Networks of spontaneous brain activity in the rodent brain

Alessandro Gozzi, PhD

Functional Neuroimaging Laboratory
Italian Institute of Technology,
Center for Neuroscience and Cognitive Sciences
Rovereto, Italy
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
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)
Synopsys of fMRI

STIMULUS

fMRI

↑ Neural Activity
↑ Local Energy Metabolism
↑ CMRO₂
↑ CMRGlc
↑ dHb
↑ CBF
↑ CBV

CBV: Cerebral Blood Volume
CBF: Cerebral Blood Flow
CMRO₂: Cerebral Metabolic O₂ consumption
CMRGlc: Cerebral Metabolic Glucose consumption
Hb: Oxygenated hemoglobin
BOLD Endogenous Contrast

- **Blood Oxygenation 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

Fox et al., 2007
Functional Segregation
Specialised areas exist in the cortex

Functional Integration
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
→ At best, task-related modulation explains 20% of BOLD variance
→ Spontaneous ongoing activity explains 50-80% of BOLD variance
Resting-state (= spontaneous) fMRI signal is temporally correlated between functionally related regions

→ fMRI connectivity networks

Biswal et al., 1995

Van Dijk et al., 2010
Altered intrinsic connectivity patterns typically observed in all major brain disorders!

Zhao et al., 2013 Front Human Neuroscience
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”

Cellular biology/Physiology

Mouse Neural Systems

Explanatory gap

Human Neural Systems

Liska and Gozzi, 2016
Talking about a revolution

- GENE
  - PROTEIN
  - Behaviour
  - Development
  - Pathology
  - Physiology

- NEURONAL
  - CELL
  - Function
  - Behaviour

Transgenic models

Optogenetics
Pharmacogenetics
Light anesthesia preserves rsfMRI network organization

Awake (DMN)

Unconscious (DMN)

Difference

Akei et al (2015) eLIFE
Motion-free images - reliable network mapping

The mouse brain is organised in homotopic connectivity clusters

Human – ICA

Mouse – ICA

Smith et al., 2009

Sforazzini et al., 2014
Psychiatric disorders affect large-scale networks of the brain.
Distributed rsfMRI networks in the mouse brain

Seed in parietal cortex

Seed in insular cortex

Sforazzini et al., 2014, Neuroimage
A mouse homologue of the human salience network?

Mouse

Human

Seeley et al., 2007 J. Nsci.

Sforazzini et al., 2014 Neuroimage
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 psychopathology

Beckmann et al., 2005 Philos Trans B
The mouse brain has a “default mode network”

Gozzi & Schwarz, 2016
A structural correlate of the mouse default mode network

Jennifer Whitesell & Julie Harris, Allen Institute, Seattle
Whitesell et al., in preparation
fMRI signal in the mouse DMN is anticorrelated to that in motor-sensory cortices

→ Cardinal feature of the human DMN

→ Competitive engagement of medial prefrontal and lateral cortical systems?
Graph representation of brain functional networks

Bullmore and Sporns, Nature 2009

High connection diversity
High connection strength
Functional communities of the mouse brain

Liska et al., Neuroimage (2015)
High connection diversity hubs

Liska et al., Neuroimage (2015)
Zing et al. Cell. 2014
High “connection strength” hubs are evolutionarily-conserved

Paxinos & Vogt, 2015

Mouse

Human

Liska et al., 2015

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
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Explanatory gap

Liska and Gozzi, 2016
Can disease-related connectivity aberrancies be translated across species?
Autism Spectrum Disorders (ASD)

Set of highly heterogeneous conditions

Highly heritable, yet remarkable genetic heterogeneity
The disrupted connectivity theory of autism

Reduced

Supekar et al., 2013

Increased

Holiga et al., 2018

Increased and decreased
Deconstructing the spectrum with cross-species fMRI

Liska and Gozzi, Front Nsci (2016)
Prefrontal under-connectivity in human 16p11.2 del carriers

Bertero et al. BRAIN (2018)
Prefrontal under-connectivity in a mouse model of 16p11.2 deletion
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

- **Early development**
  - Thalamus
  - PFC
- **Late development**
  - Thalamus
  - PFC

*Benjumeda et al., 2014*

*Bertero et al. BRAIN (2018)*
Unweaving the Spectrum

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
Reduced long-range connectivity is predictive of impaired social communication

Pagani et al. J Nsci 2019
Neural miswiring in the prefrontal cortex of Shank3B\(^{-/-}\) mice

Pagani et al. J Nsci 2019
Take-Home Messages

✓ rsfMRI allows to map the functional organization of the human brain at rest

✓ Cross-species fMRI can help probe the neural basis of human connectopathies
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