Manganese-Enhanced MRI for Functional Imaging of Freely Moving Animals

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Functional imaging

- Brain function relies on complex interactions between large populations of neurons across many brain regions

- Exploratory

  Whole brain level = No prior assumption about the involved regions

  Regions = population of neurons depending on the spatial resolution

- Functional

  Difference of neural activity

  Intergroup / Between two groups of subjects

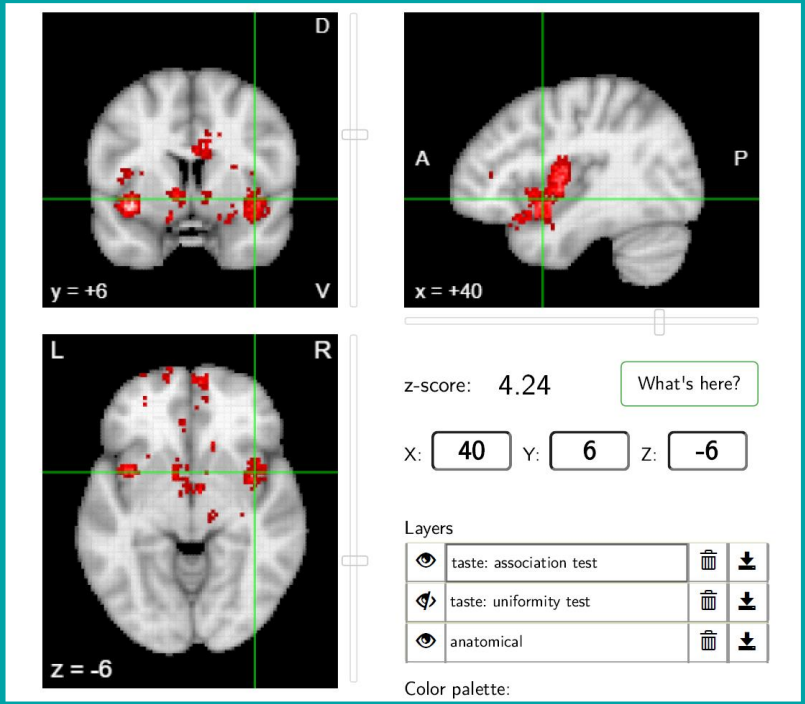
  Intrasubject / Within the same subject

Blood Oxygenated Level Dependent
+
Magnetic Resonance Imaging

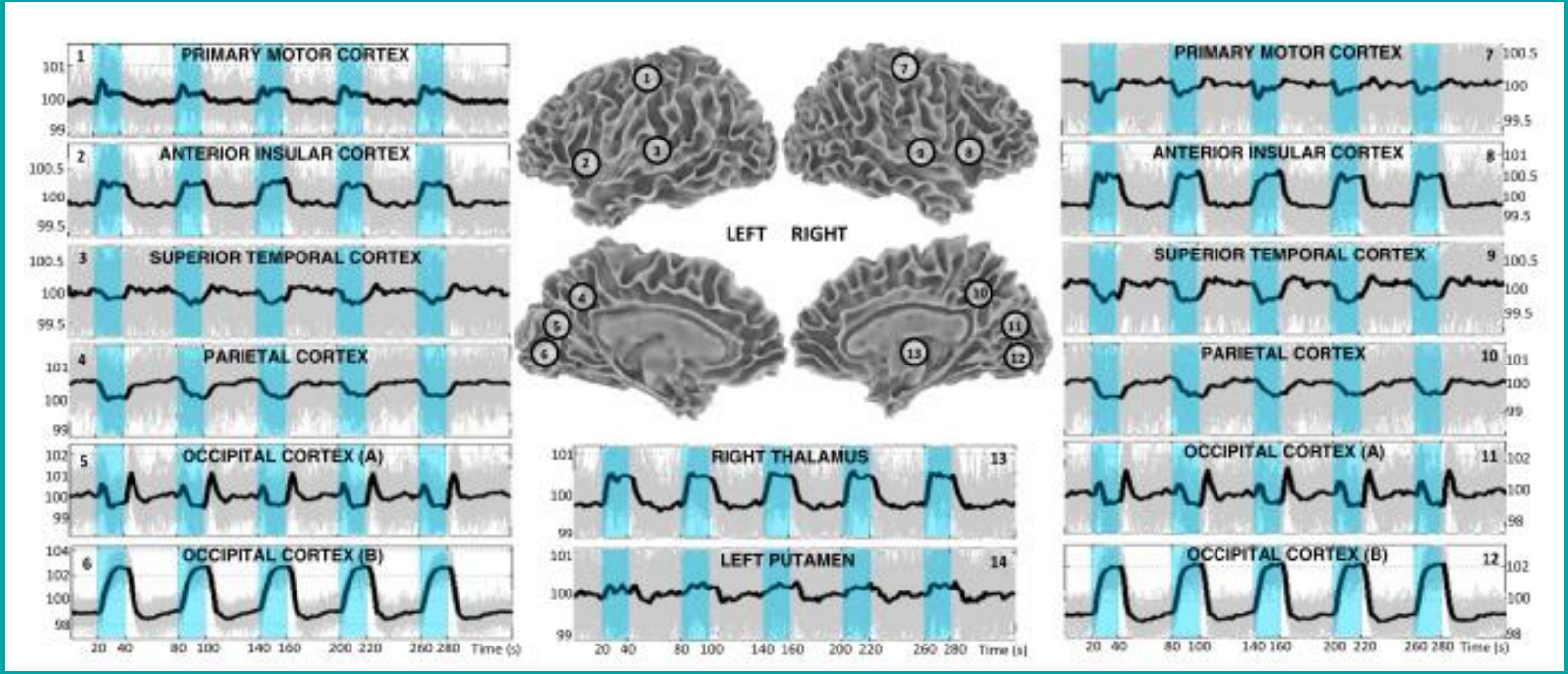
= BOLD fMRI

Human fMRI

neurosynth.org
“Neurosynth is a platform for large-scale, automated synthesis of **functional magnetic resonance imaging (fMRI) data**
It takes thousands of published articles reporting the results of fMRI studies, chews on them for a bit, and then spits out images that look like this …”



BOLD transient responses



Gonzales-Castillo *et al.* (2012) doi: 10.1073/pnas.1121049109

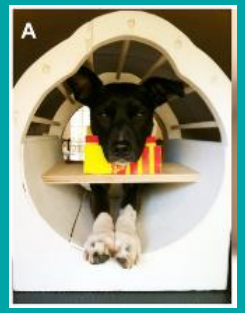
BOLD fMRI on animals ?

- Neural responses are transient
  - Neural activity should be “active/established” in the MR magnet during data acquisition

- Motion generates artifacts on the MR images
  - Sedation / Anesthesia
  - ... but anesthesia affects neural activity in an agent- and dose-dependent manner Xu et al. (2022) doi: 10.1177/0271678X211062279

BOLD fMRI / Other options

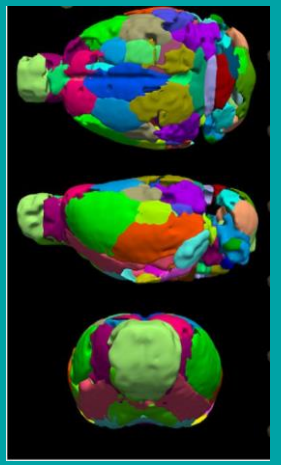
- Trained awake dogs



“reward” hand signal > “no-reward” hand signal

Berns et al. (2012) doi:10.1371/journal.pone.0038027

- Head-fixed awake rat



Parcellation of the task-free MR acquisitions

Paasonen et al. (2022) 10.1016/j.neuroimage.2022.118924

Manganese
+
Magnetic Resonance Imaging

= ME(nhanced)MRI

MEMRI principles

- Mn^{2+}
  - Calcium analog
  - Paramagnetic intracellular contrast agent
  - Entry in the excitable cells through voltage-gated calcium channels
  - Activity-dependent transport along the axons of neurons and across synapses

- Long brain retention
  - Half-life of 51 to 74 days

Allows to decouple the Mn uptake period on awake animals from the image acquisition on anesthetized ones

MEMRI fMRI experiment outline

Mn administration

Stimulation on freely-behaving animals

MRI under anesthesia

Group comparison

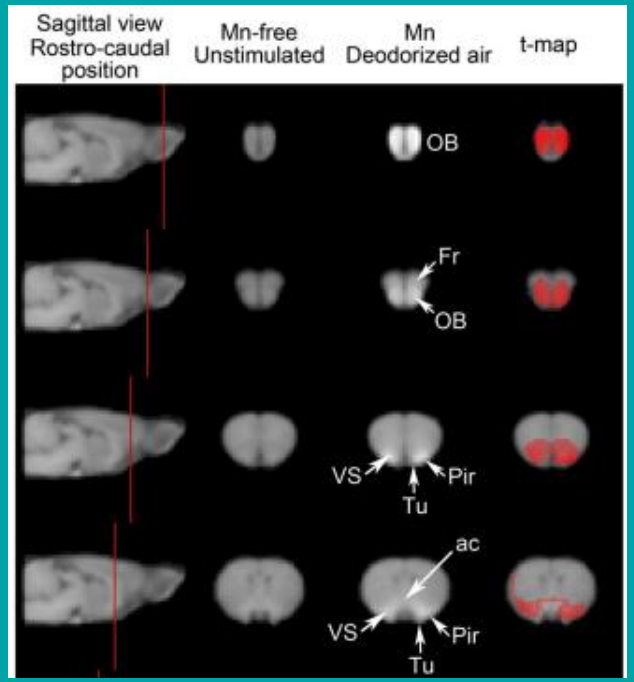
Prerequisites

- Administration methods
  - Local — Natural entries, intracerebral injections
  - Systemic — Intravenous, intraperitoneal, oral (…)

- Due to its neurotoxicity, Mn dose should be adapted to the chosen administration route

Systemic administration preferable for an exploratory whole-brain activation induced MEMRI experiment

Transsynaptic transport in olfactory pathways



- Conditions

Mn administration in nostrils
MRI +48h post-injection
2 groups of rat (n=9 free, n=7 Mn)

Enhancements also depend on the odor

See Lehallier *et al*. (2012) doi.org/10.1371/journal.pone.0048491

Recent application

Collaboration with S. Rabot, Micalis Institute, INRAe, AgroParisTech, CNRS, Université Paris-Saclay, 78350 Jouy-en-Josas

Analysis of the brain structures involved in stress and anxiety-like behavior in germ-free rats using MEMRI

Experimental design

- 2 groups of axenic (AX) and control (CO) – n = 8
- Mn-injection IP 30 mg/Kg
- 3D MRI at 11.7T – 24h post-injection
- Post-processing
  - Quantitative reconstruction of T1$\propto 1/[Mn]$
  - Inter-animal coregistration
  - Non parametric two sample t-test for group comparison

Results

- Anxiogenic-like behavior shown by the open field tests

Increase in the number of grooming and defecation for AX rats

- T1(Axenic)>T1(Controls)

No voxel with a significant difference

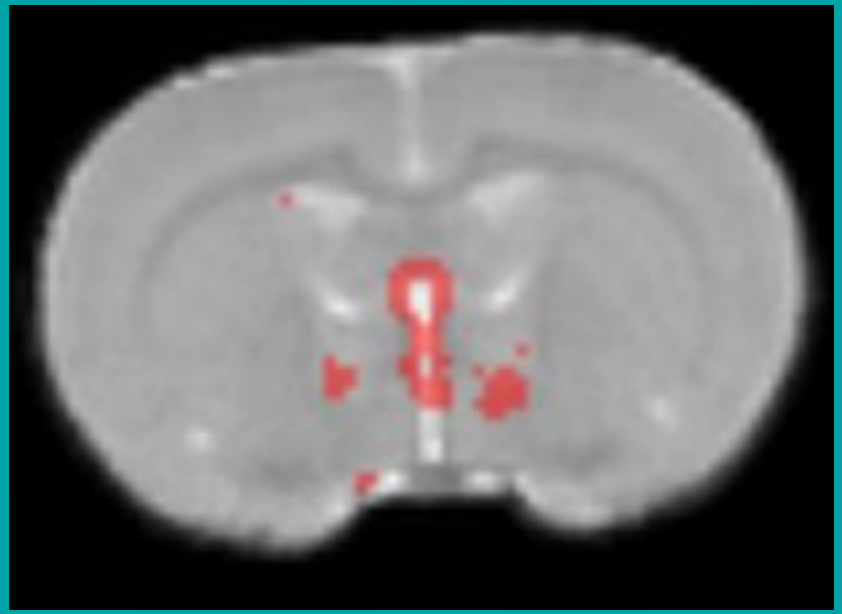
i.e. no brain regions uptaking more Mn in the CO group than in the AX group

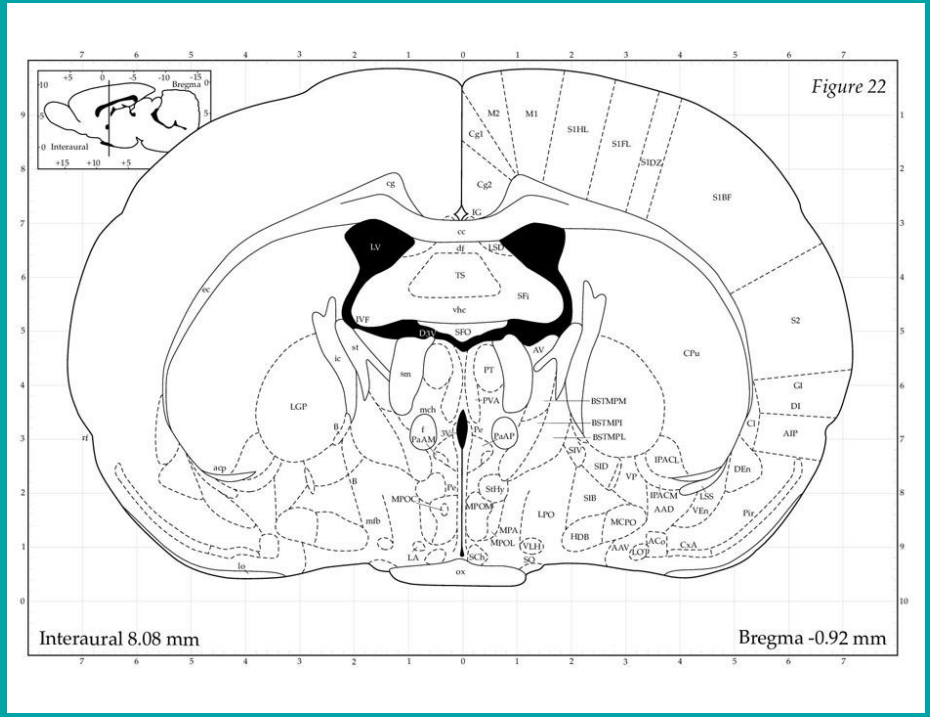
T1(Axenic)<T1(Controls) = More [Mn] in several regions

In the CSF

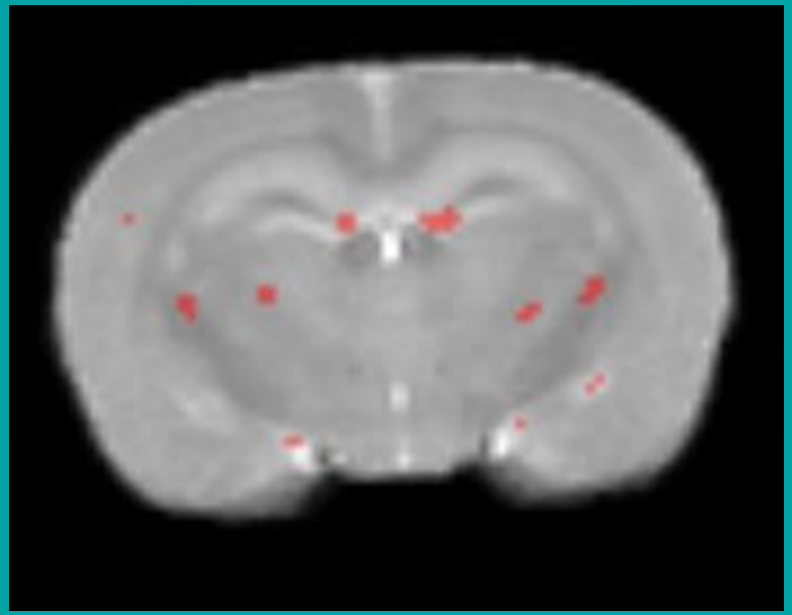
In subcortical regions

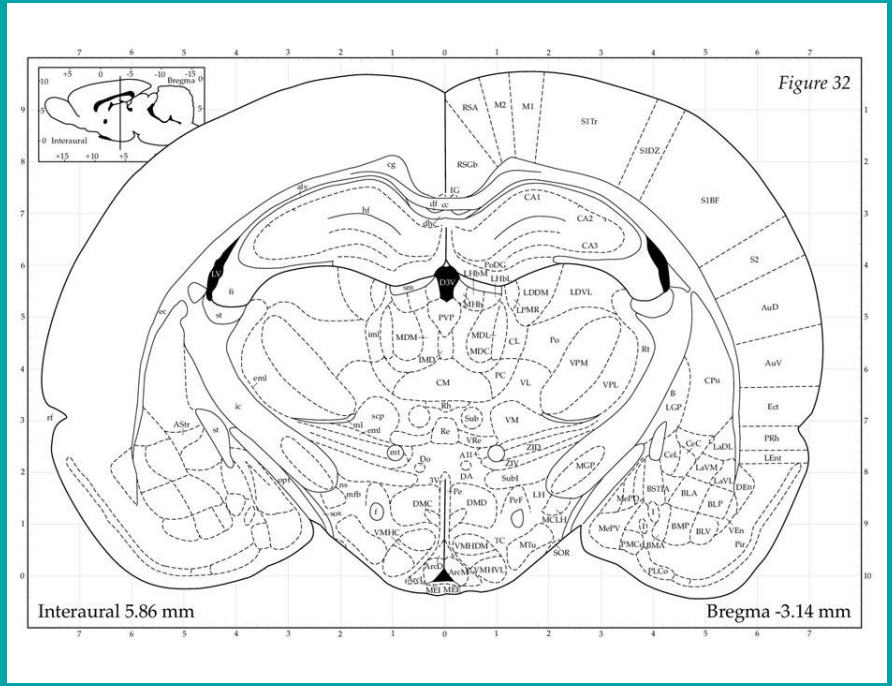
MEMRIcrobiote : results





MEMRIcrobiote : results





MEMRI : Take-home messages

Valuable option for fMRI on behaving animals

- **Exploratory**
- Allow distorsion-free MRI at **high spatial resolution**

Integration of the neural activity

- Time period = From the Mn administration to MRI
- Well-adapted to the **characterization of chronic states**

Contact

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High field MRI
http://www6.inra.fr/agroresonance

AgroResonance

In vivo multimodal imaging

IVIA IBiSA infrastructure
https://www.ibisa.net/plateformes/detail.php?tri=&srch=&q=495