Networks of spontaneous brain activity in the rodent brain

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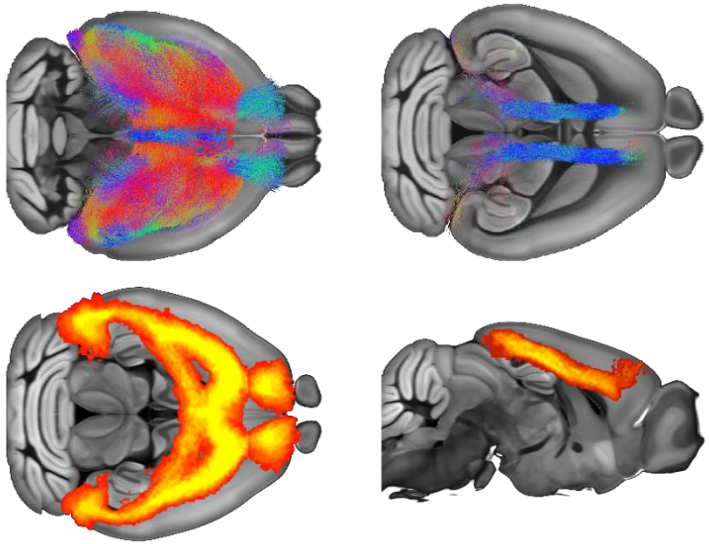

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The Functional Neuroimaging lab
IIT@CNCS - Rovereto

Bruker Pharmascan MRI scanner

- ***7 Tesla superconductive magnet***
- ***16 cm bore, 72 mm clear access***
- ***4 RF channels for parallel imaging***

➢Species → Rats & Mice

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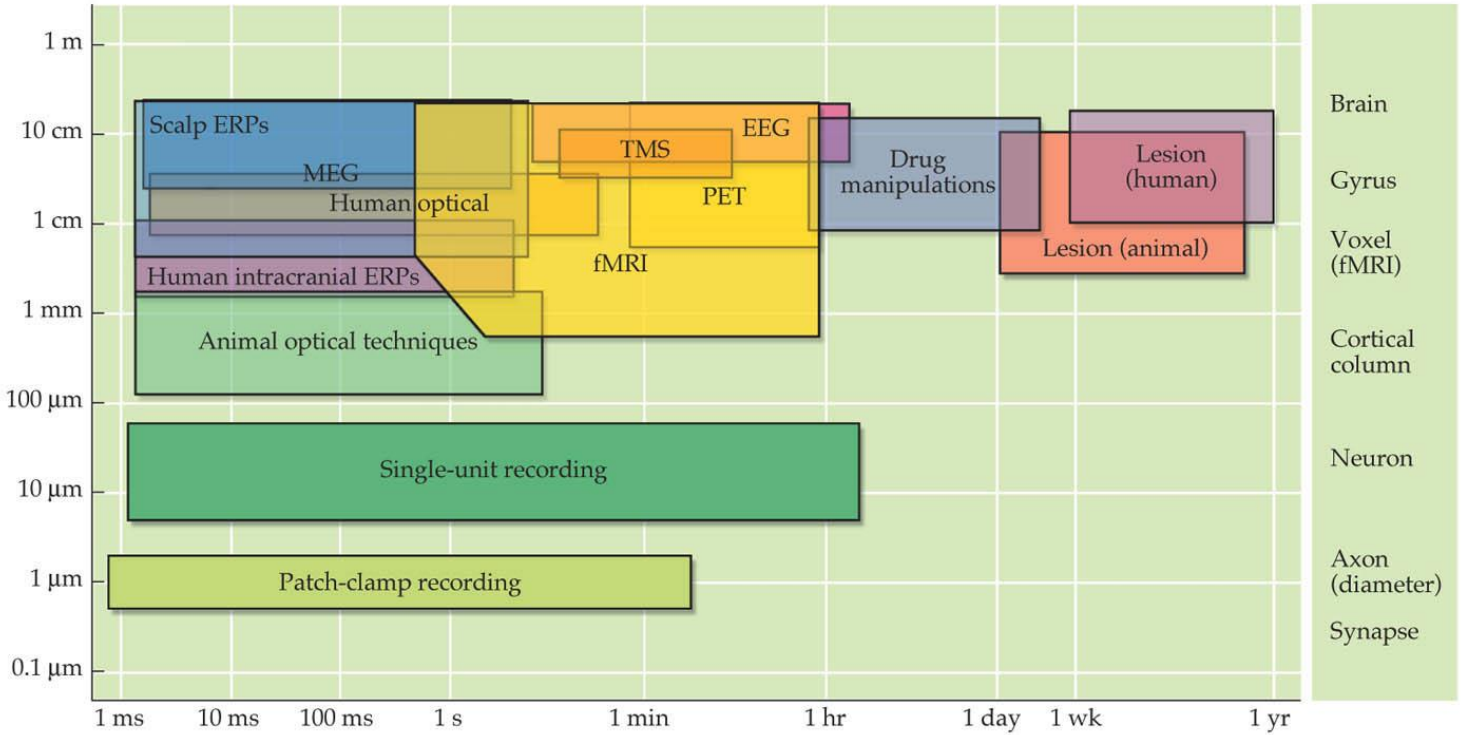
Presentation outline

1. Refresher on fMRI
2. Mapping spontaneous brain activity with resting-state fMRI
3. rsfMRI networks in the rodent brain
4. Mapping the connectional landscape in autism

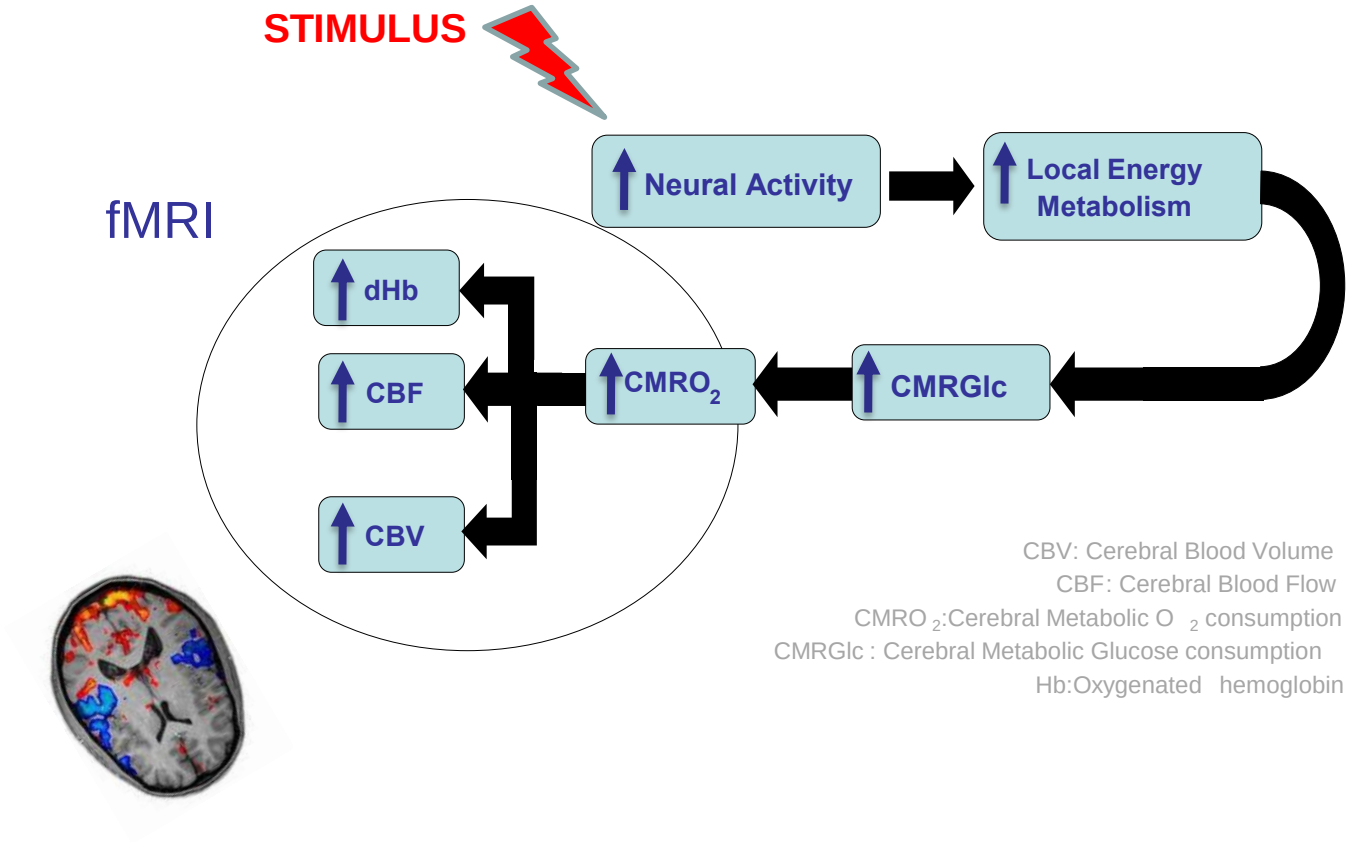
Neuroimaging methods: spatio-temporal resolution



fMRI measures hemodynamic correlates of evoked (and spontaneous) neuronal activity

- Uses a standard MRI scanner
- Acquires a series of images
- Measures changes in blood oxygenation and flow
- Use non-invasive, non-ionizing radiation
- Can be repeated many times; can be used for a wide range of subjects
- Combines good spatial (< 1 mm) and reasonable temporal resolution (ca. 1 s)

Synospys of fMRI



CBV: Cerebral Blood Volume
CBF: Cerebral Blood Flow
$CMRO_2$:Cerebral Metabolic O_2 consumption
CMRGlc : Cerebral Metabolic Glucose consumption
Hb:Oxygenated hemoglobin

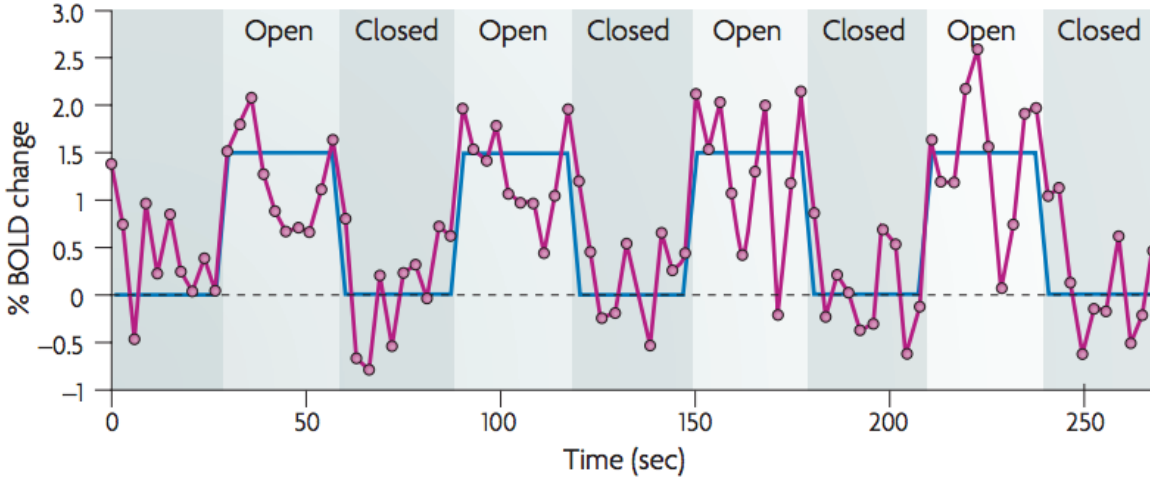
BOLD Endogenous Contrast

- Blood Oxyenation Level Dependent Contrast
  - Deoxyhemoglobin is paramagnetic
  - Magnetic susceptibility of blood increases linearly with increasing oxygenation

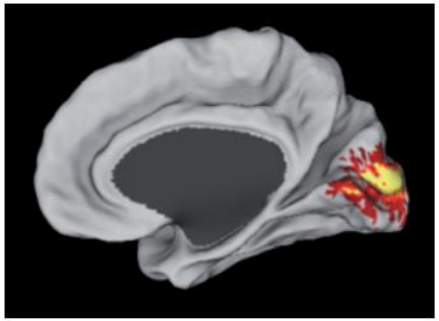
- Oxygen is extracted during passage through capillary bed
  - Brain arteries are fully oxygenated
  - Venous (and capillary) blood has increased proportion of deoxyhemoglobin
  - Difference between oxy and deoxy states is greater for veins → BOLD sensitive to venous changes

Task-related activation paradigm

- changes in BOLD signal attributed to experimental paradigm
- brain function mapped onto brain regions



Open – Closed =



Fox et al., 2007

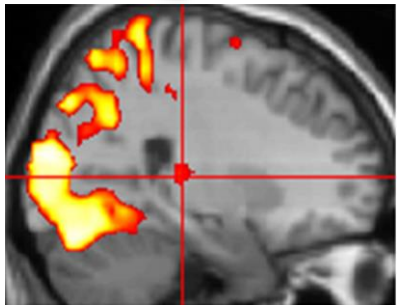
Functional Segregation ⟷ Functional Integration

Specialised areas exist in the cortex

Networks of interactions among specialised areas

What is the neuroanatomical correlate of… ?

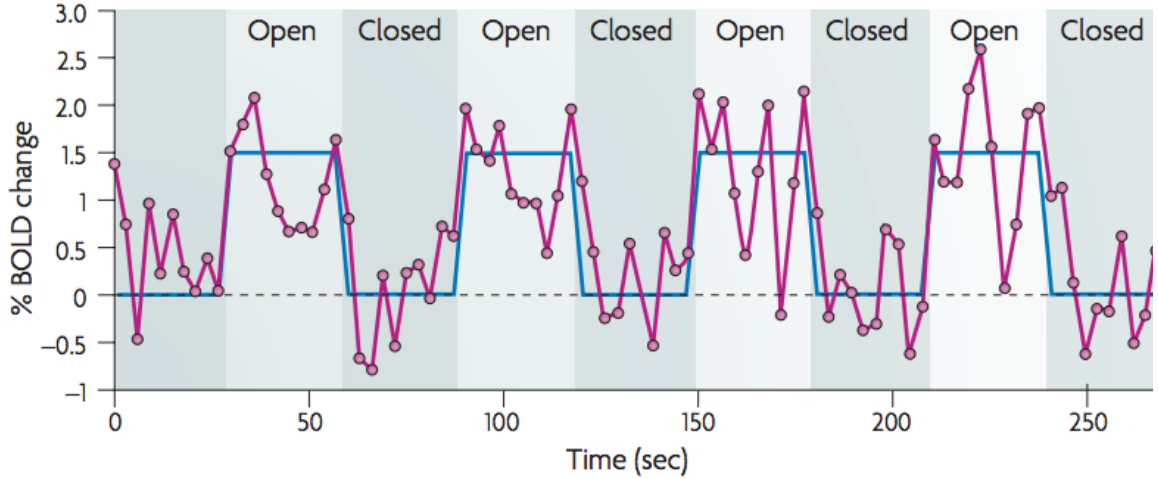
How do neural components interact … ?



Resting state

fMRI

Courtesy of Josh Kahan, UCL



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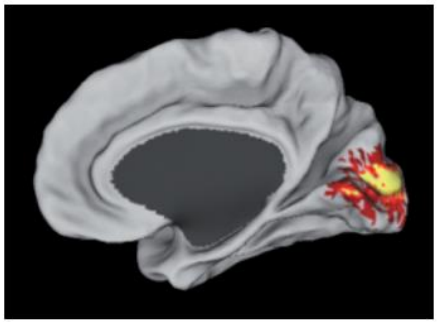
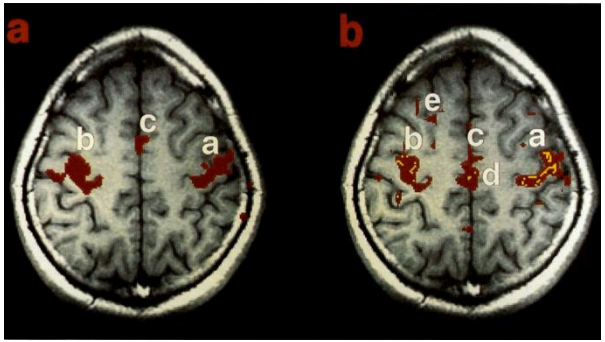


→ At best, task-related modulation explains 20% of BOLD variance

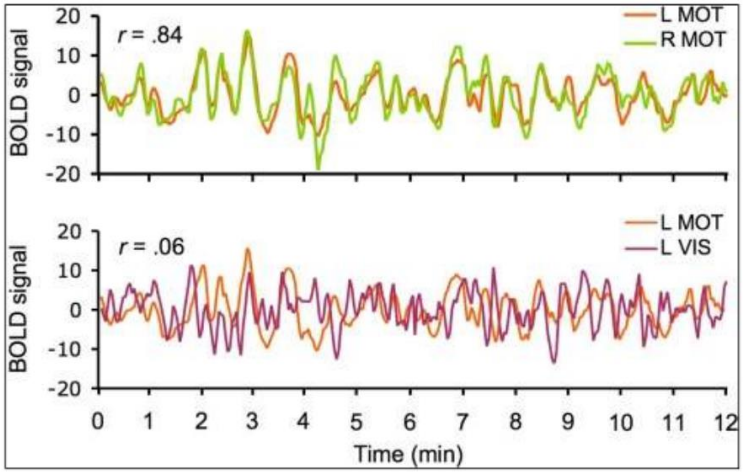
→ Spontaneous ongoing activity explains 50-80% of BOLD variance



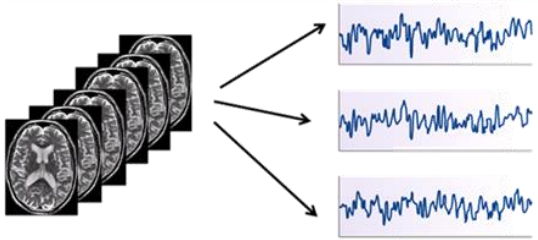
Biswal et al., 1995

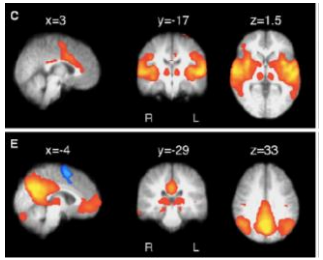
Resting-state (= spontaneous) fMRI signal is temporally correlated between functionally related regions

→ fMRI connectivity networks



Van Dijk et al., 2010

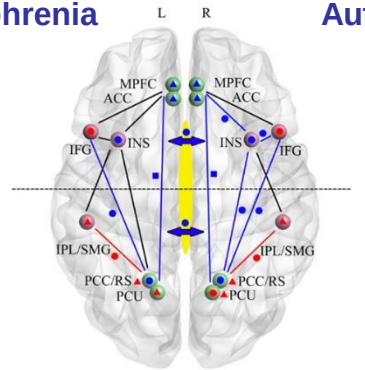




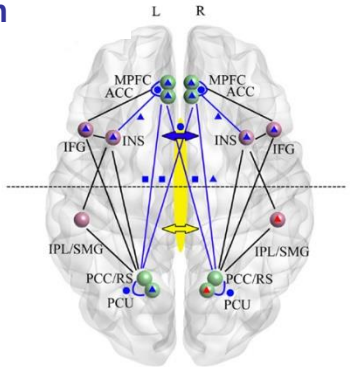
Beckmann et al., 2005, HBM

Altered intrinsic connectivity patterns typically observed in all major brain disorders!

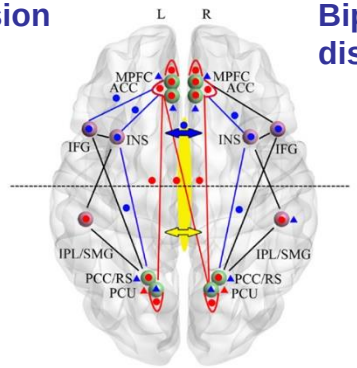
Schizophrenia



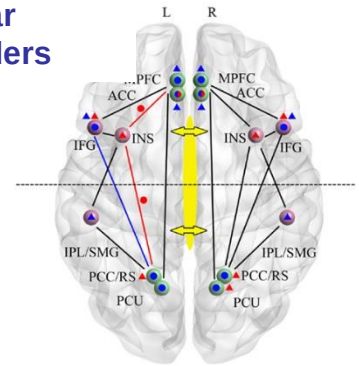
Autism



Depression



Bipolar disorders



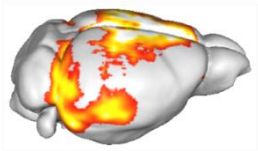
Zhao et al., 2013 Front Human Nueroscience

Open questions

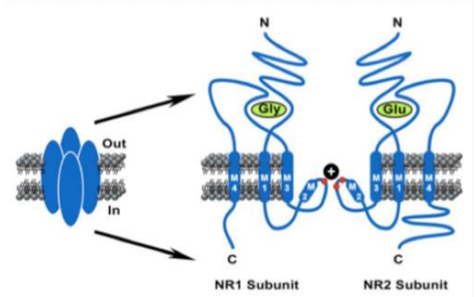
- What neural elements are necessary for the establishments of rsfMRI couplings?
- What causes rsfMRI aberrancies in human brain disorders?
- Are rsfMRI oscillations hierarchically or directionally driven by specific cortical or subcortical substrates?
- How do local brain perturbation affect topology of macroscale networks?

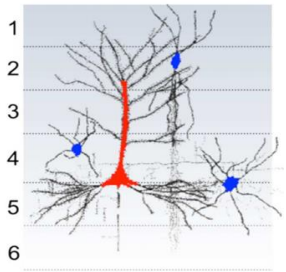
Bridging the “explanatory gap”

Mouse Neural Systems



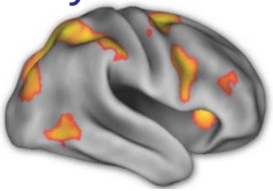
Cellular biology/Physiology





Explanatory gap

Human Neural Systems

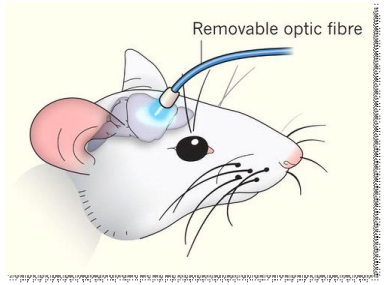


Liska and Gozzi, 2016

Talking about a revolution

Transgenic models

GENE
PROTEIN



Optogenetics
Pharmacogenetics

NEURONAL
CELL

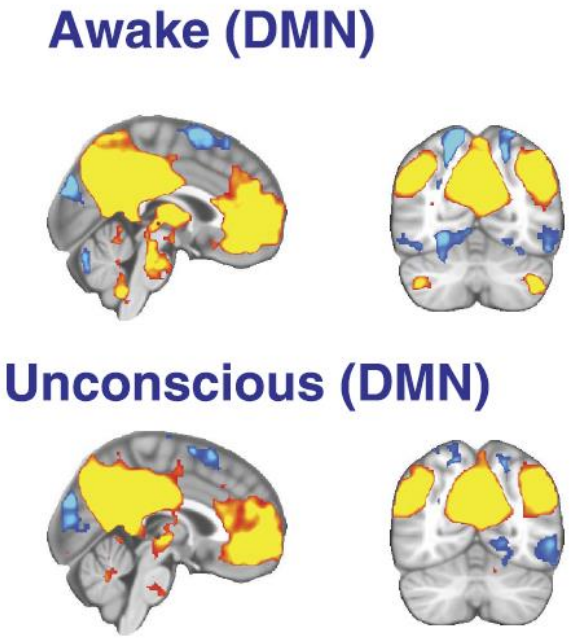
- Behaviour
- Development
- Pathology
- Physiology

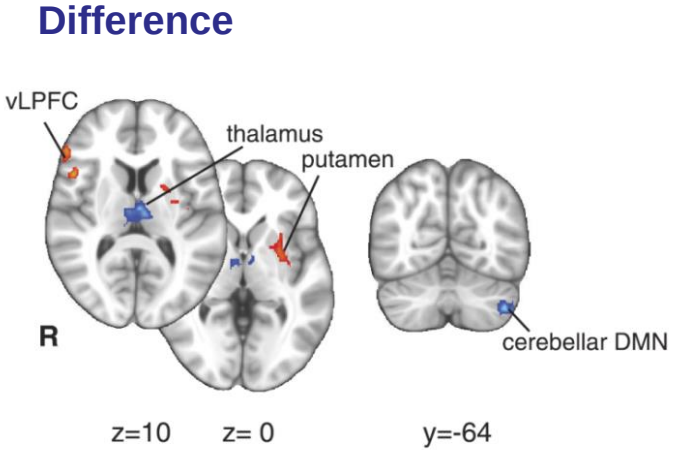
NETWORK

- Function
- Behaviour

NETWORK

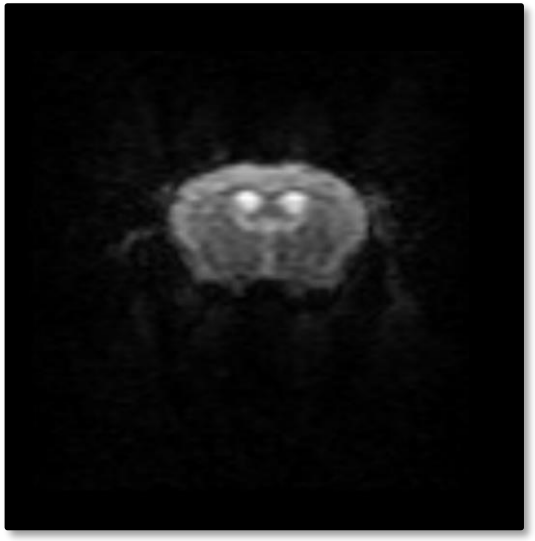
Light anesthesia preserves rsfMRI network organization

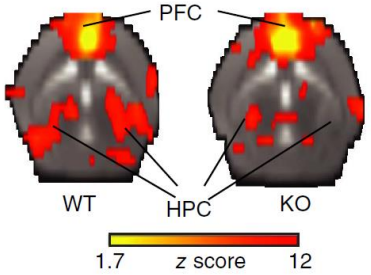


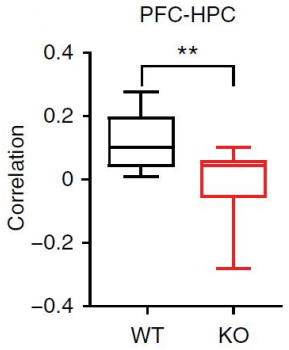


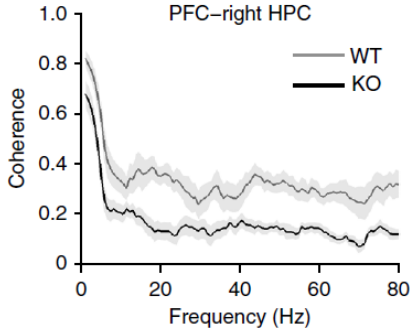
Akei et al (2015) eLIFE

Motion-free images - reliable network mapping









Zhan et al., (2014) Nature Neuroscience

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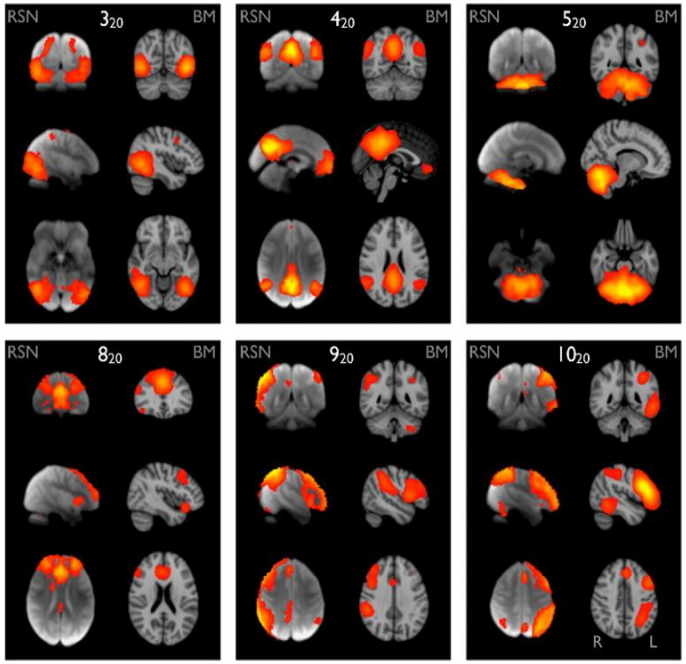
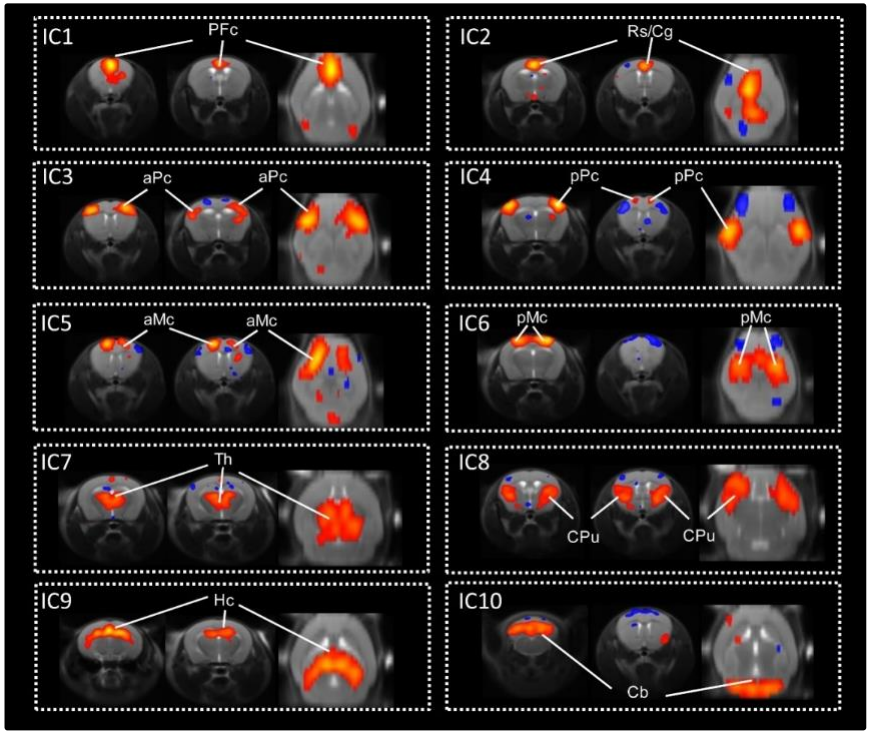
The mouse brain is organised in homotopic connectivity clusters

Human – ICA



Smith et al., 2009

Mouse – ICA



Sforazzini et.,al 2014

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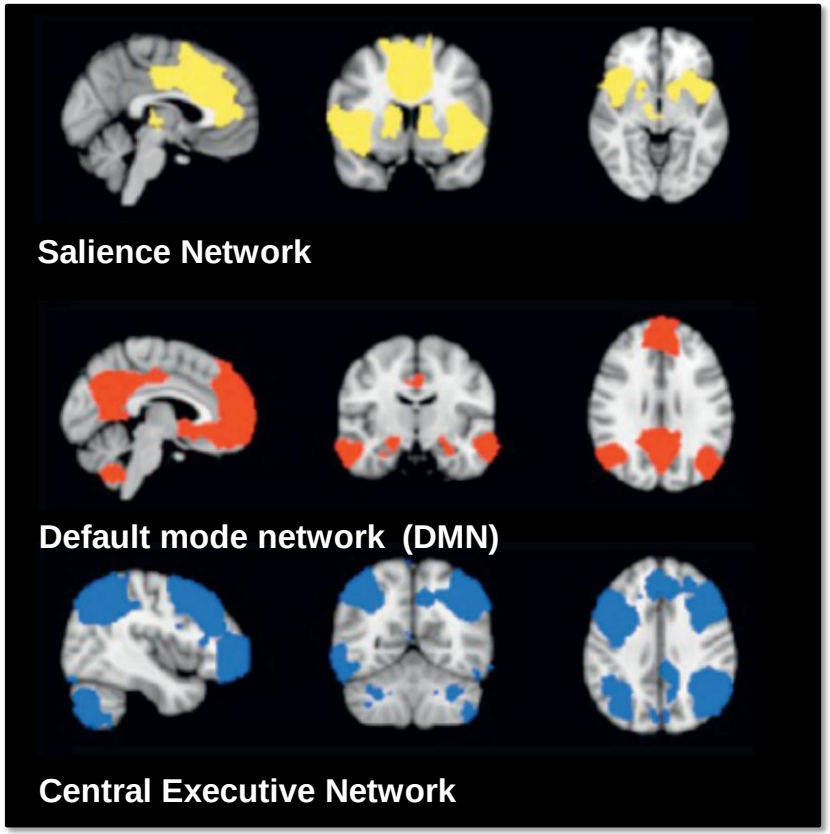
Psychiatric disorders affect large-scale networks of the brain



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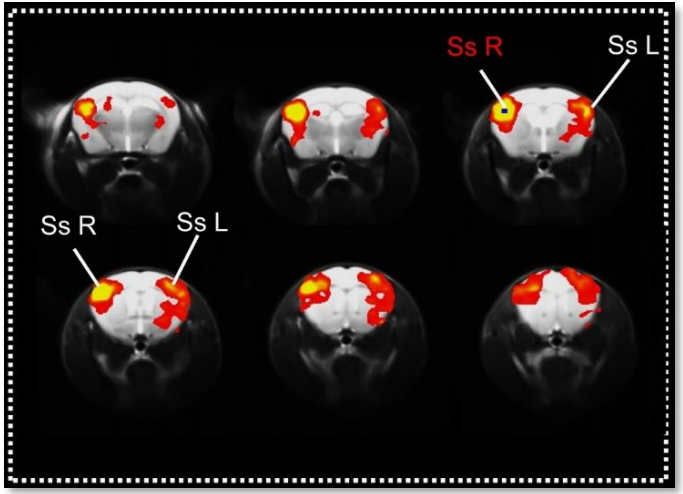
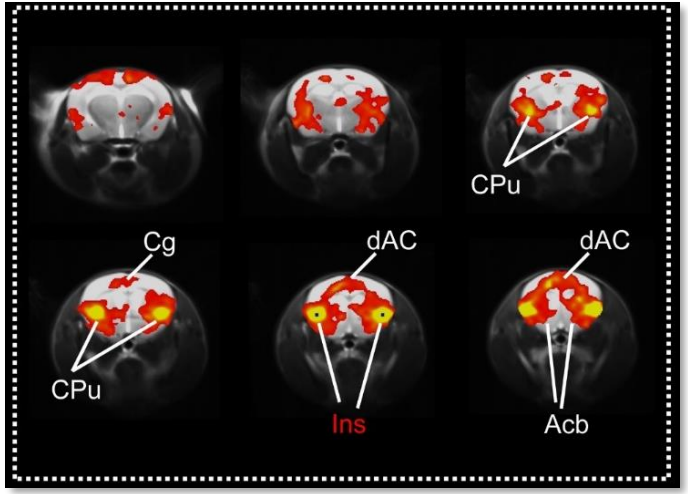
Distributed rsfMRI networks in the mouse brain

Seed in parietal cortex



Seed in insular cortex



Sforazzini et al., 2014, Neuroimage

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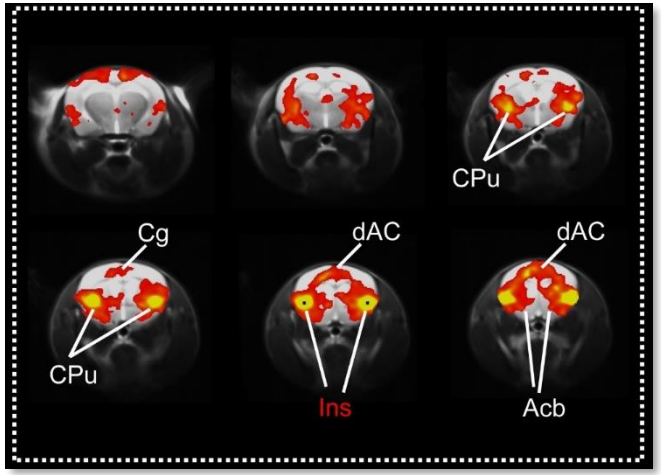
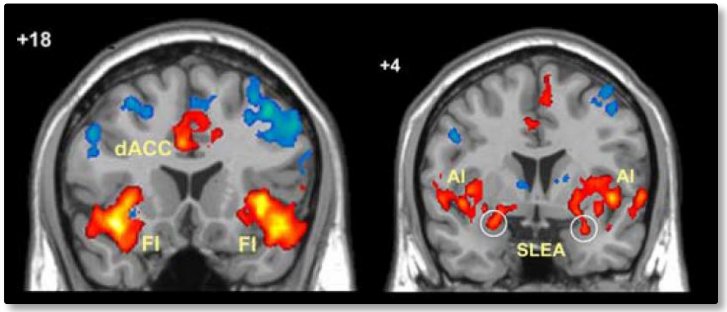
A mouse homologue of the human salience network?

Mouse



Sforazzini et al., 2014 Neuroimage

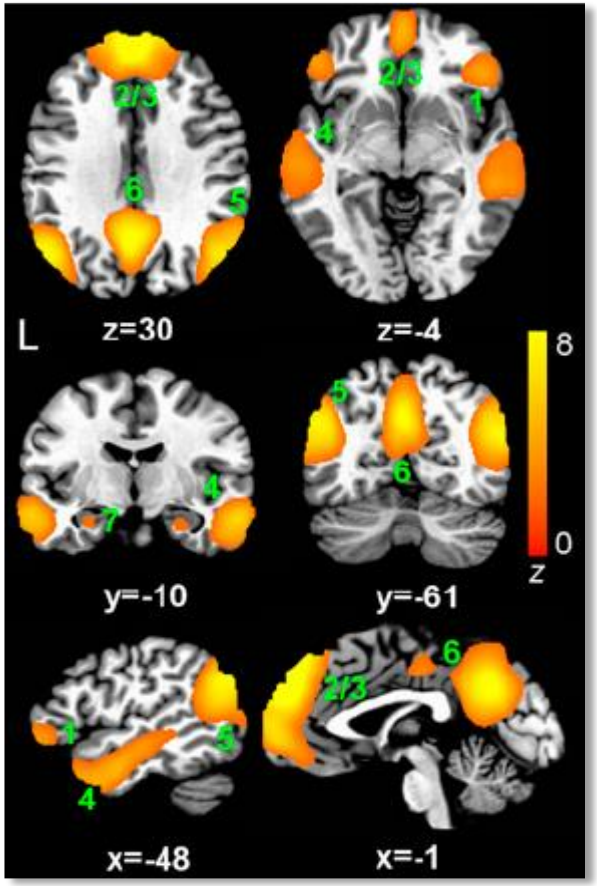
Human



Seeley et al., 2007 J. Nsci.

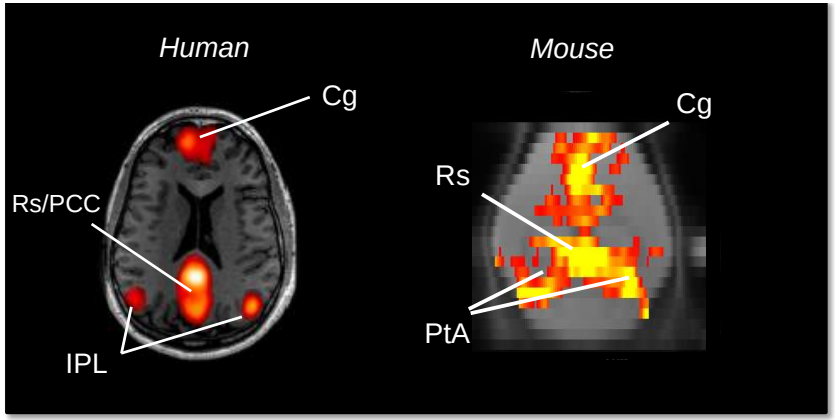
What about the Default Mode Network (DMN)?

- Exhibits strong correlations in the absence of an explicit task
- Deactivates when brain switches from “rest” to an active cognitive task
- Involved self-referential functions considered to be unique to humans
- Recently identified in non human primates
- Transcends levels of consciousness (mapped in sleep/light anaesthesia)
- Substrate of connectivity alterations in psychopatology

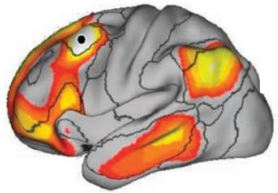


Beckmann et al., 2005 Philos Trans B

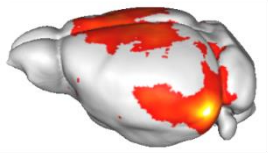
The mouse brain has a “default mode network”



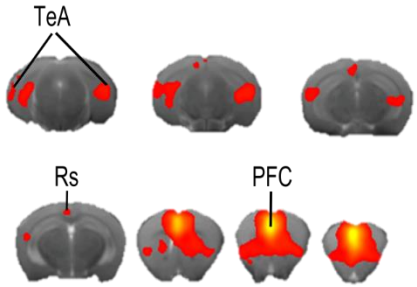
Gozzi & Schwarz, 2016



Human



Mouse



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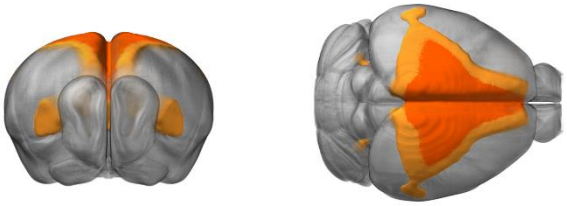
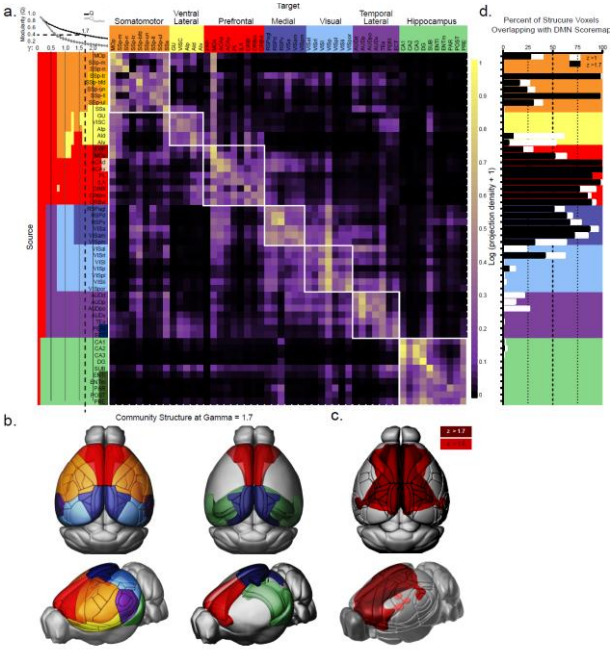
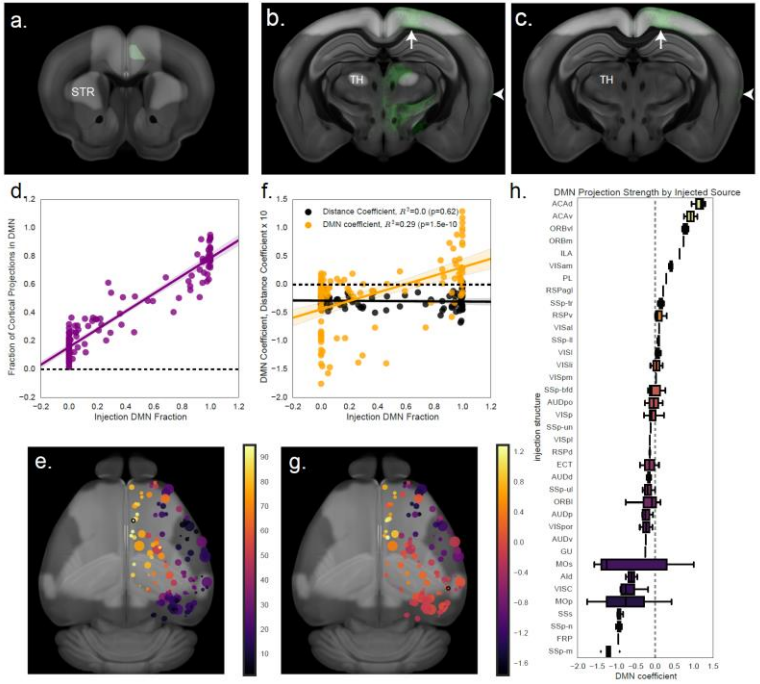
A structural correlate of the mouse default mode network



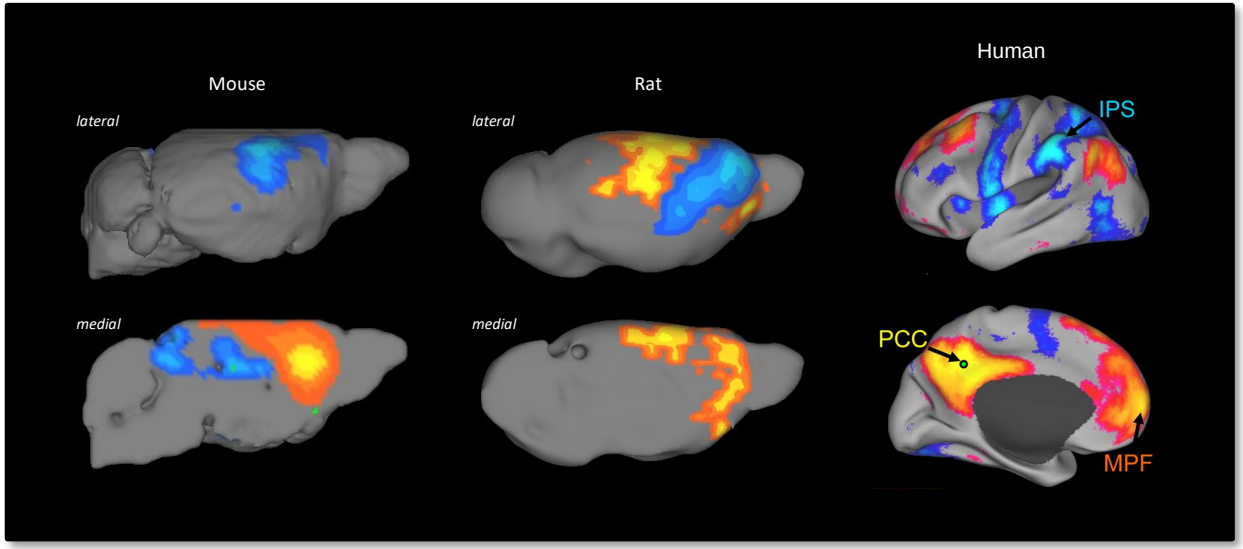




Jennifer Whitesell & Julie Harris, Allen Institute, Seattle
Whitesell et al., in preparation

ALLEN INSTITUTE

fMRI signal in the mouse DMN is anticorrelated to that in motor-sensory cortices



Gozzi and Schwarz (2016) Neuroimage

→ Cardinal feature of the human DMN

→ Competitive engagement of medial prefrontal and lateral cortical systems?

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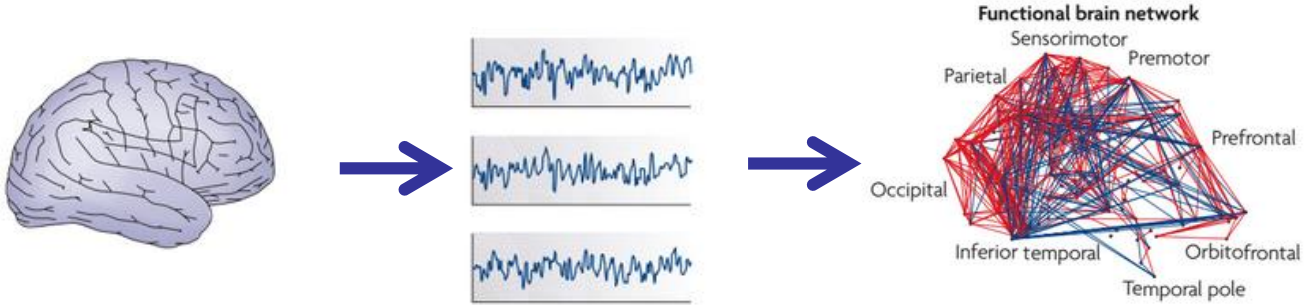
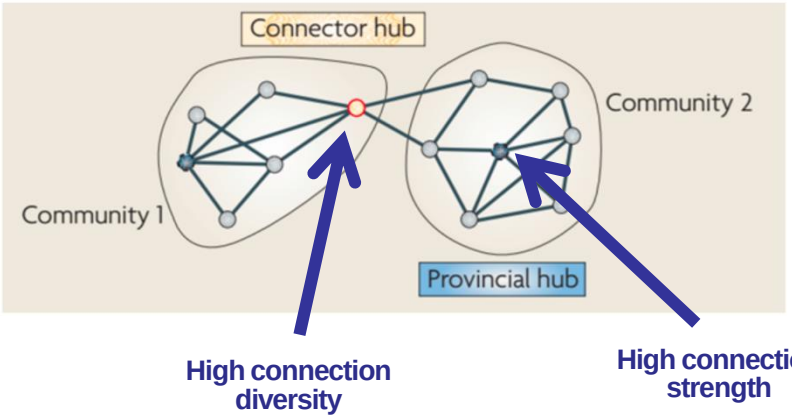
Graph representation of brain functional networks



Bullmore and Sporns, Nature 2009



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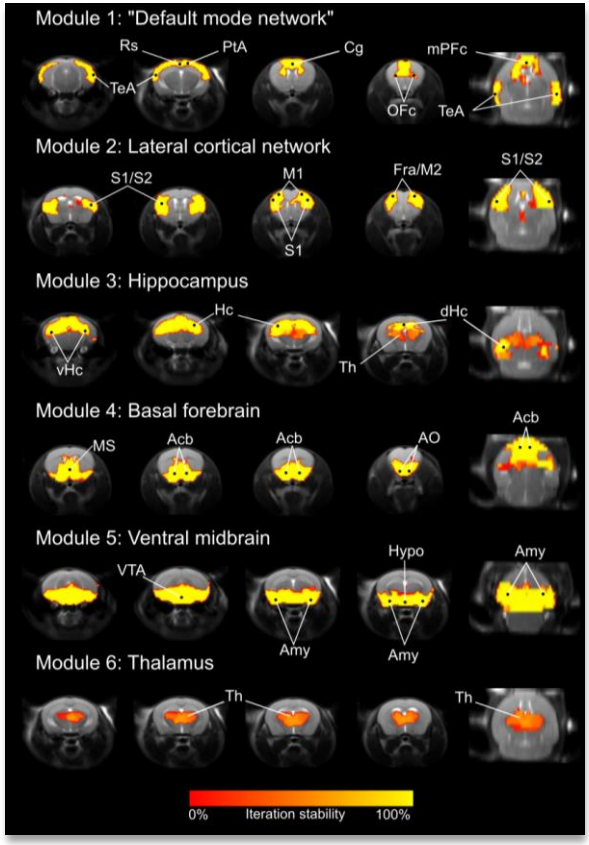
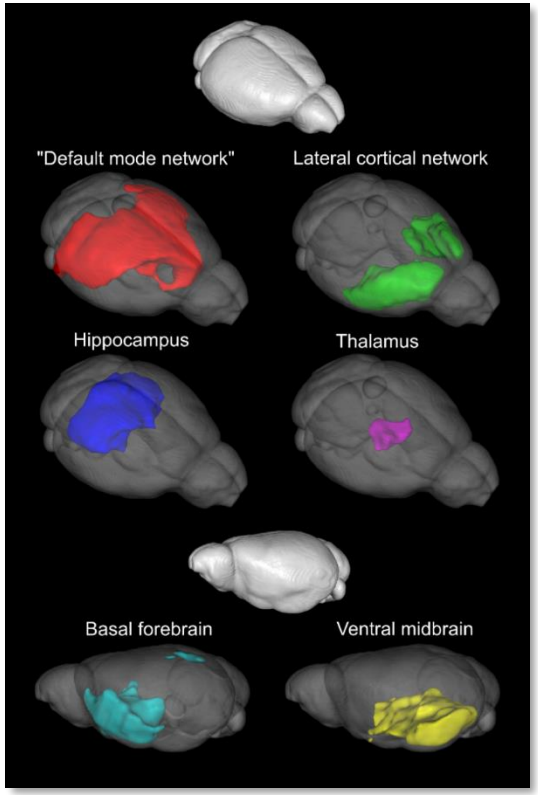
Functional communities of the mouse brain

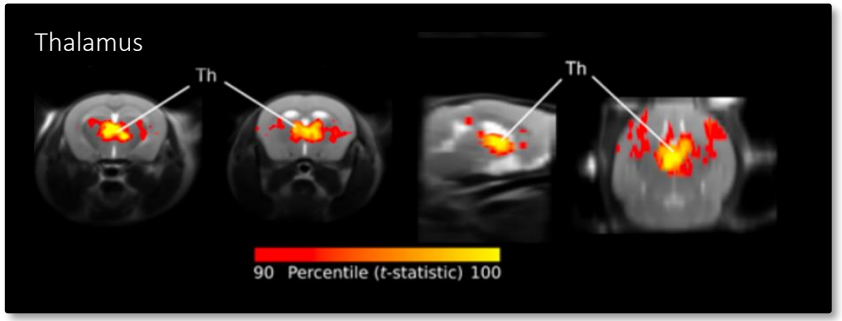
Adam Liska

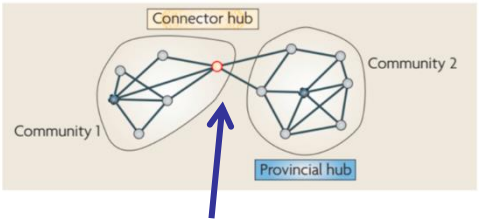




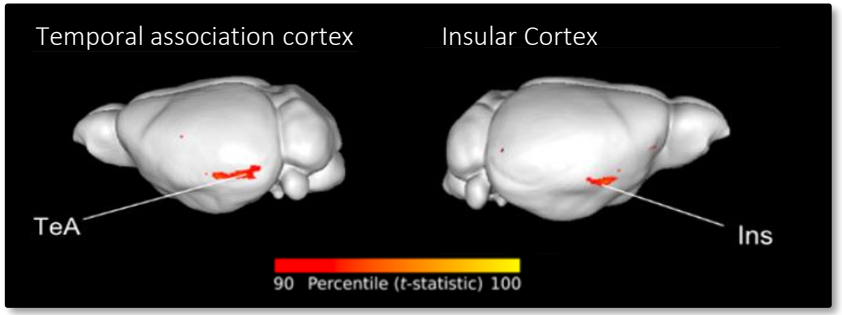
Liska et al., Neuroimage (2015)

High connection diversity hubs

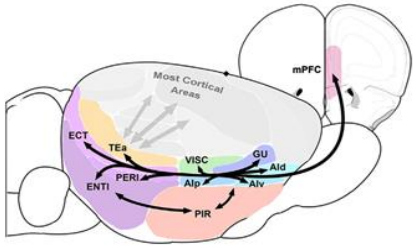




High connection diversity

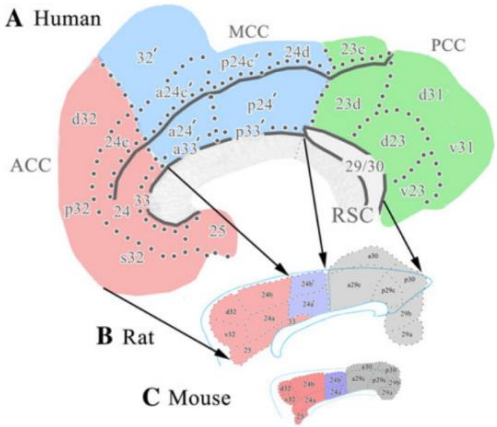


Liska et al., Neuroimage (2015)

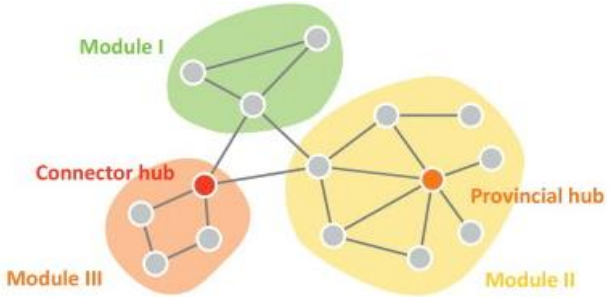


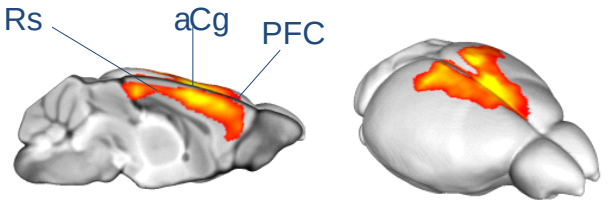
Zing et al. Cell. 2014

High “connection strength” hubs are evolutionarily-conserved



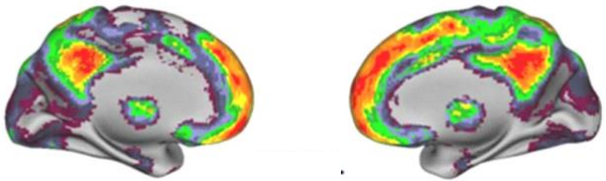
Paxinos & Vogt, 2015





Mouse

Liska et al., 2015



Human

Buckner et al. 2009

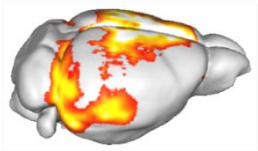
Interim Results

1. Intrinsic rsfMRI activity can be reliably mapped in the mouse brain

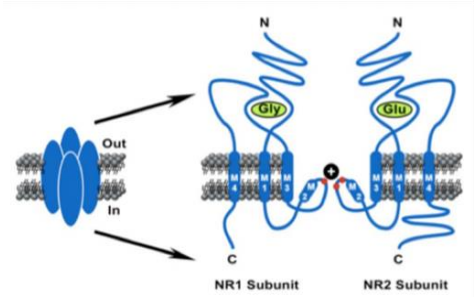
2. Mouse brain rsfMRI networks
   i. are homotopic
   ii. recapitulate human distributed networks (e.g. salience, DMN)
   iii. are tightly constrained by anatomical connectivity
   iv. their network topology is evolutionary conserved

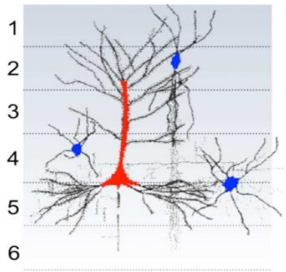
Bridging the “explanatory gap”

Mouse Neural Systems



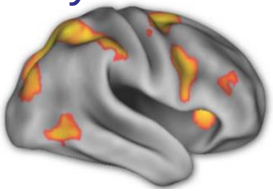
Cellular biology/Physiology





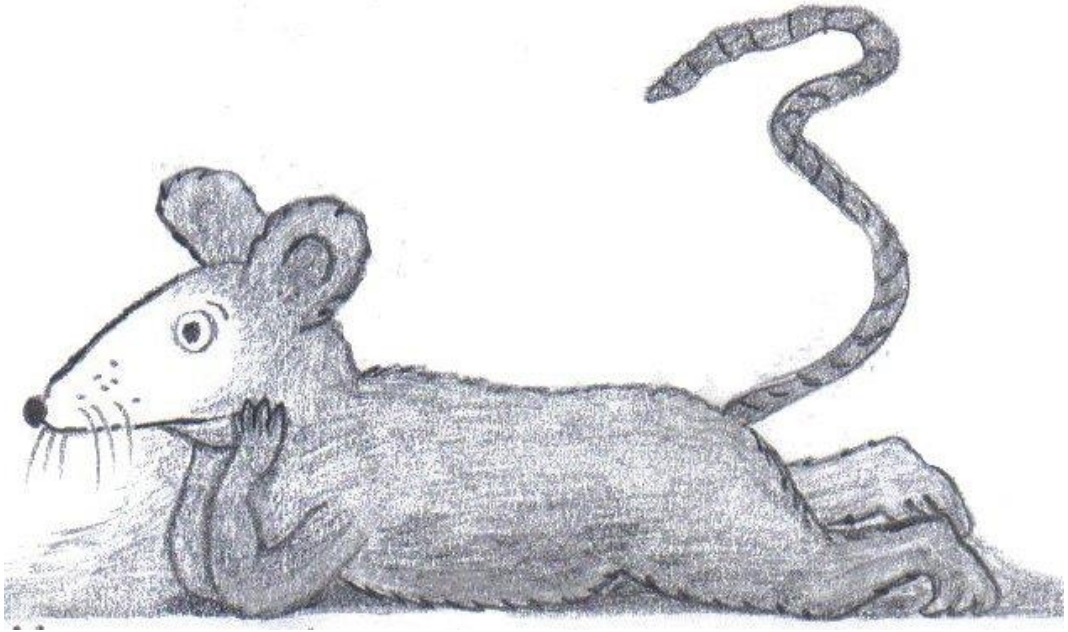
Explanatory gap

Human Neural Systems



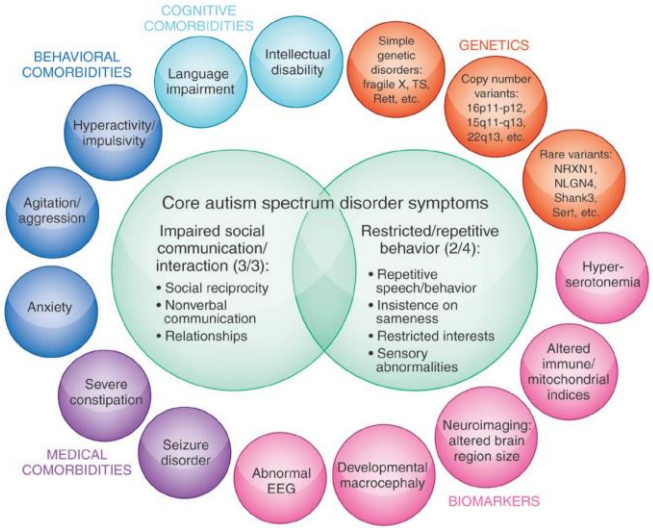
Liska and Gozzi, 2016

Can diseade-related connectivity aberrancies be translated across species?

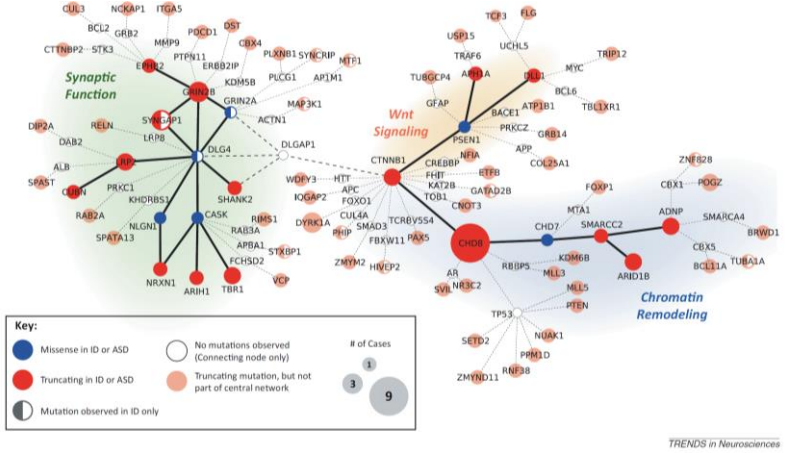


http://psychologyrats.edublogs.org/

Autism Spectrum Disorders (ASD)

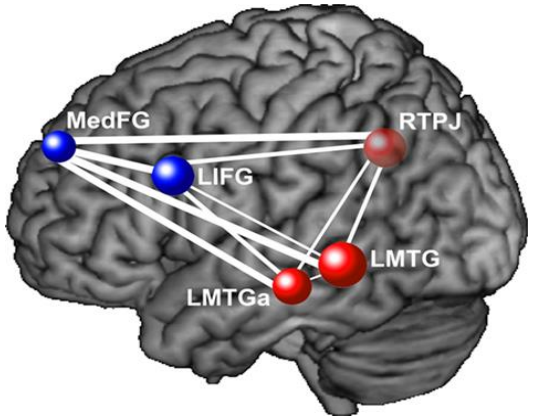


Set of highly heterogeneous conditions



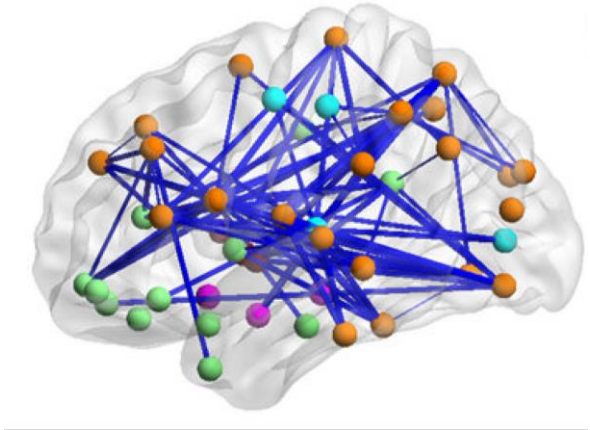
Highly heritable,
yet remarkable genetic heterogeneity

The disrupted connectivity theory of autism



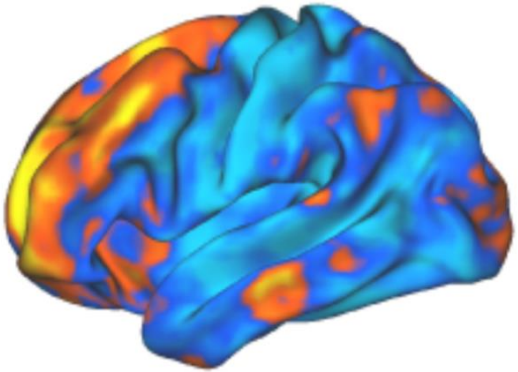
Schipul et al., 2011

Reduced



Supekar et al., 2013

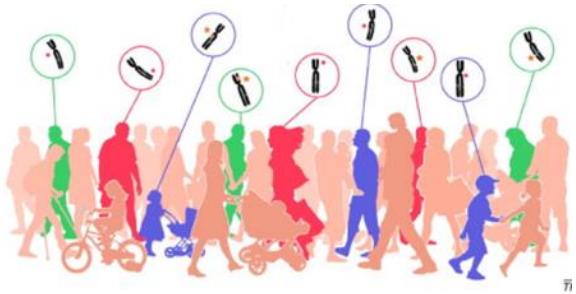
Increased



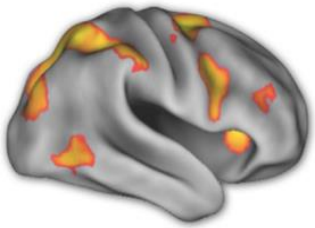
Holiga et al., 2018

Increased and decreased

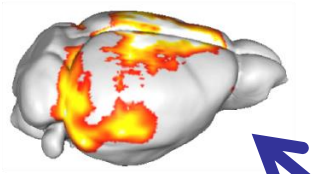
Deconstructing the spectrum with cross-species fMRI



Syndromic ASD mutations

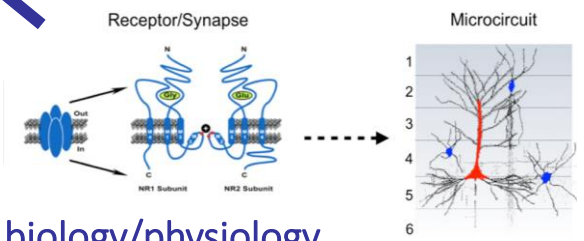


rsfMRI connectivity



rsfMRI connectivity

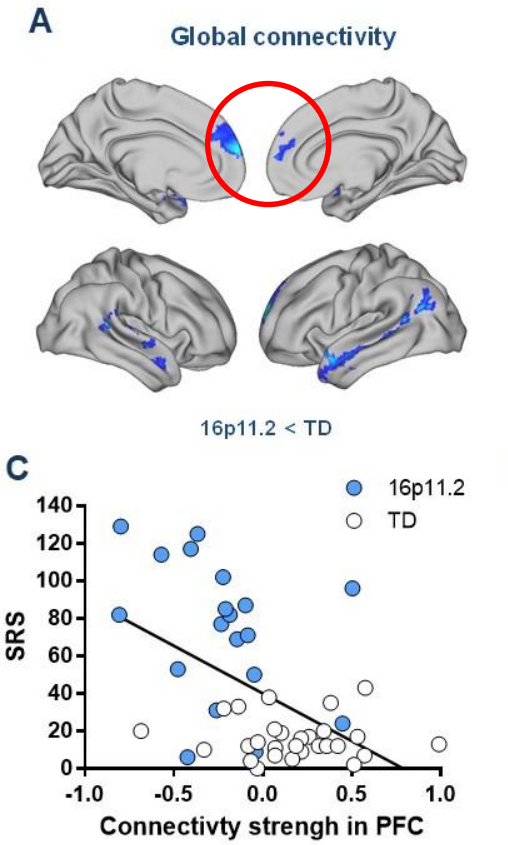
Mouse ASD models



Cellular biology/physiology

Liska and Gozzi, Front Nsci (2016)

Prefrontal under-connectivity in human 16p11.2 del carriers



Bertero et al. BRAIN (2018)

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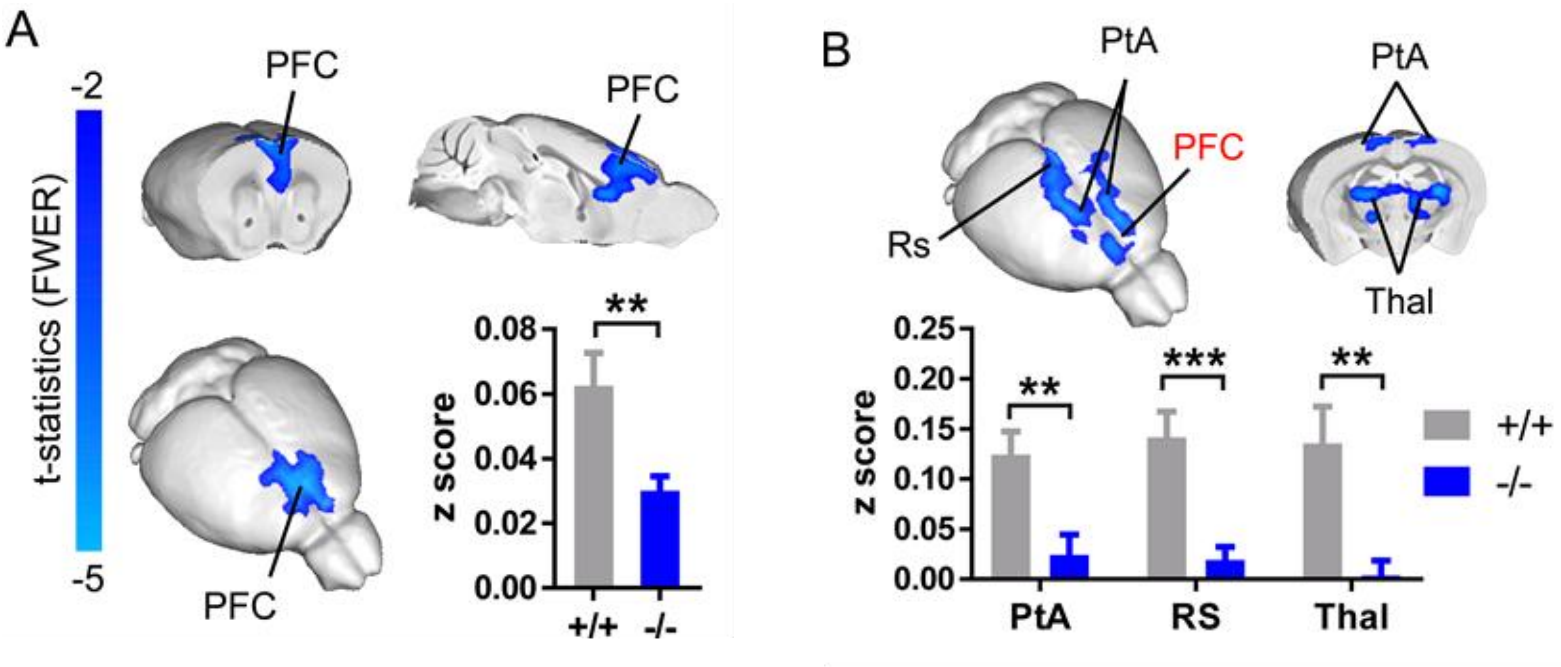
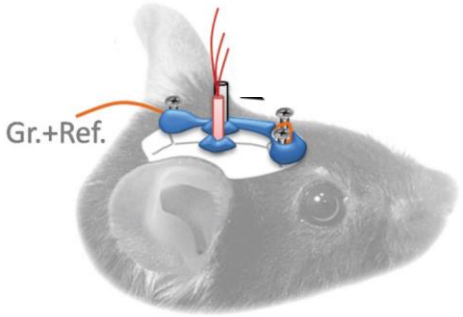
Prefrontal under-connectivity in a mouse model of 16p11.2 deletion

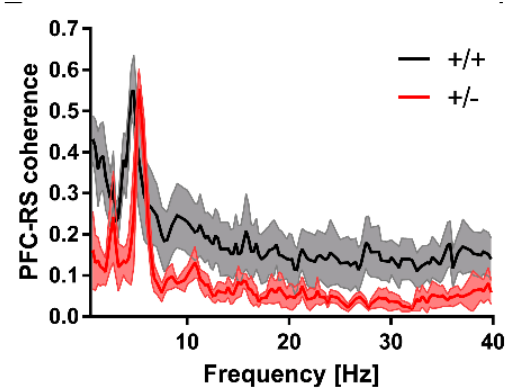


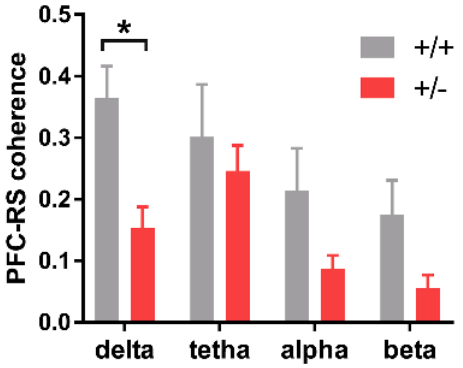
Bertero et al. BRAIN (2018)

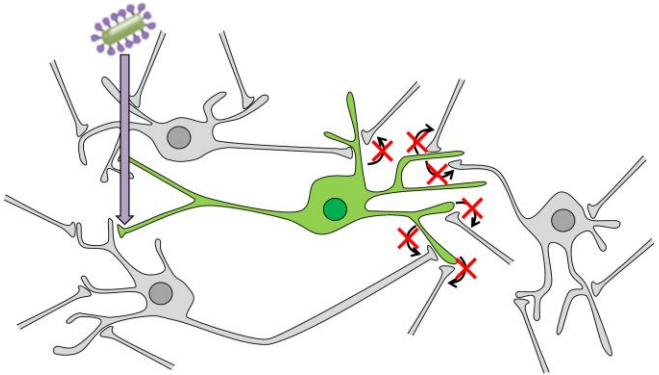
Altered thalamo-frontal wiring and synchronization in 16p11.2 del mice

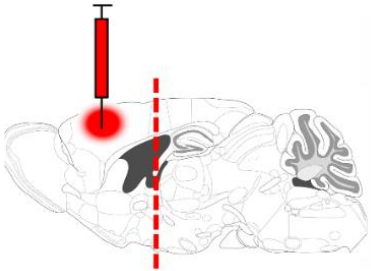


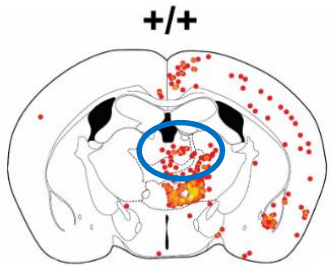
Senkov et al., 2015

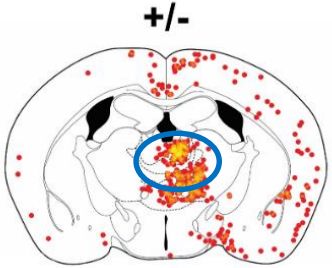






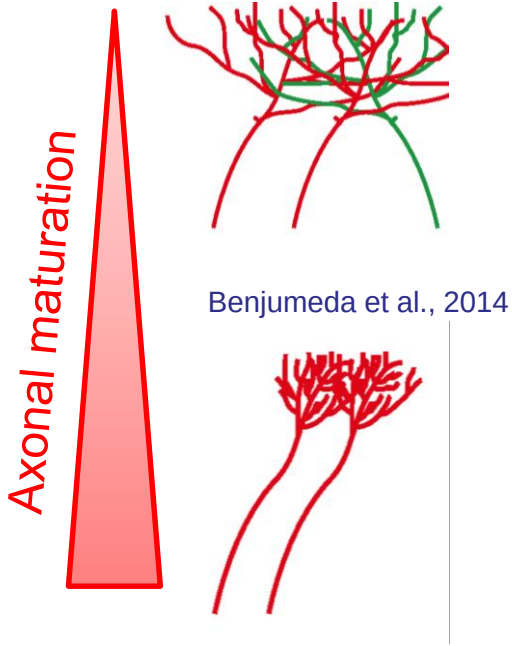






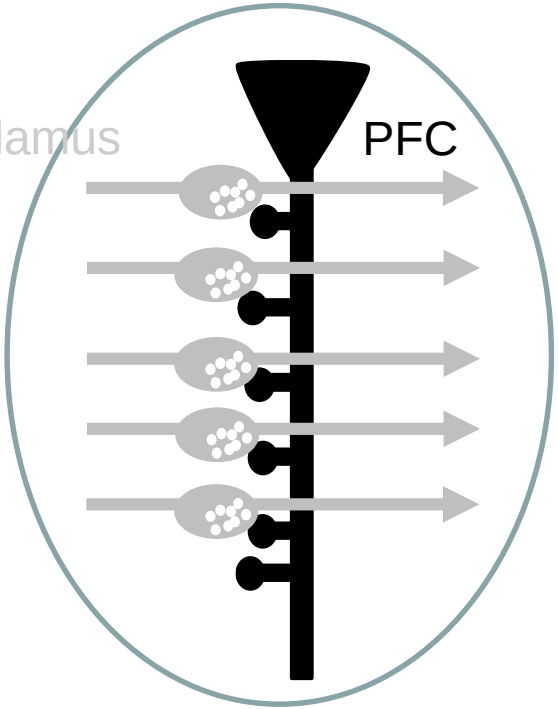
Bertero et al. BRAIN (2018)

Model for immature axonal pruning in 16p11.2 deletion



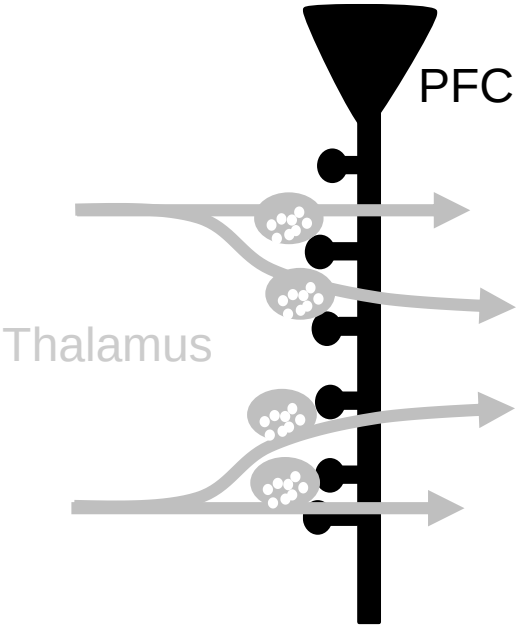
Benjumeda et al., 2014

Early development



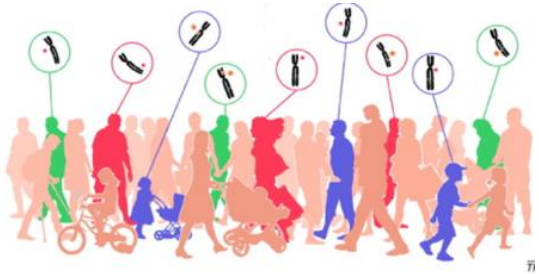
16p11.2 del

Late development



Bertero et al. BRAIN (2018)

Unweaving the Spectrum



Syndromic ASD mutations

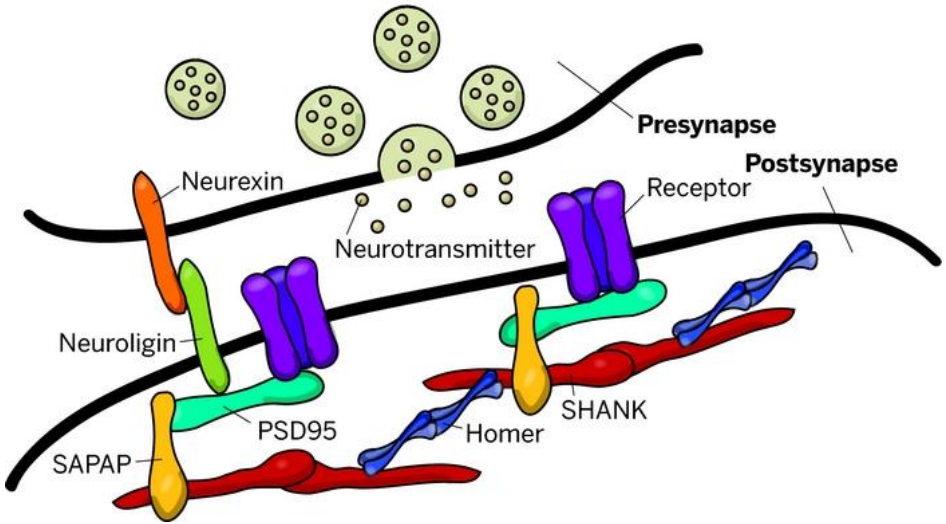
Mouse mutant models

How do individual ASD mutations affect functional connectivity?

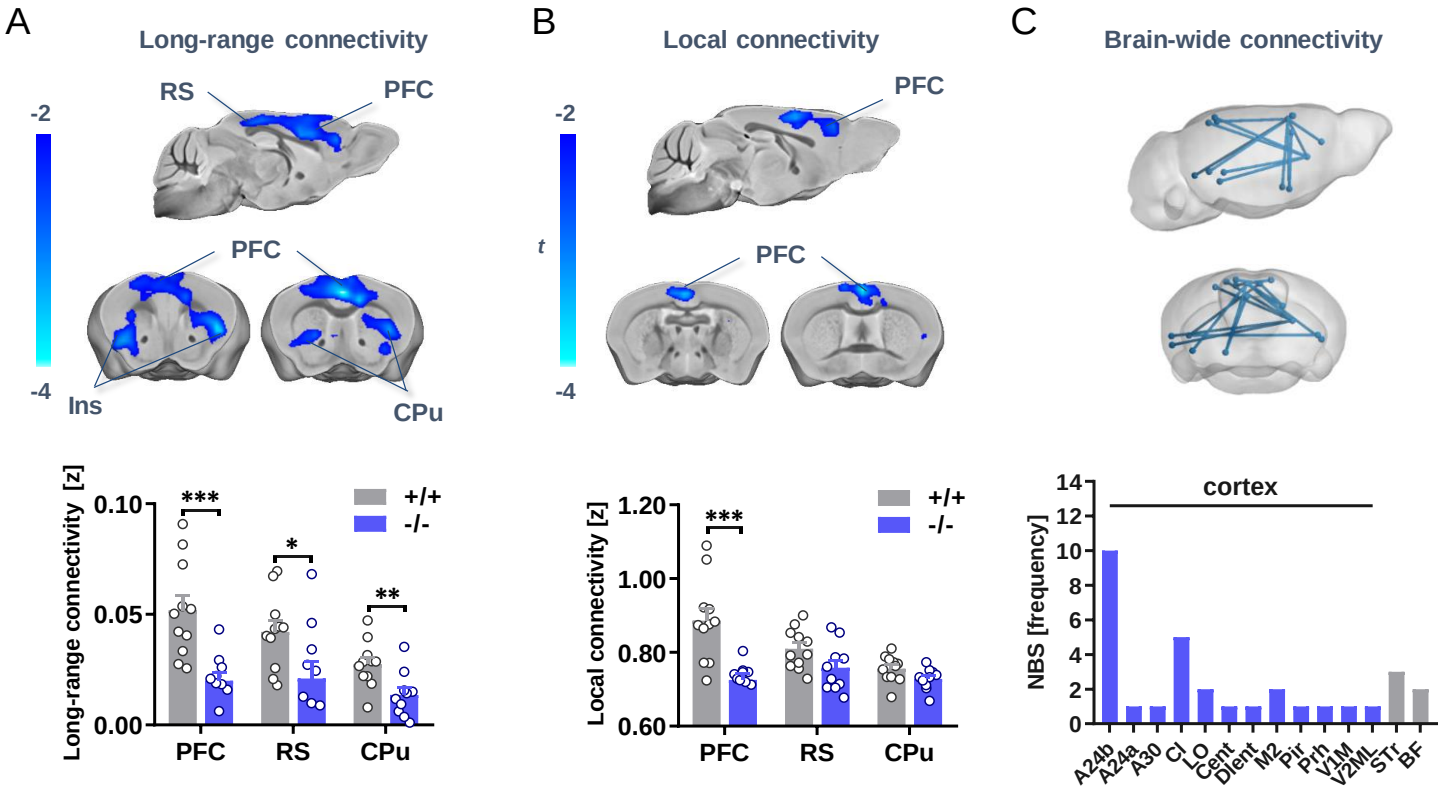
Does genetic heterogeneity explain connectional variability?

The autism-risk gene Shank3

- ✓ Synaptic scaffolding protein
- ✓ Strongly implicated in ASD & Phelan-McDermid syndrome
- ✓ Shank3-KO mice show self-injurious grooming
- ✓ Intellectual disability and language impairments in humans



Reduced long-range connectivity in prefrontal cortex of Shank3B$^{-/-}$ mice



Pagani et al. J nsci 2019

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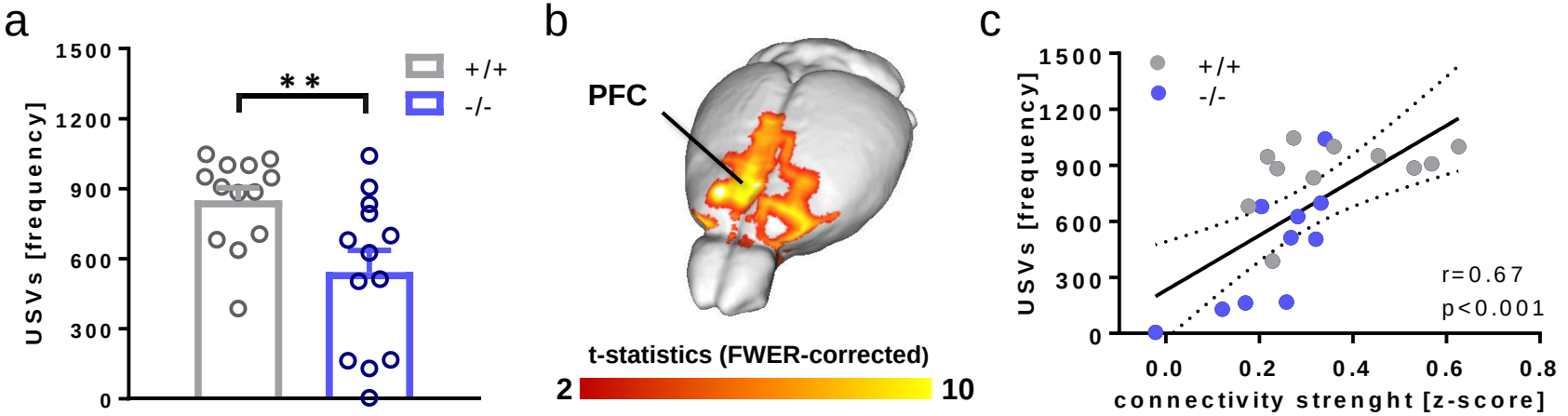
Reduced long-range *connectivity* is predictive of impaired social communication



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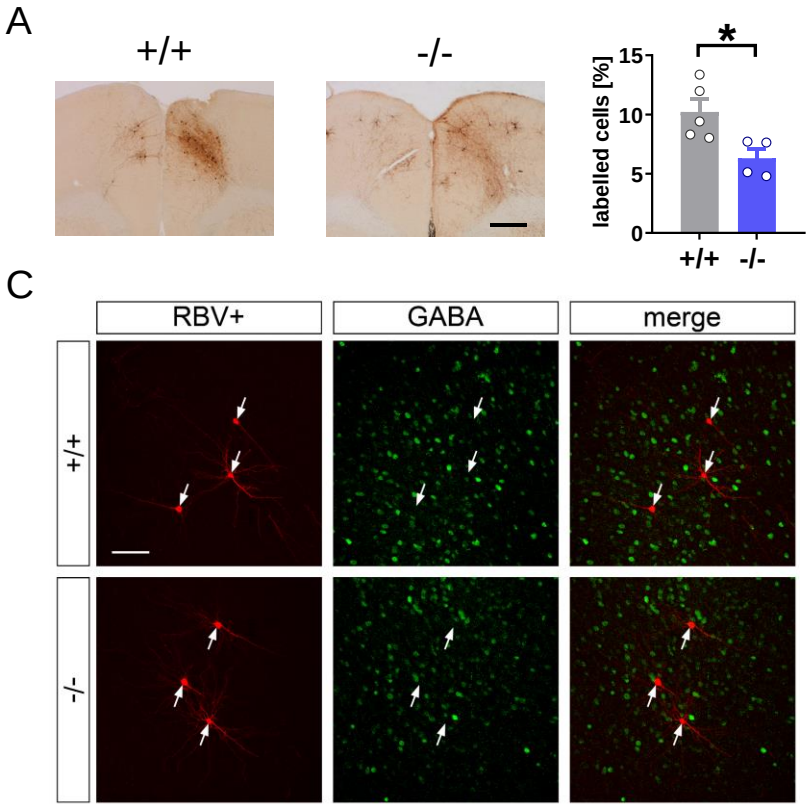
Neural miswiring in the prefrontal cortex of Shank3B$^{-/-}$ mice



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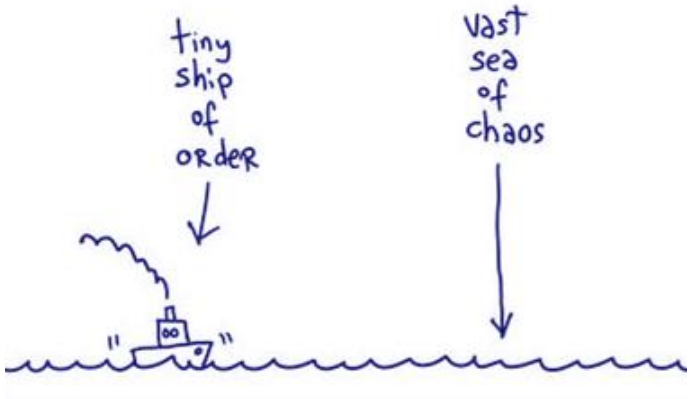
Take-Home Messages

- ✓ rsfMRI allows to to map the functional organization of the human brain at rest
- ✓ Cross-species fMRI can help probe the neural basis of human connectopathies



Thanks!

- Istituto Italiano di Tecnologia
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  - **Alberto Galbusera**
  - **Carola Canella**
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  - **Maria Luisa Scattoni**
- ETH Zurich
  - **Nicole Wenderoth**
  - **Valerio Zerbi**

Lilly

NIH National Institutes of Health

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