Chasing causality – what can we learn from controlling neuronal activity?

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Necessary and sufficient

A -> B -> C

A -> X -> X	B is necessary
A -> X -> C	B not necessary
X -> B -> C	B sufficient
X -> B -> X	B not sufficient

In formal logic: true N&S is that it implies equivalence between the two statements, allowing one to be a definition of the other

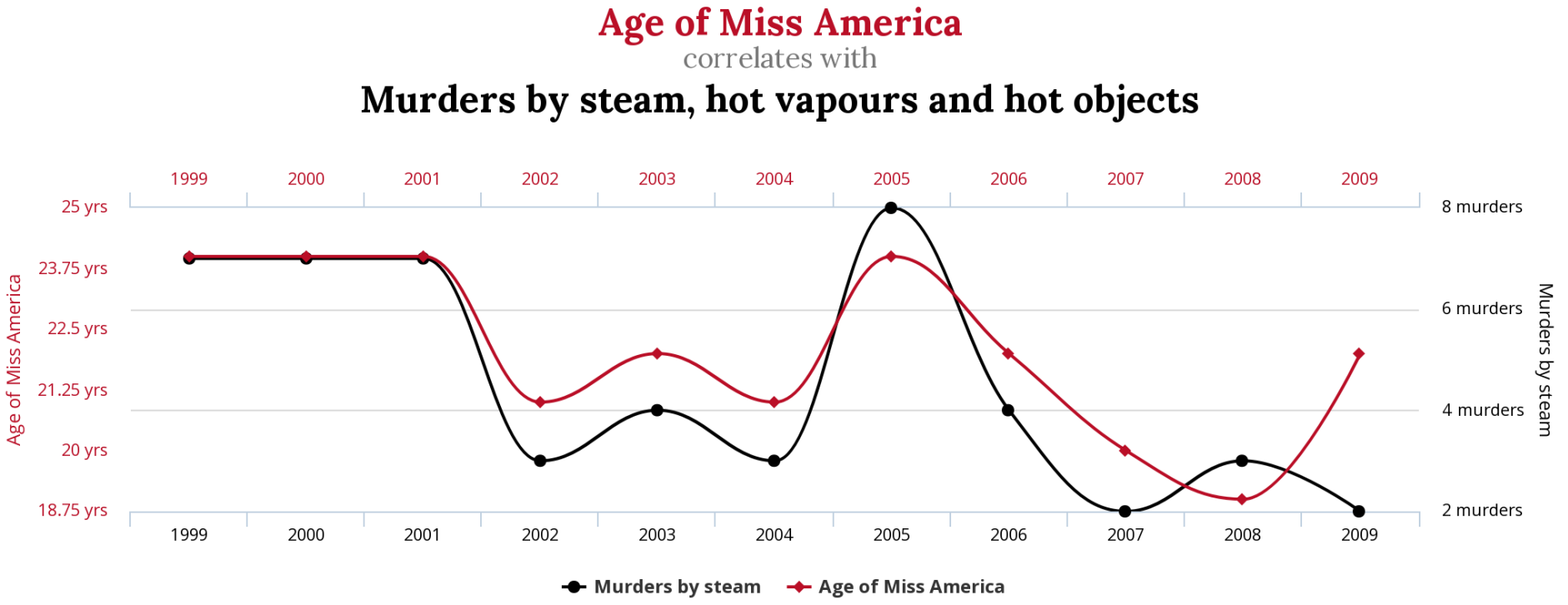
→ *indispensable and inducing*

Yoshihara & Yoshihara 2018

What's the point?

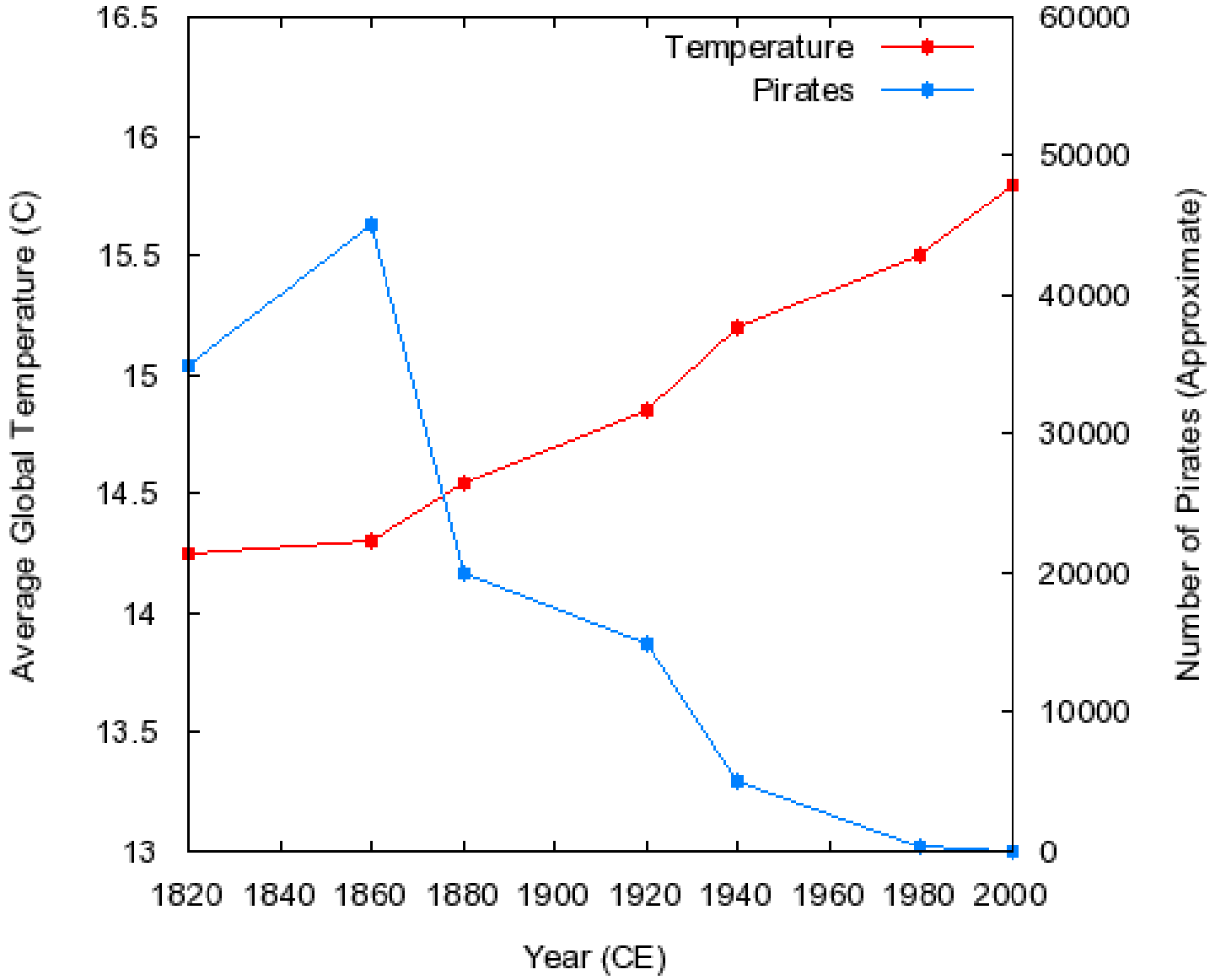
To establish causality observation is not sufficient, we need to manipulate brain activity
The ***scientific method***: hypothesis -> experiment

<u>Causality vs correlation</u>



http://www.tylervigen.com/spurious-correlations

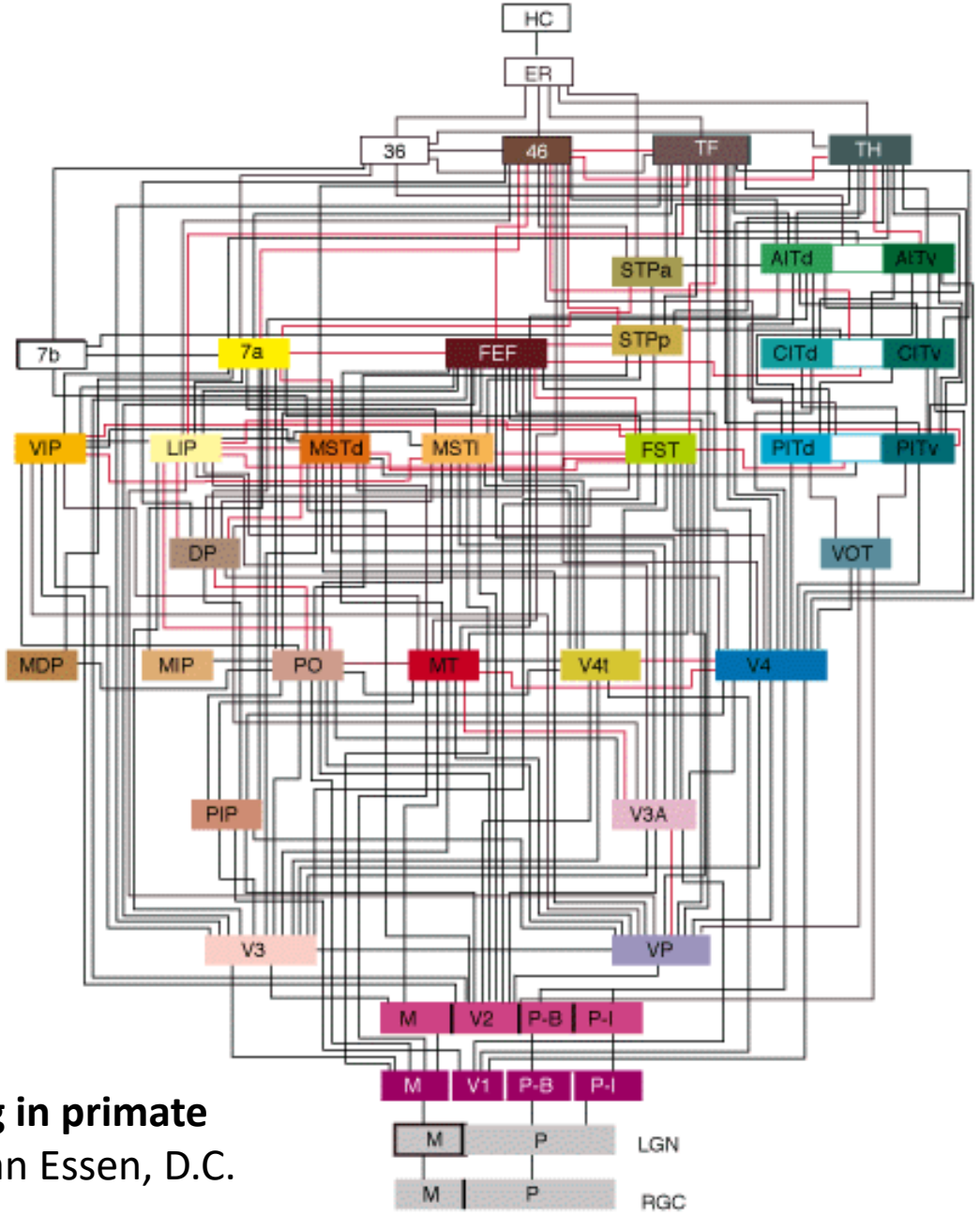
The lack of pirates caused global warming!



How do we test causality?

Manipulate brain activity in a controlled manner

… GLHF …



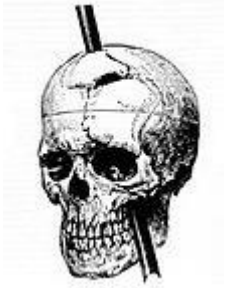
Distributed hierarchical processing in primate visual cortex. Felleman, D.J. and Van Essen, D.C. (1991) Cerebral Cortex, 1: 1-47

How to control neuronal activity

1. Lesion
    1. TBI
    2. Stroke
    3. Artificial (phototrombic) stroke
    4. Freezing
2. Inactivation
    1. Pharmacology
        1. Permanent (e.g.: *N*-methyl-dl-aspartic acid)
        2. Temporary (e.g.: muscimol)
    2. Cooling
    3. Pharmacogenetics (DREADDS)
    4. Light
3. Activation
    1. TMS
    2. Electrical stimulation
        1. Peripheral (e.g: driving a cockroach)
        2. Central stimulation of brain regions
            1. During surgery
            2. Parkinson's treatment (DBS)
    3. Pharmacogenetics (DREADDS)
    4. Light

History of inactivation is a history of injuries

~1600 BC: Edwin Smith Papyrus: classification of head injuries



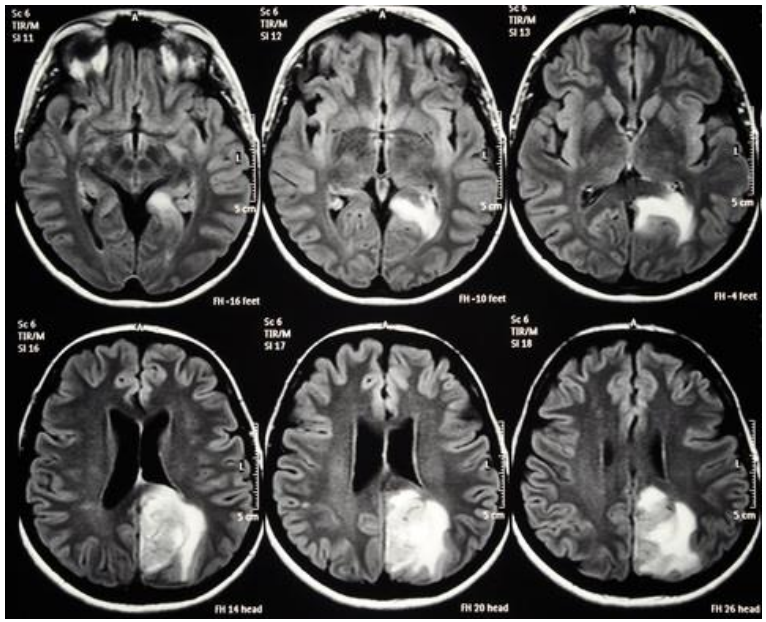
1850's: Phineas Gage: severe, possibly temporary personality change

20th century: lesion studies

causes: injury, inflammation, tumor, ischemic stroke etc.

frontal lobotomy to "cure" mental illness

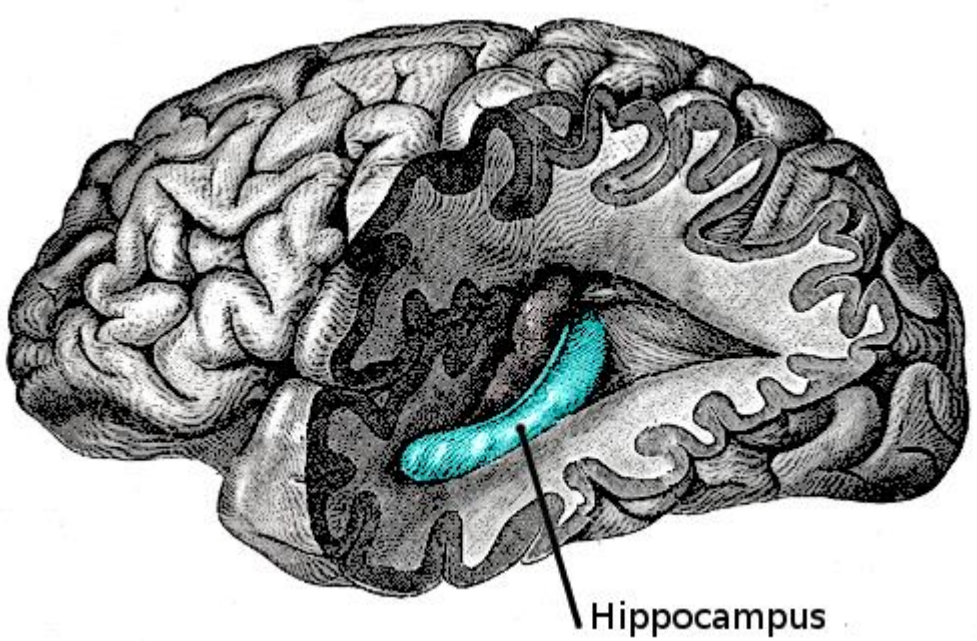
epilepsy: corpus callosotomy
(Dr. William P. van Wagenen and
Roger W. Sperry)



The Legacy of Patient H.M. for Neuroscience – Squire 2008

Loss of recent memory after bilateral hippocampal lesions.
SCOVILLE WB, MILNER B, 1957

- Patient H.M.: severe epilepsy following childhood bike accident
- Treatment: bilateral hippocampal lesion at age 27 (actually: hippocampus, amygdala, and the adjacent parahippocampal gyrus)
- "side effect": severe memory impairment: no memory consolidation
- intact intellectual and perceptual functions



Brain lesions studies in humans in the 21st century

Goal: link an identified brain region to function in behavior

Value: there are not many non-invasive ways to manipulate neuronal activity in humans, lesions are a crucial tool supplementing imaging approaches.

Difficulty: old lesion studies provide inaccurate descriptions
modern lesion studies: often single patient, huge variability, no reproducibility, thus the data may not generalize

Solutions: increased sample sizes (USA: 800,000 diagnoses of stroke)
combination with imaging methods for better documentation
meta-analysis algorithms for better statistical power

What can be tested:

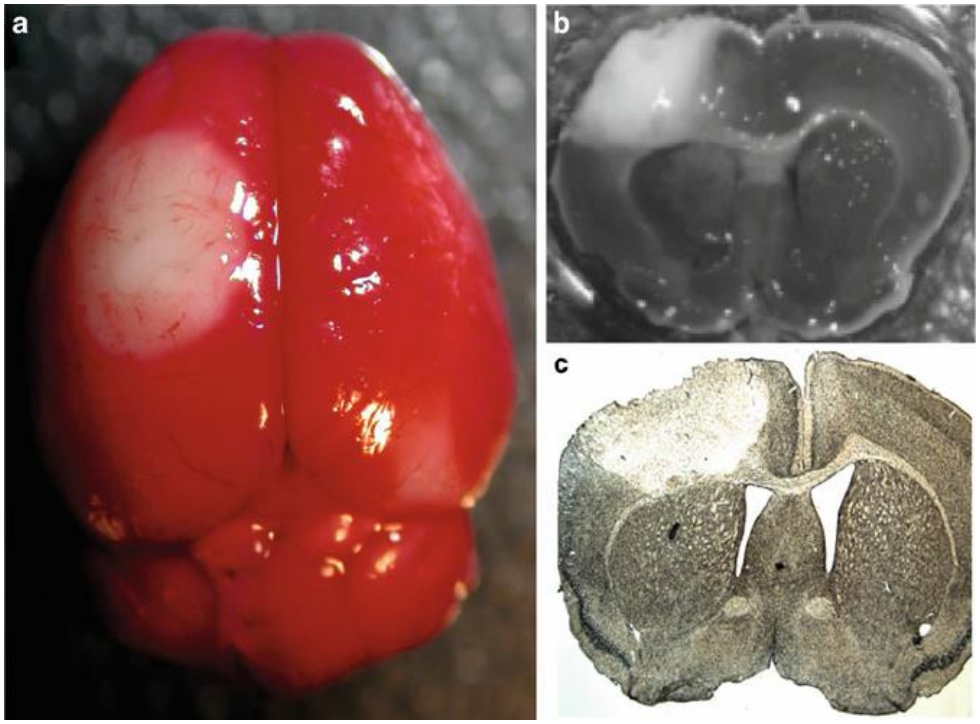
1) Are brain networks redundant (several options for same function)?
2) What happens to brain networks (fMRI) when a node is lesioned?

Controlled inactivation

1. Pharmacology
    1. Permanent (e.g.: *N*-methyl-dl-aspartic acid, phototrombic lesion)
    2. Temporary (e.g.: muscimol)
2. Cooling
3. Pharmacogenetics (DREADDS)

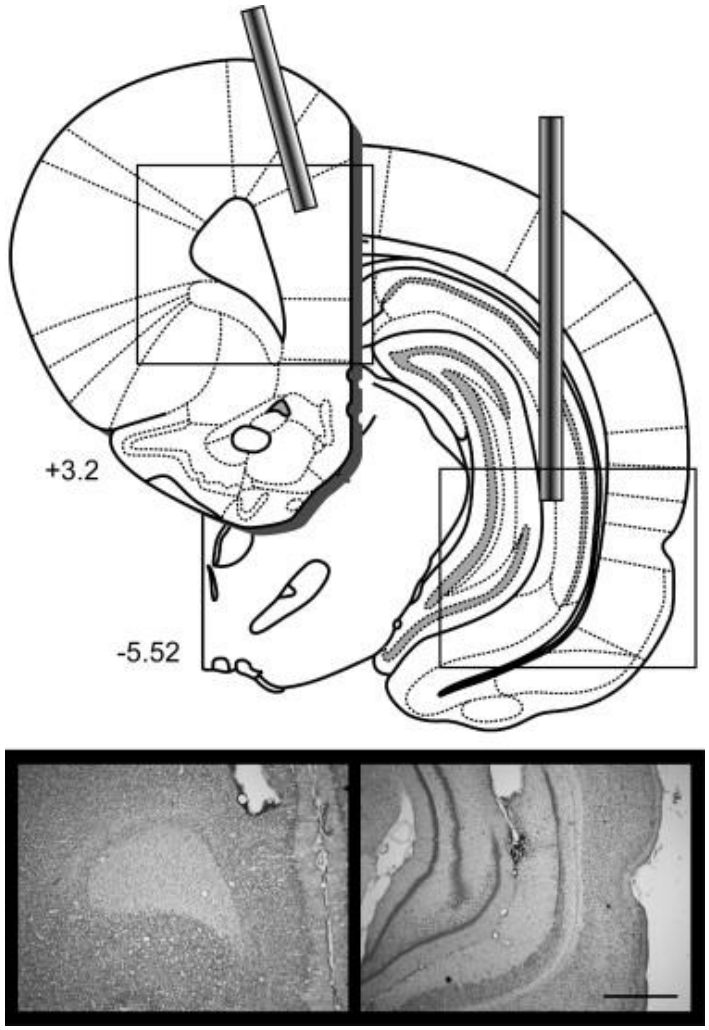
Goal: is this bran region / neuronal population “necessary”?

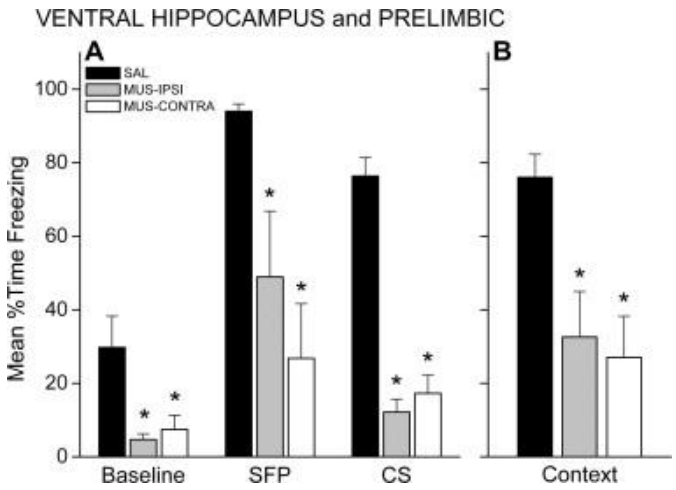
Approach:
1-2: non-selective, larger region
3: can be cell specific (Cre-loxP system)



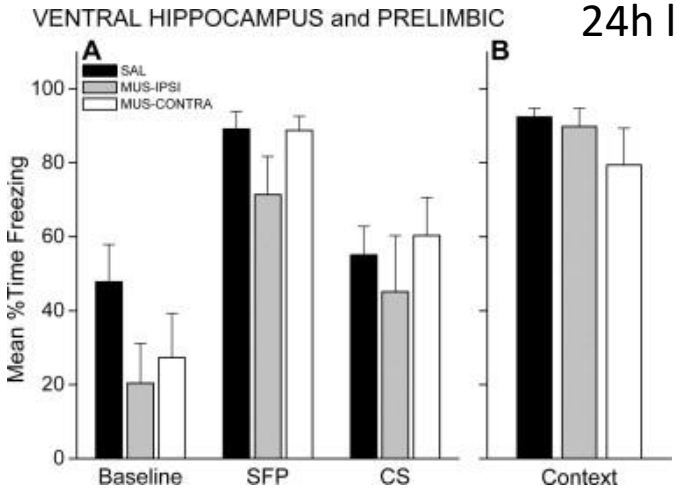
TTC (2,3,5-triphenyltetrazolium chloride) staining visualizes hypoxic brain tissue

Altering behavior via temporary inactivation of brain regions



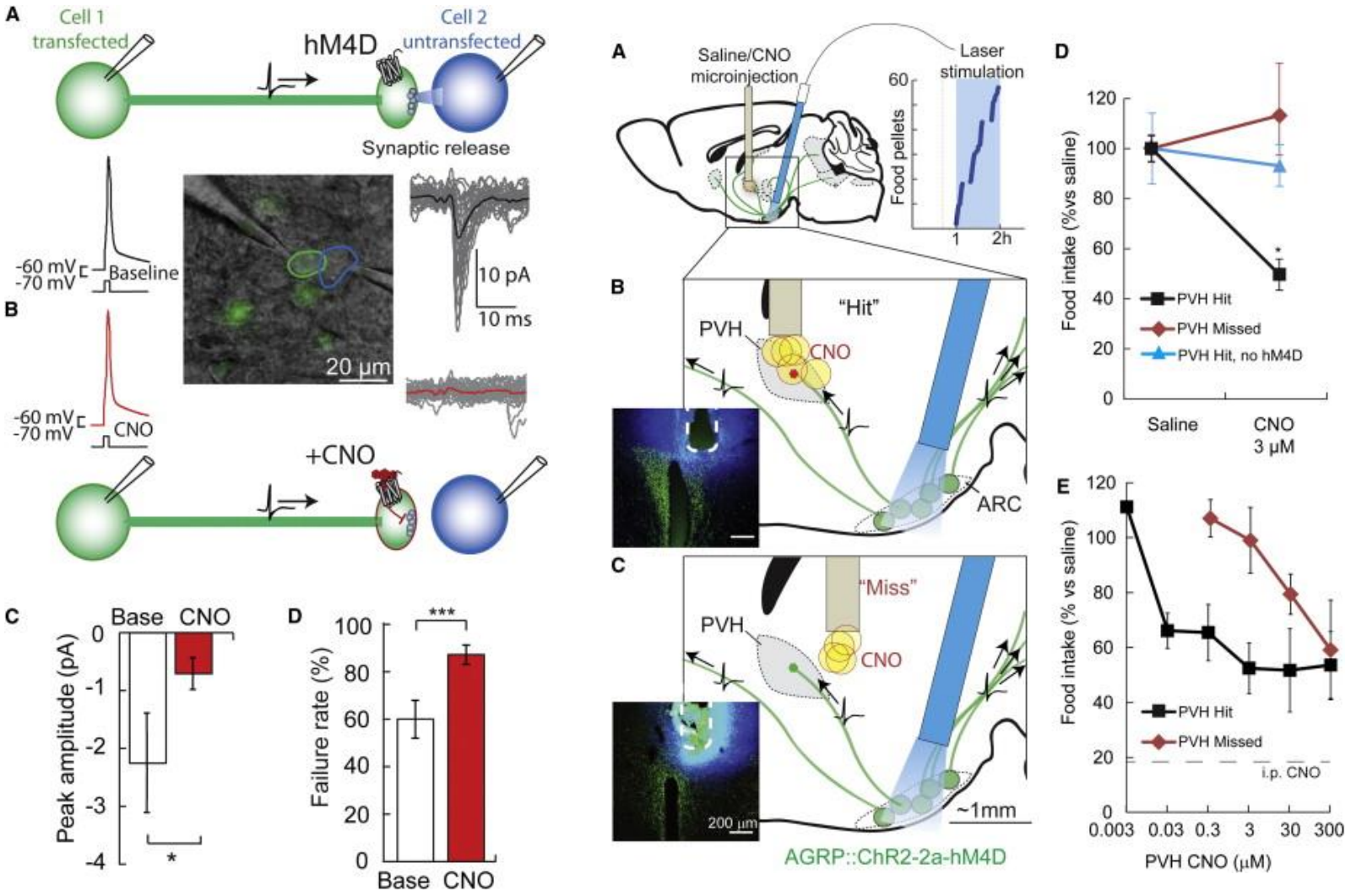


24h later



Trace and contextual fear conditioning are impaired following unilateral microinjection of muscimol in the ventral hippocampus or amygdala, but not the medial prefrontal cortex. Gilmartin et al., 2012

Inactivating specific synapses with DREADDs



Chemogenetic Synaptic Silencing of Neural Circuits Localizes a Hypothalamus→Midbrain Pathway for Feeding Behavior. Stachinak et al., Neuron 2015

Controlled activation of neurons

1. TMS
2. Electrical stimulation
    1. Peripheral (e.g: driving a cockroach)
    2. Central stimulation of brain regions
        1. During surgery
        2. Parkinson's treatment (DBS)
3. Pharmacogenetics (DREADDS)

Goal: is this bran region / neuronal population “sufficient”?

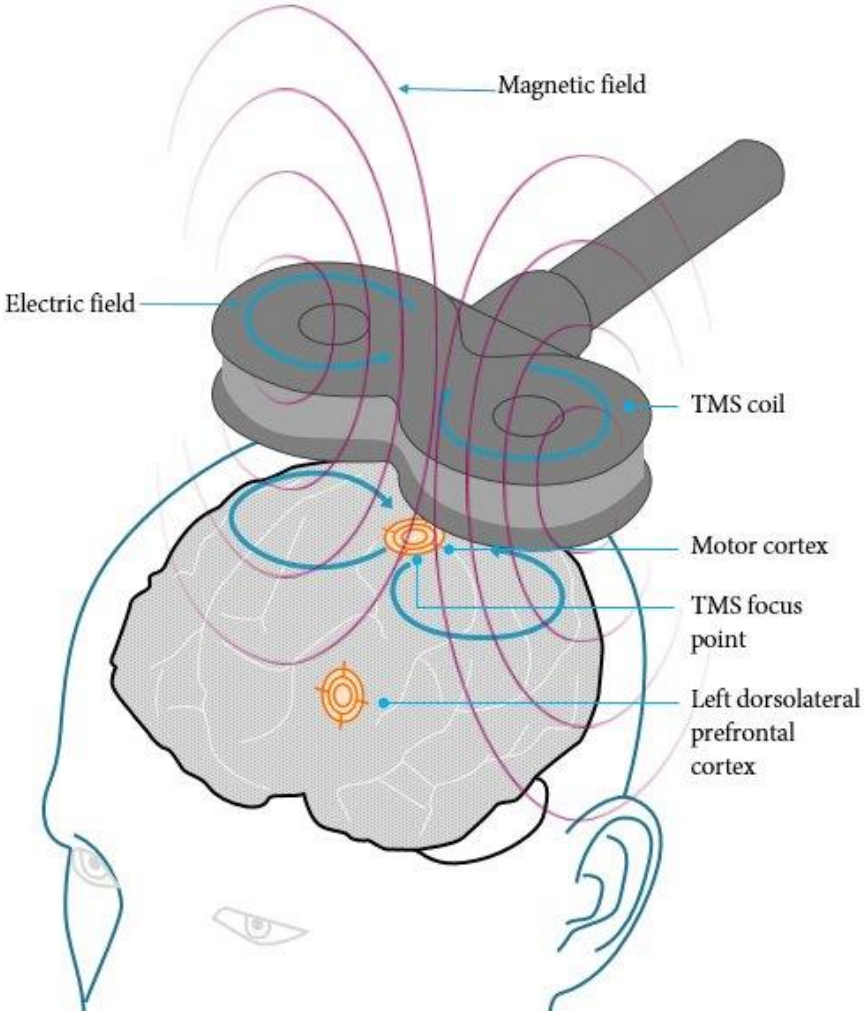
Approach:
1: can be reasonably constrained with small electrodes or in specific brain regions (nuclei)
2: can be cell specific (Cre-loxP system)

Transcranial magnetic stimulation

Non-invasive (can be used in humans)
Changing magnetic field generates electrical current via electromagnetic induction
Has diagnostic and therapeutic potential, but may cause seizures and fainting.
Causes severe physical discomfort.

"Some of the studies have shown promising but not conclusive evidence for the efficacy of TMS in depression. But TMS has not been shown to be effective in the treatment of obsessive compulsive disorder, posttraumatic disorder, or schizophrenia. The patient sample size has been a cause of concern in most studies."

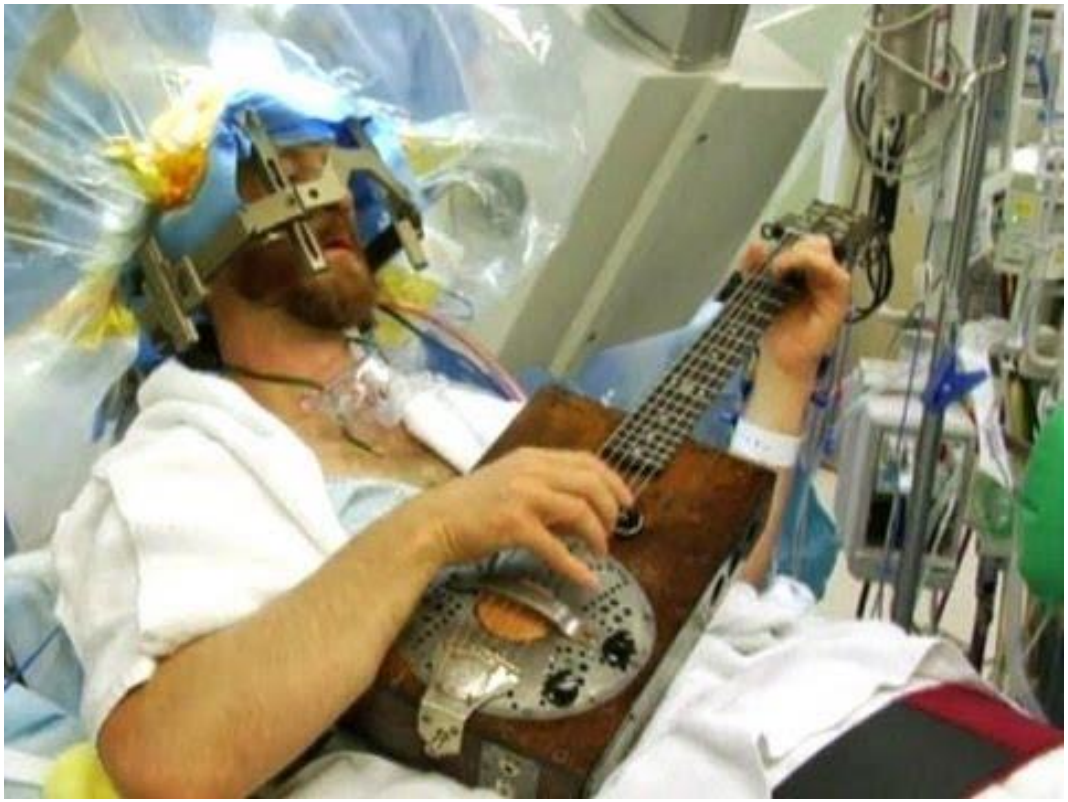
Basil et al 2005.



Electrical brain stimulation

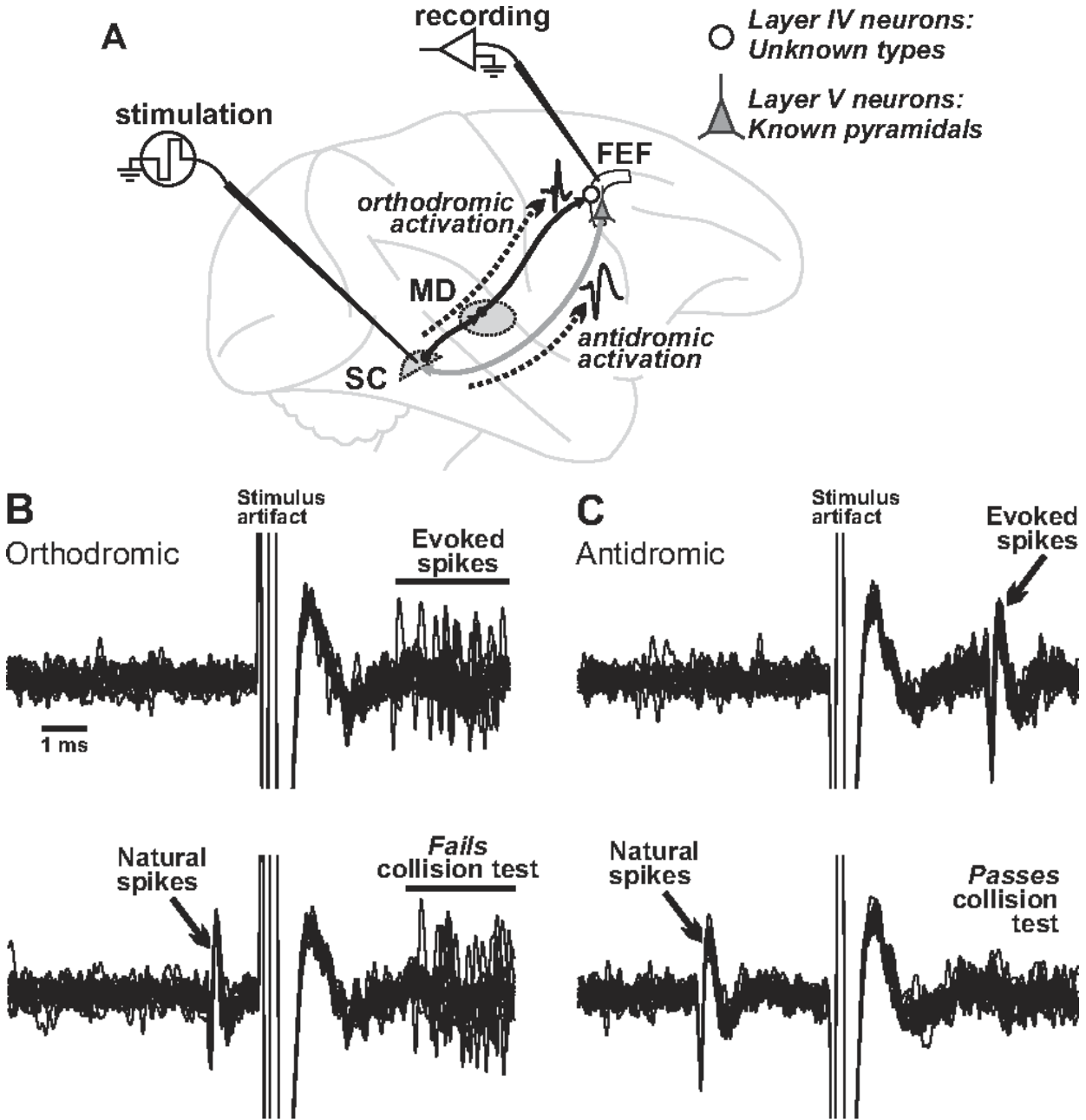
Electrical discharges delivered to defined brain areas in **awake** patients

Goal is to map their functional involvement in sensation and movement, or cognitive functions such as language and memory.

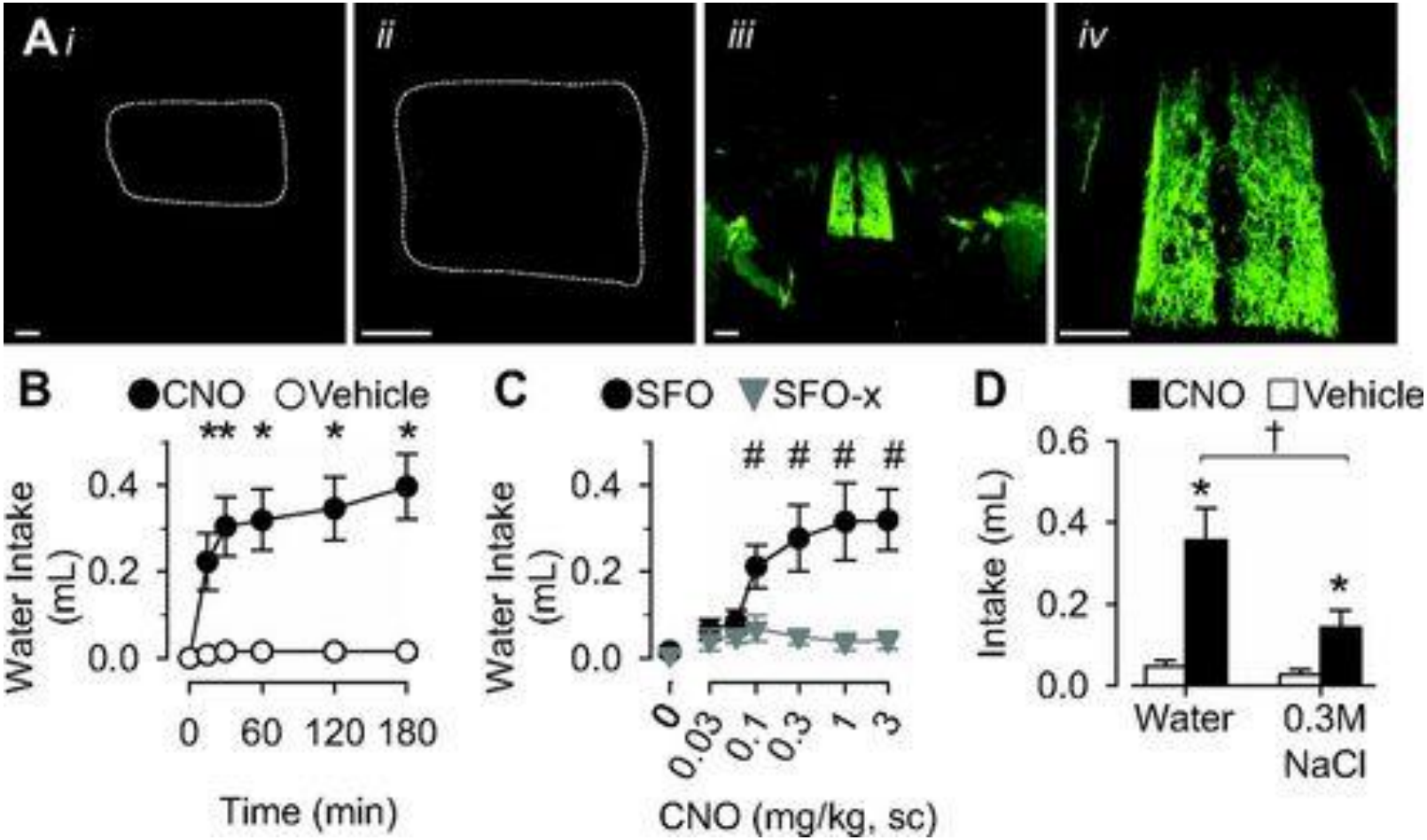


Electrical stimulation of the human brain: perceptual and behavioral phenomena reported in the old and new literature. J Parvizi 2010

Electrical activation: antidromic identification of neuronal projections



DREADD activation increases water and salt consumption



DREADD-induced activation of subfornical organ neurons stimulates thirst and salt appetite. Nation et al. 2016

In any inactivation experiment, what we really study is how the rest of the brain compensates for the loss of a functional part of the nervous system