hypoconnectivity

Horowitz et al. 1988, Just et al. 2004, Cherkassky et al. 2010,

Hyperconnectivity

Supekar et al. 2013, Mizuno et al. 2006

Both hypo- and hyperconnectivity

Di Martino et al. 2014, Keown et al. 2013

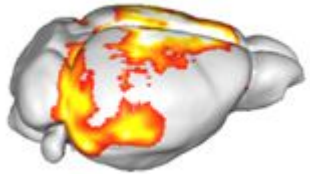
Greater inter-subject variability or intra-subjects dynamics

Hahamy et al. 2015, Falahpour et al 2016

Potential of animal models in brain imaging

Liska and Gozzi. Front Neurosci. 2016

Mouse Neural Systems



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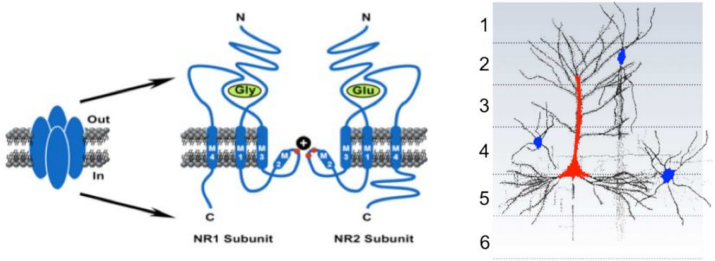

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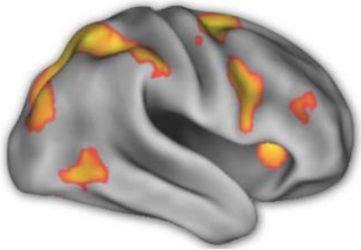

Potential of animal models in brain imaging

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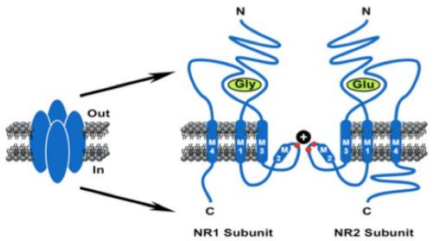
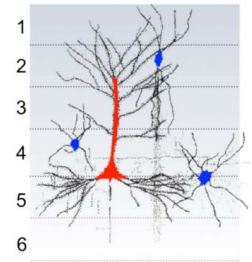
Disease mutations

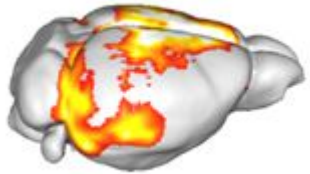
Mutant models

Cellular biology/Physiology



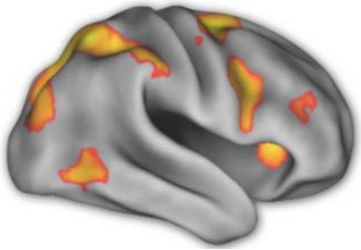


Mouse Neural Systems



Explanatory gap

Neural Systems



Autism risk gene CNTNAP2

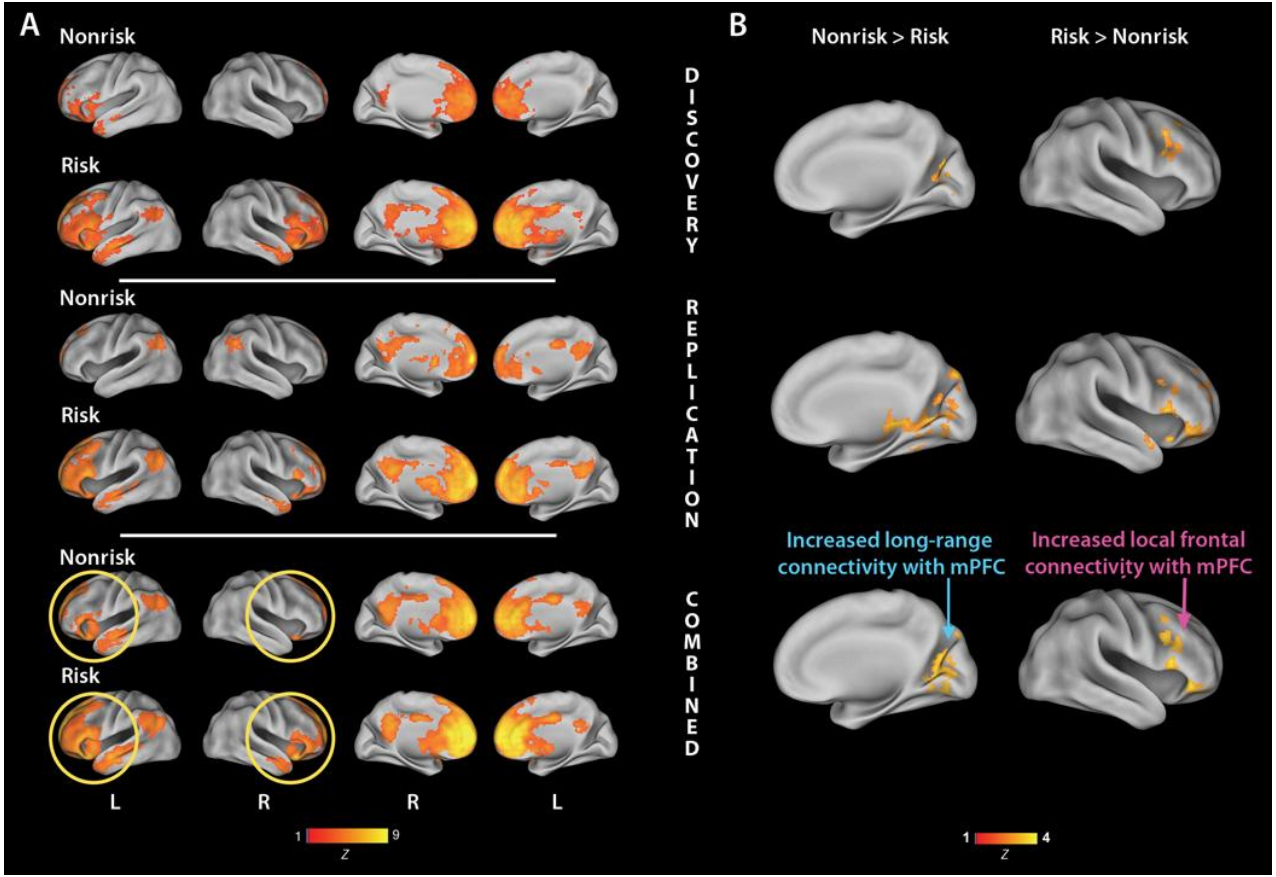
Contactin Associated Protein-Like 2, a neurexin-family member

A recessive mutation in CNTNAP2 causes *cortical dysplasia–focal epilepsy* (CDFE) syndrome

Variants in CNTNAP2 are associated with ASD-related endophenotypes, such as language disorders

Frontal lobe connectivity associated with common genetic variants in CNTNAP2

Functional connectivity with the mPFC associated with CNTNAP2



Scott-Van Zeeland et al.
Sci. Transl. Med. 2010

Cntnap2 knockout mouse model

Cell

Absence of CNTNAP2 Leads to Epilepsy, Neuronal Migration Abnormalities, and Core Autism-Related Deficits

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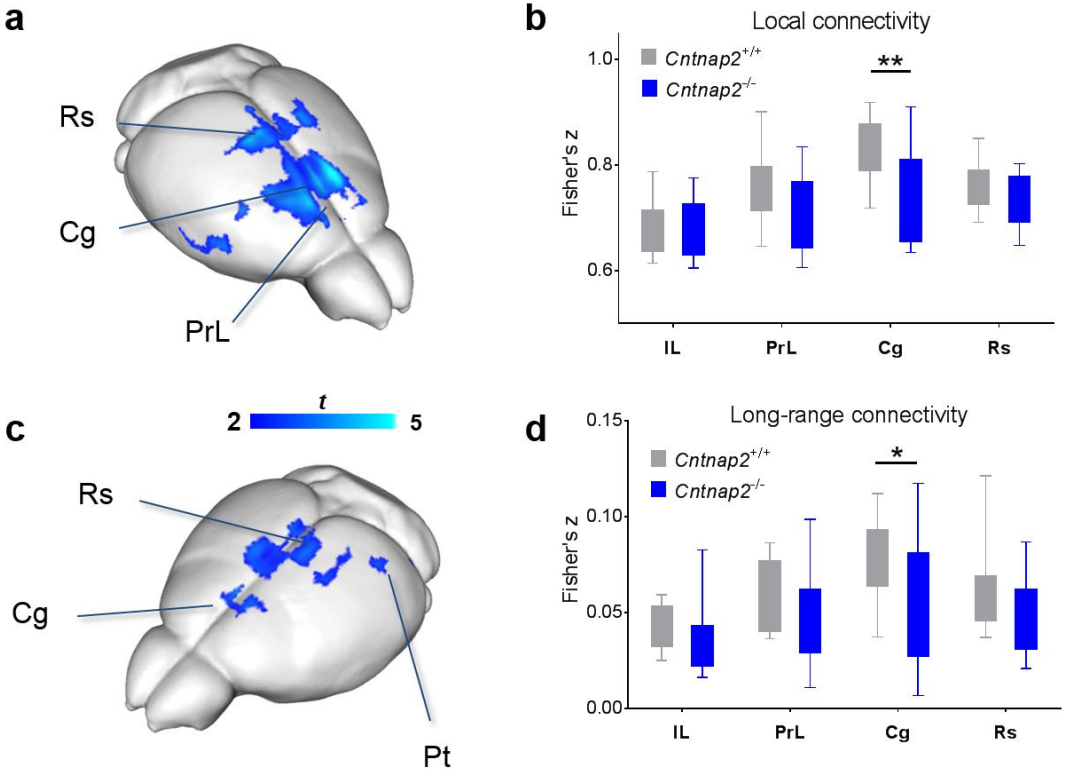
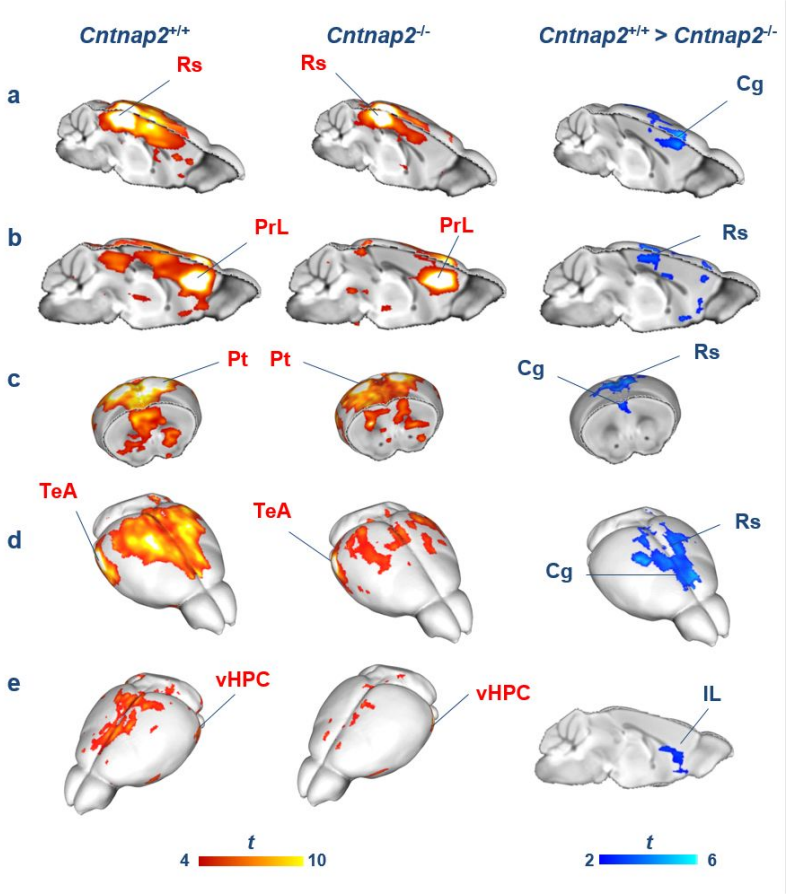
Reduced local and long-range connectivity in *Cntnap2*$^{-/-}$ mutants



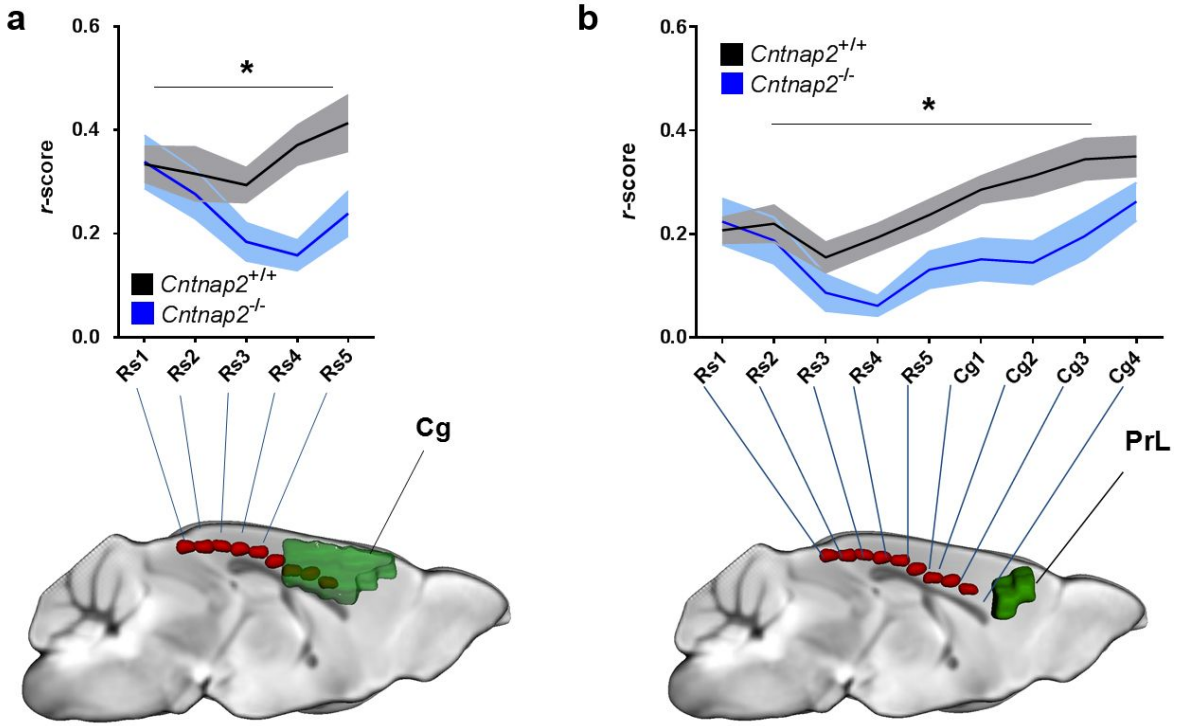
Liska et al. Cereb Cortex. 2017

Altered connectivity networks in *Cntnap2*$^{-/-}$ mutants



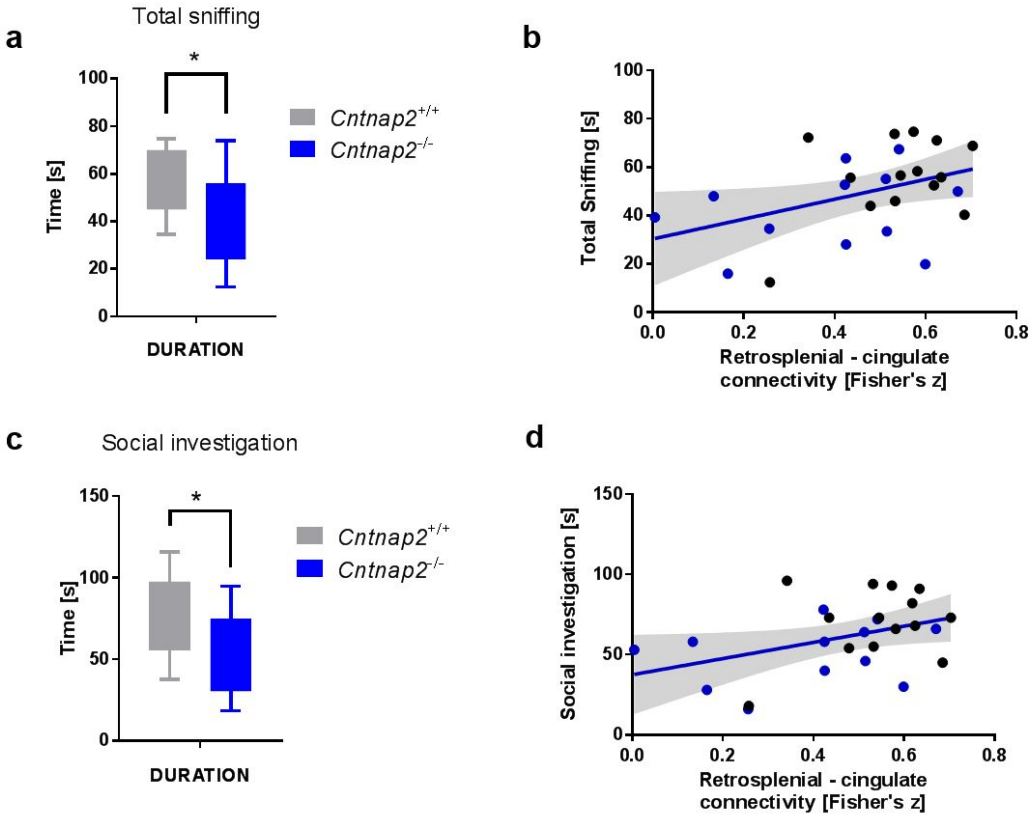
Liska et al. Cereb Cortex. 2017

Reduced fronto-posterior connectivity in *Cntnap2*$^{-/-}$ mutants



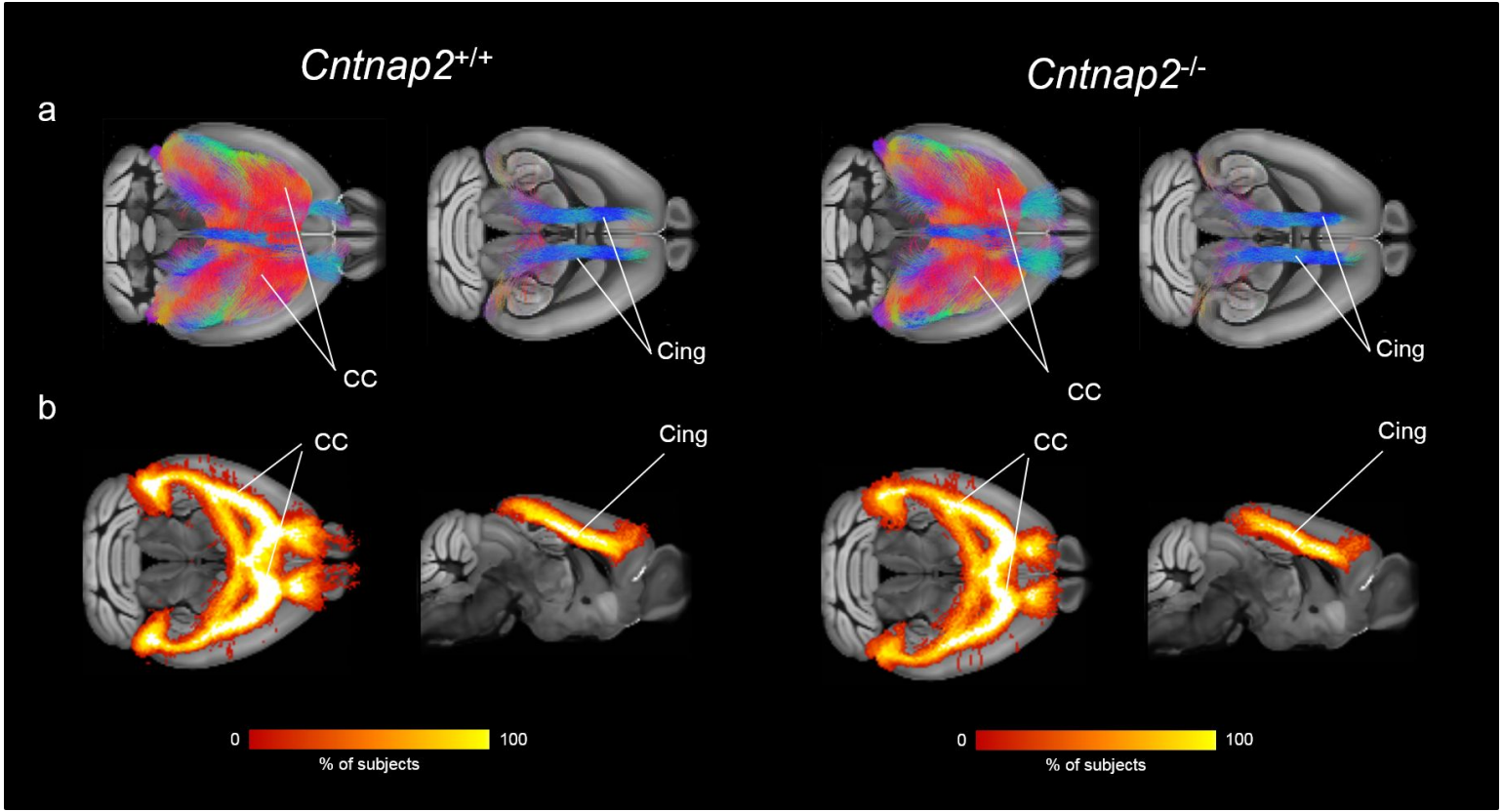
Liska et al. Cereb Cortex. 2017

Fronto-posterior connectivity associated with social behaviour



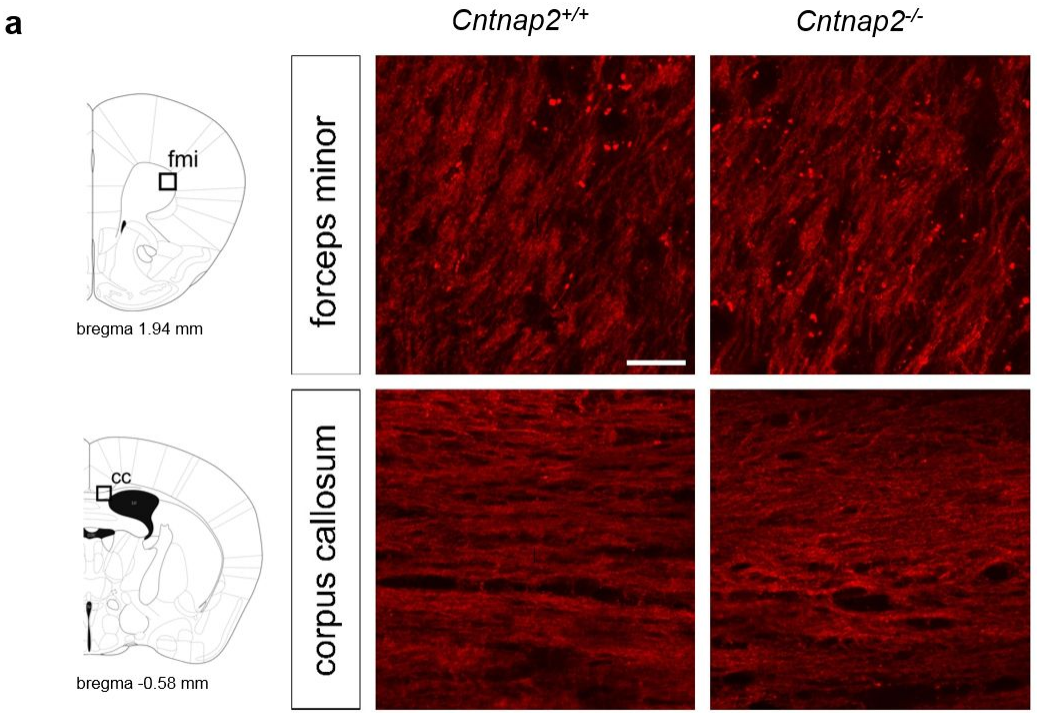
Liska et al. Cereb Cortex. 2017

Preserved white-matter organization in *Cntnap2*$^{-/-}$ mutants



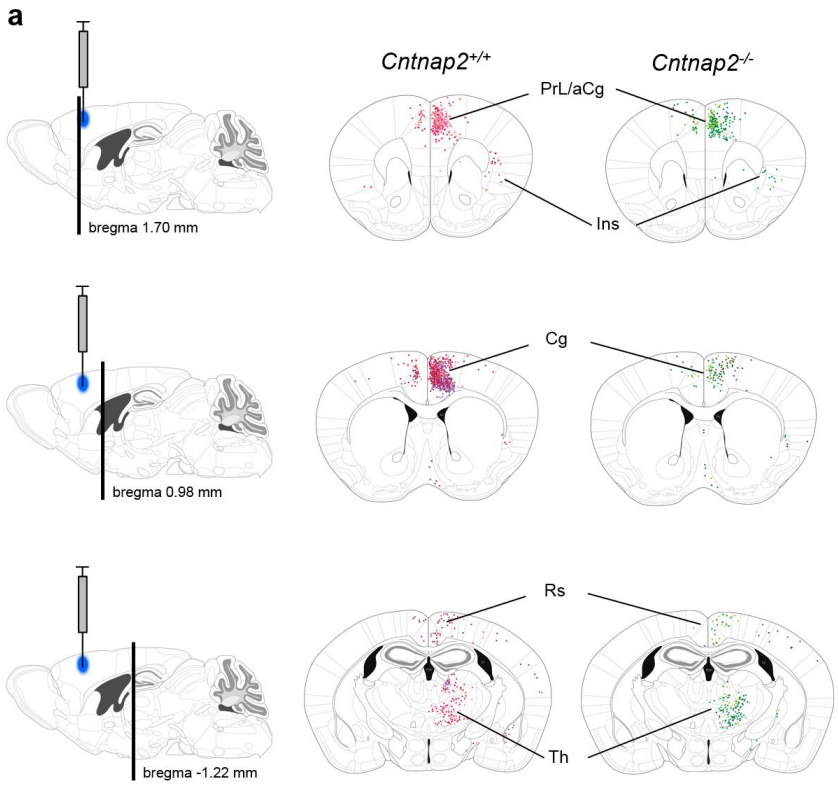
Liska et al. Cereb Cortex. 2017

Preserved white-matter organization in *Cntnap2*$^{-/-}$ mutants



Liska et al. Cereb Cortex. 2017

Reduced frequency of prefrontal-projecting neurons



Liska et al. Cereb Cortex. 2017

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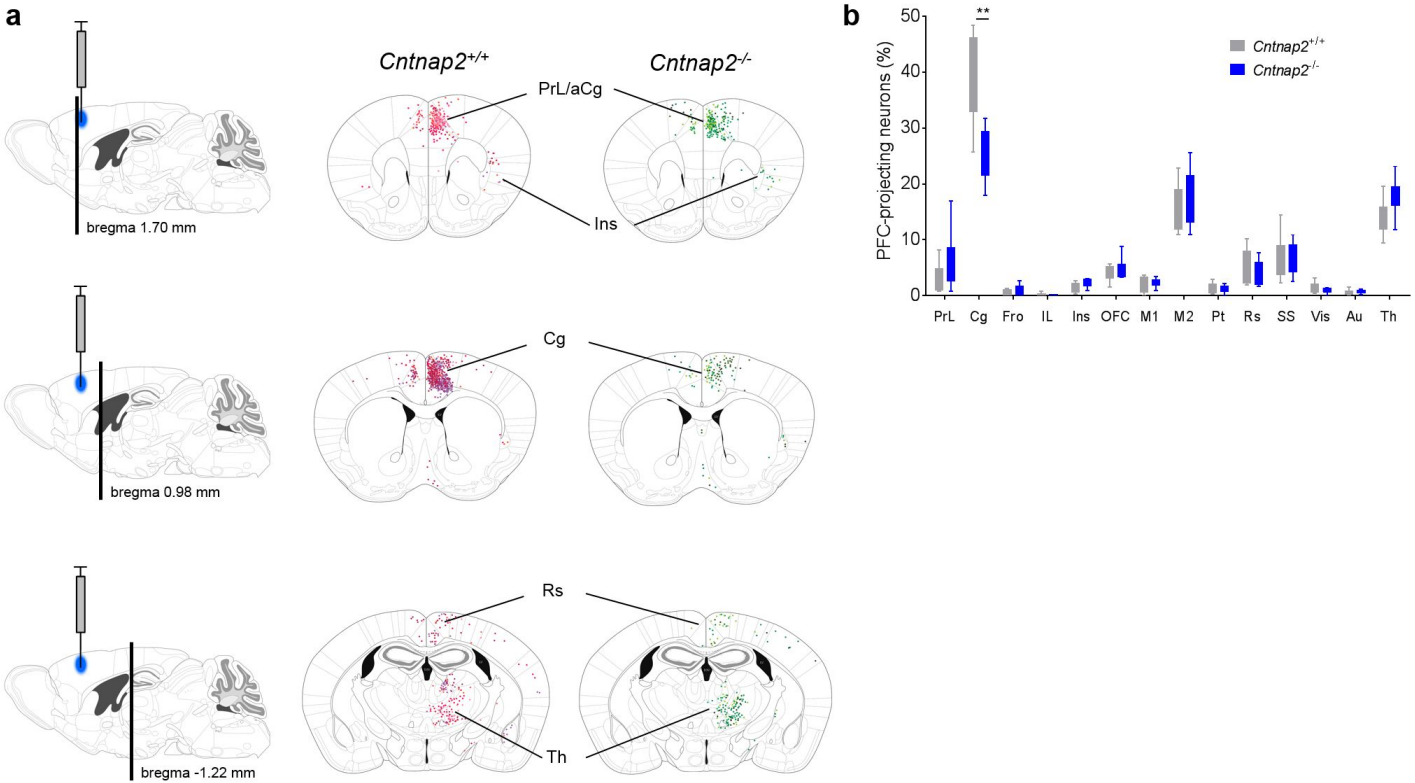

Liska et al. Cereb Cortex. 2017

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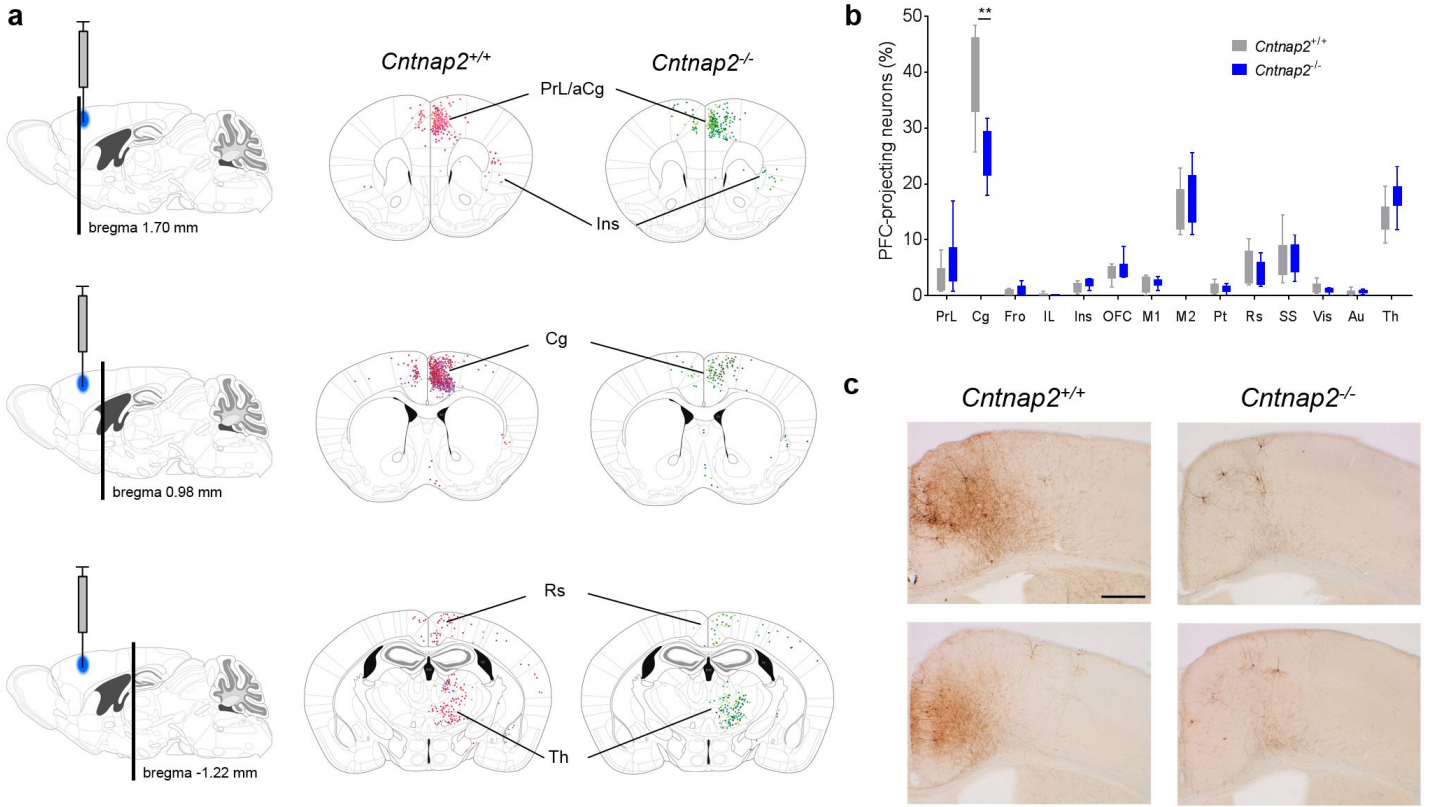

Liska et al. Cereb Cortex. 2017

Summary

The absence of Cntnap2 leads to reductions in functional connectivity and defective mesoscale wiring in prefrontal functional hubs of the mouse brain

This effect is associated with reduced social behaviour.

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