# Ketamine, brain wide recording and the neurobiology of dissociation

**Isaac Kauvar**
**Stanford University**


Egon Schiele, 1912
Self-Portrait with Physalis


Egon Schiele, 1912
Self-Portrait with Physalis


Egon Schiele, 1912
Self-Portrait with Physalis

Egon Schiele, 1915
Double self portrait

# Dissociation

**A conscious state where normally-integrated cognitive processes selectively uncouple.**

e.g. sensory stimuli disconnect from affective response

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**Example manifestations**

**Depersonalization** (e.g., the feeling that one's own body does not belong to oneself)

# Dissociation

**A conscious state where normally-integrated cognitive processes selectively uncouple.**

e.g. sensory stimuli disconnect from affective response

**Example manifestations**

**Depersonalization** (e.g., the feeling that one's own body does not belong to oneself)

**Derealization** (e.g., the feeling as if other people, objects, and the world are not real)

# The experience of dissociation

What Does Dissociation Feel Like?

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"What it feels like for me to dissociate is, **if my mind is a car, I'm in the passenger seat, looking at myself driving…**"

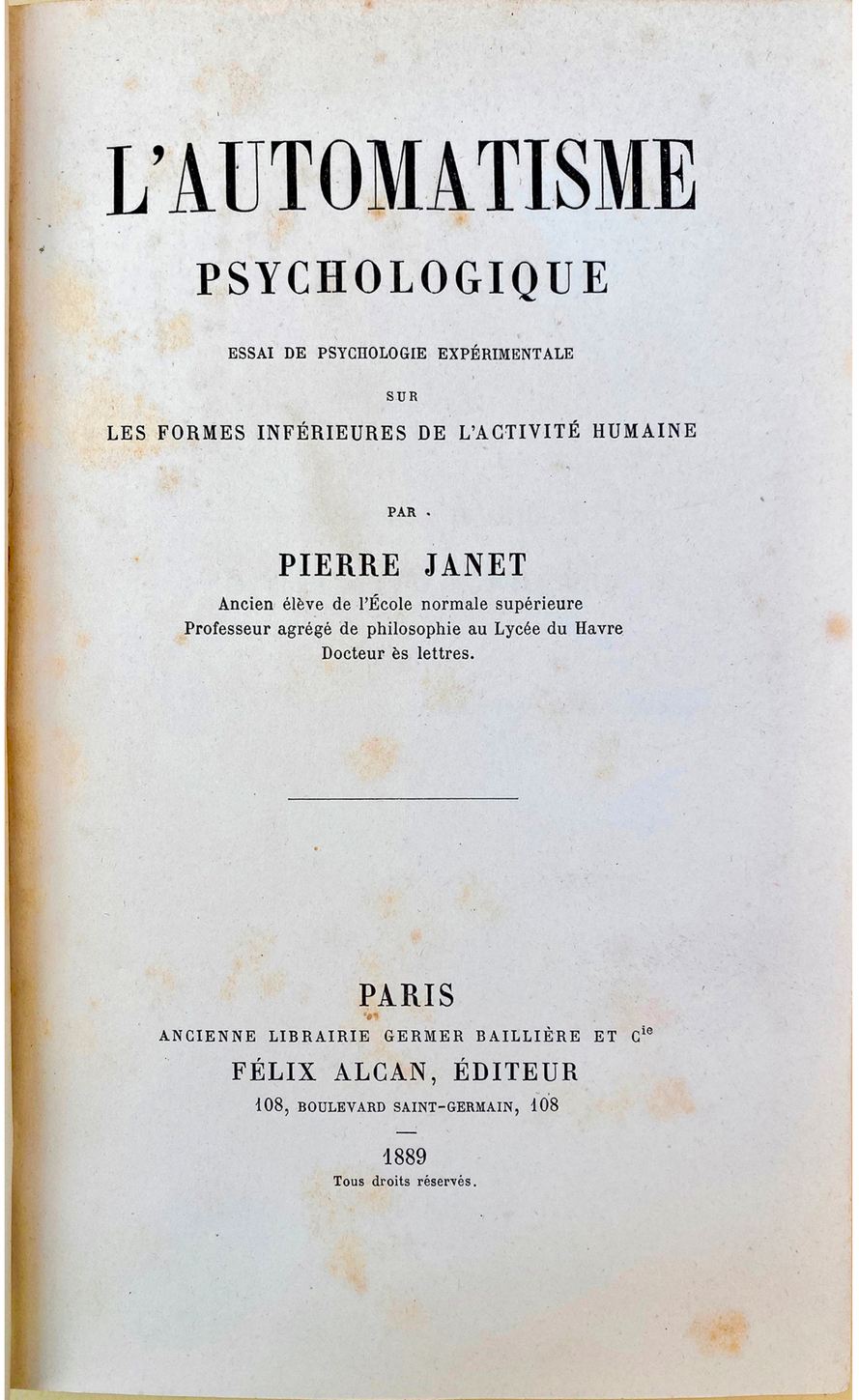
# Example causes of dissociation

**Trauma**

**Epilepsy**

**Dissociative drugs**

# Dissociation has been mysterious for a long time



L'AUTOMATISME
PSYCHOLOGIQUE

ESSAI DE PSYCHOLOGIE EXPÉRIMENTALE
SUR
LES FORMES INFÉRIEURES DE L'ACTIVITÉ HUMAINE

PAR

PIERRE JANET

Ancien élève de l'École normale supérieure
Professeur agrégé de philosophie au Lycée du Havre
Docteur ès lettres.

PARIS
ANCIENNE LIBRAIRIE GERMER BAILLIÈRE ET Cie
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1889

# Open question

**What are neural mechanisms underlying dissociation?**

# Example causes of dissociation

**Trauma**

**Epilepsy**

**Dissociative drugs**

# Example causes of dissociation

**Trauma**

**Epilepsy**

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# Open question

**What are neural mechanisms underlying dissociation?**

**How does a dissociative drug alter neural activity?**

# Open question

**What are neural mechanisms underlying dissociation?**

↓

**How does a dissociative drug alter neural activity?**

**Ketamine is a dissociative drug.**

# The experience of ketamine

"Imagine your life as a movie…if you're in the audience…**if you could watch the movie of your life** and judge every aspect of it, without any sort of emotional reaction, that's what this is like."


The Experimental Ketamine Cure for Depression

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## The experience of ketamine

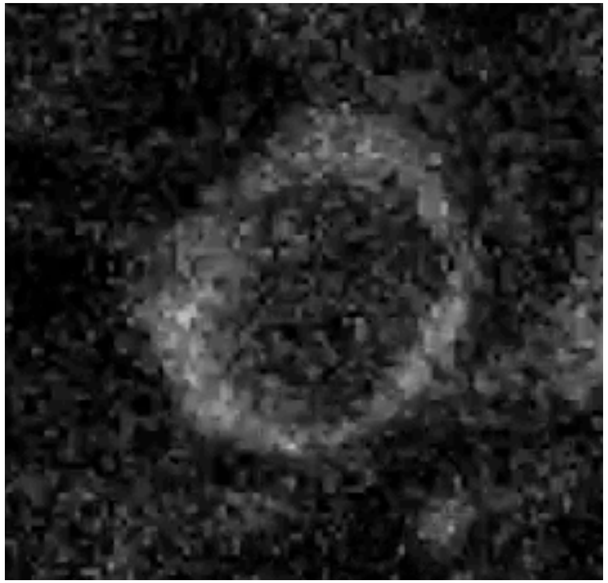
"Imagine your life as a movie…if you're in the audience…**if you could watch the movie of your life** and judge every aspect of it, without any sort of emotional reaction, that's what this is like."

## The experience of dissociation

"What it feels like for me to dissociate is, **if my mind is a car, I'm in the passenger seat, looking at myself driving…**"

# How does ketamine affect brain dynamics?

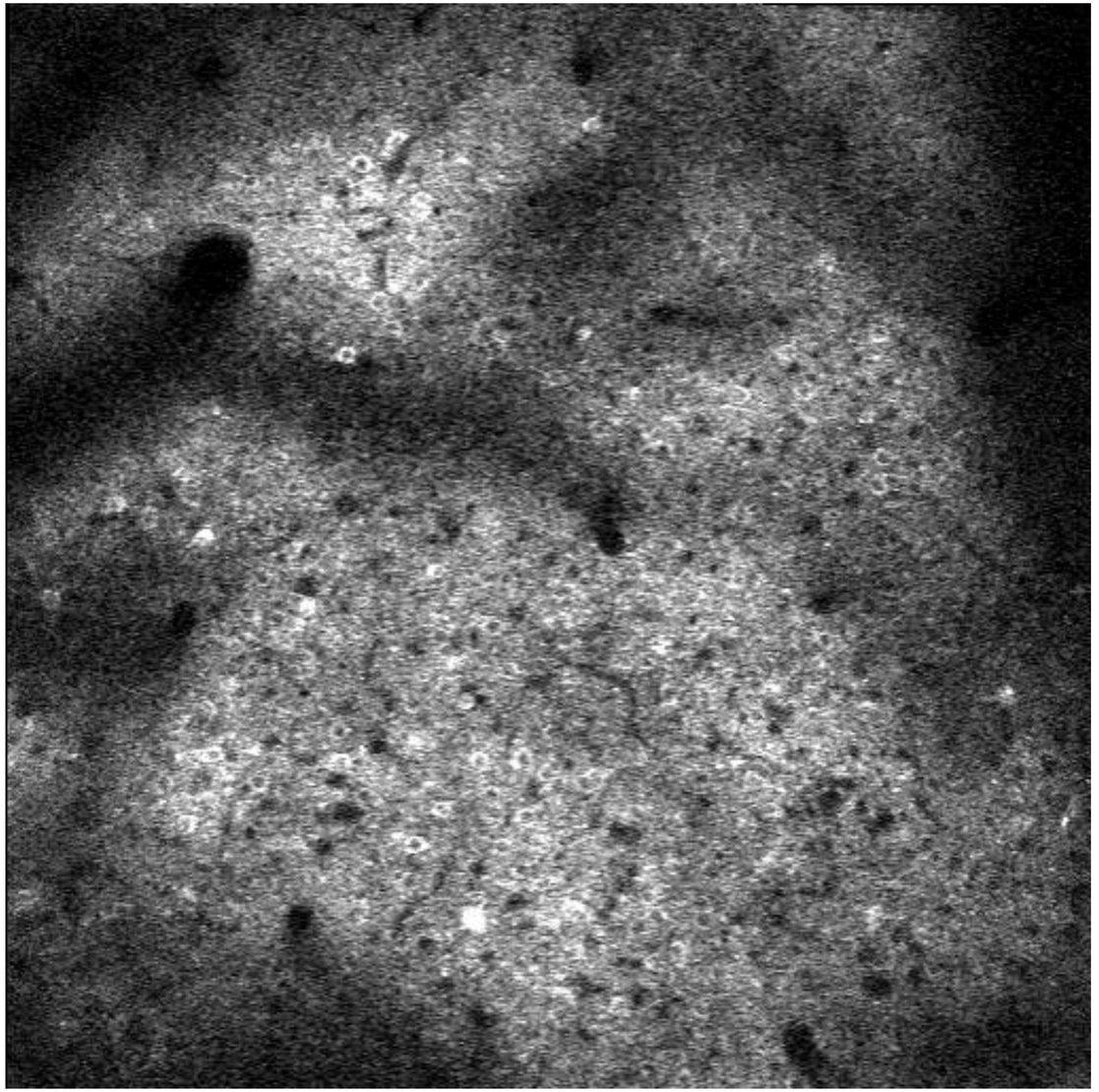
# GCaMP: A tool that allows us to *watch* neurons turn on.



0.01 mm

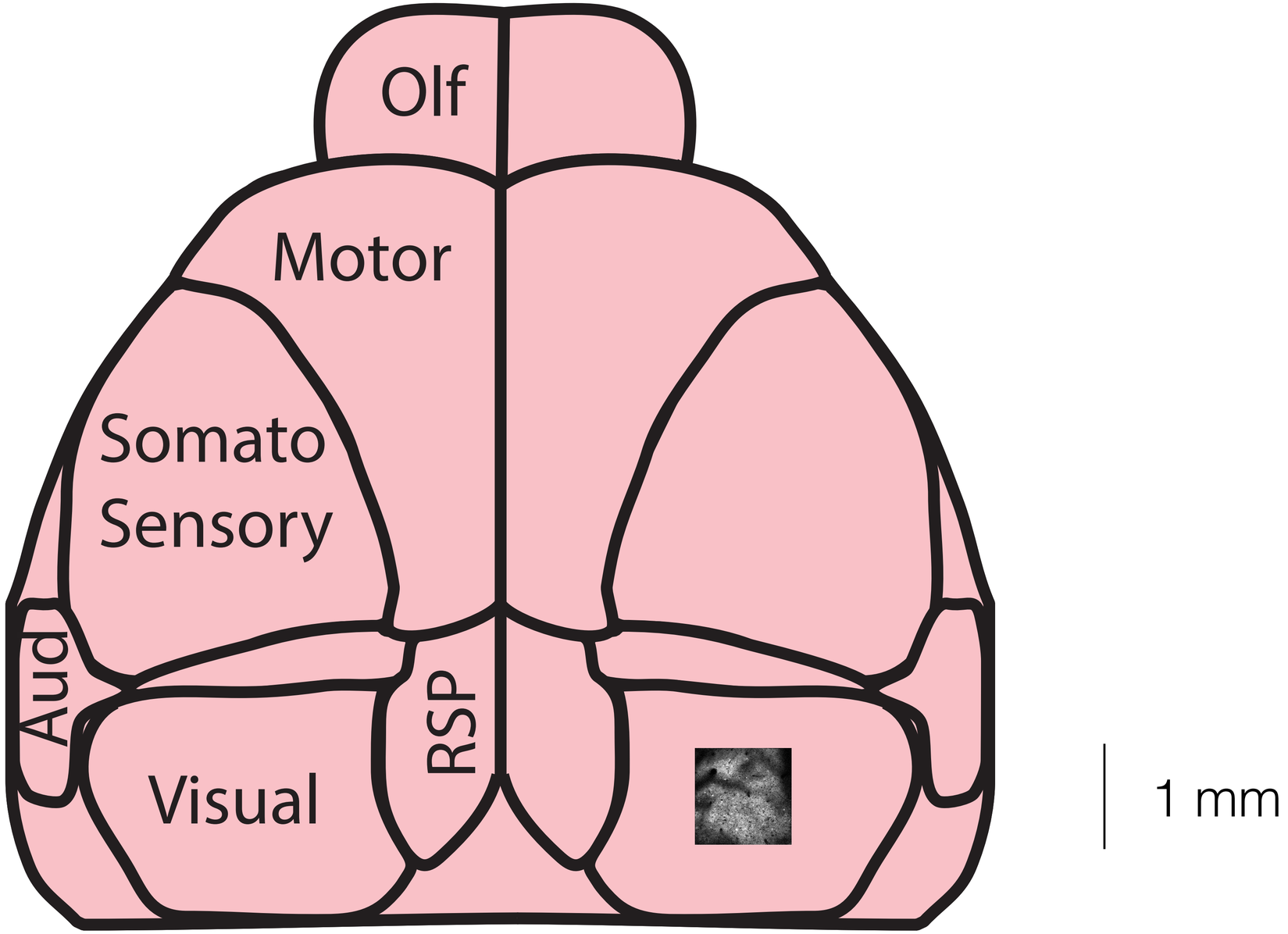
Chen, et al. 2013

# Microscopes allow us to watch hundreds of neurons turn on.

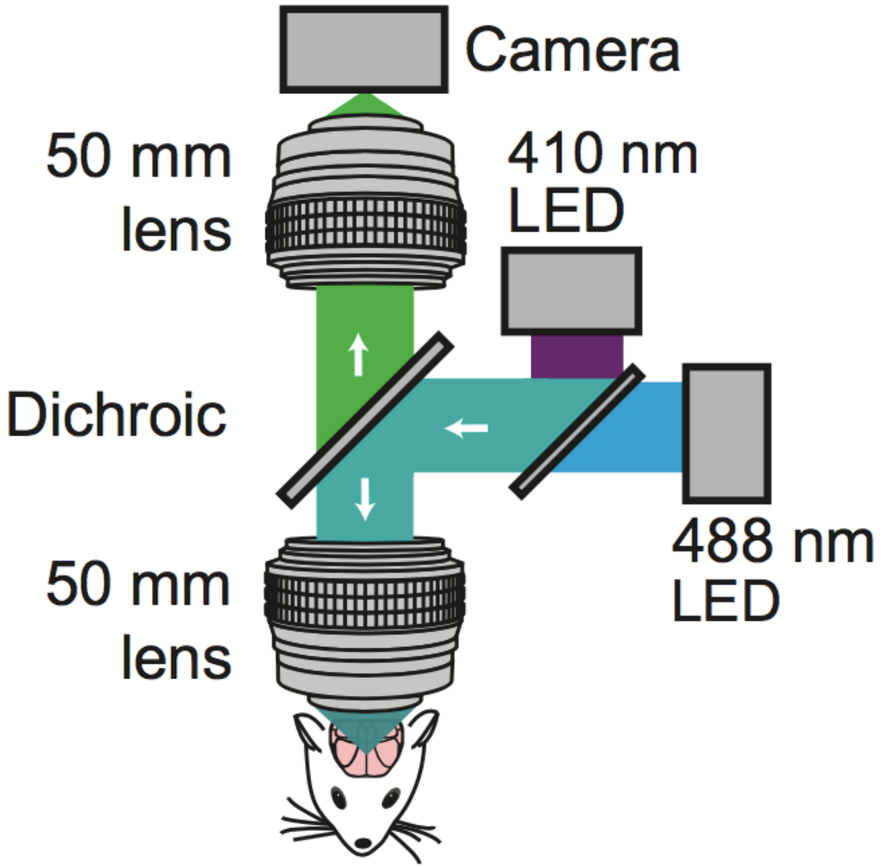


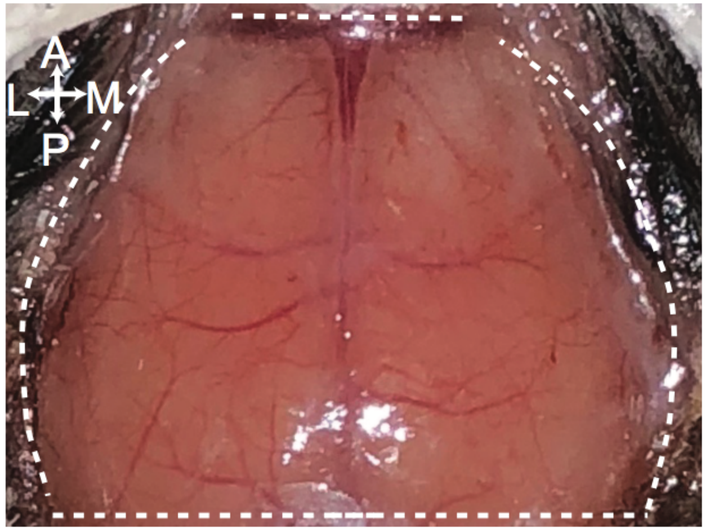
1 mm

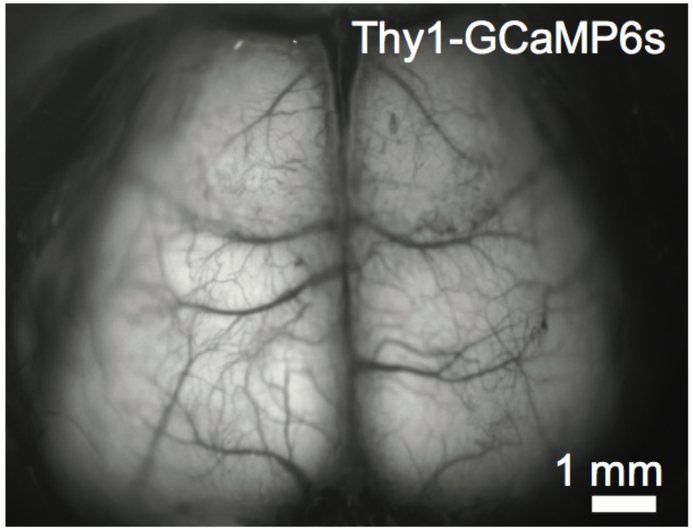
**Previous microscopes can only see small areas.**

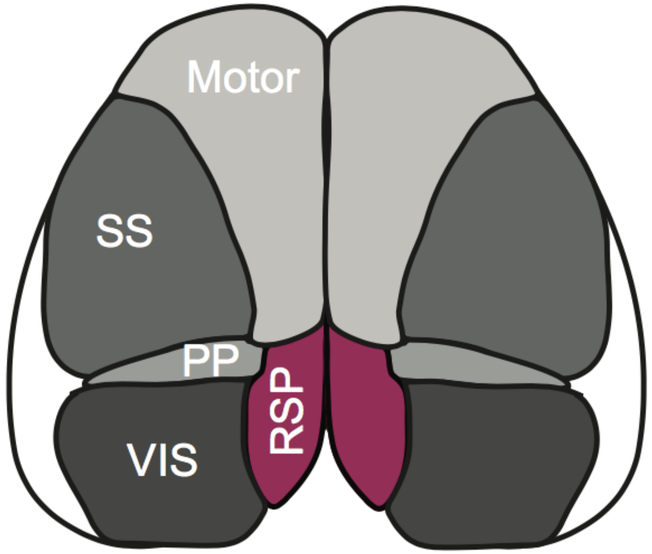


# Multiregional widefield imaging of cortex



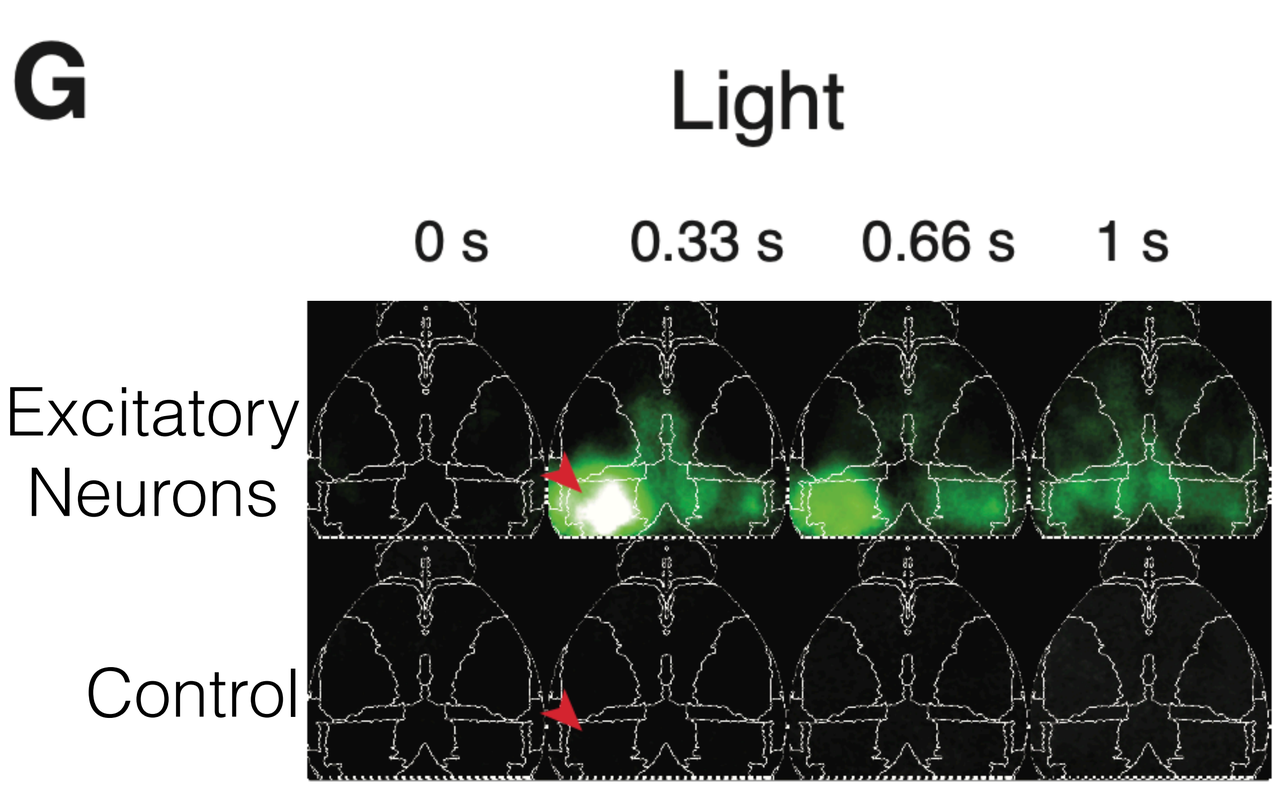



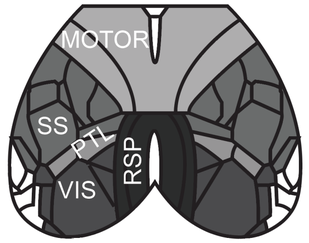



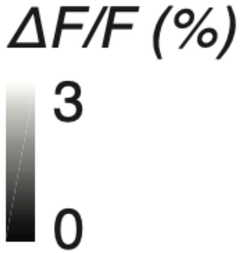



# Widefield imaging captures expected sensory signals

**G**




Allen*, Kauvar* et al., *Neuron* (2017)

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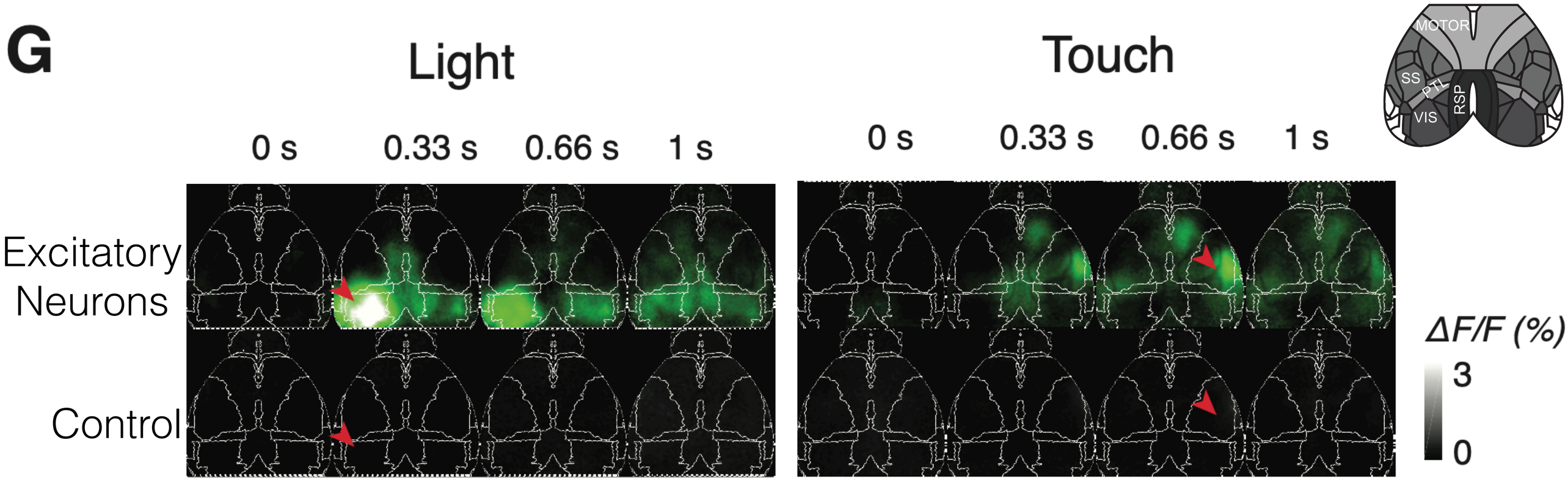
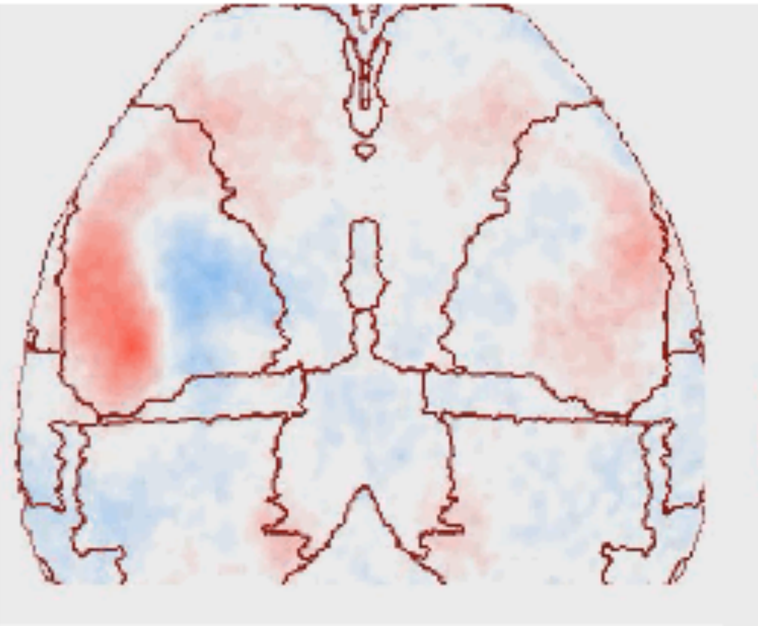


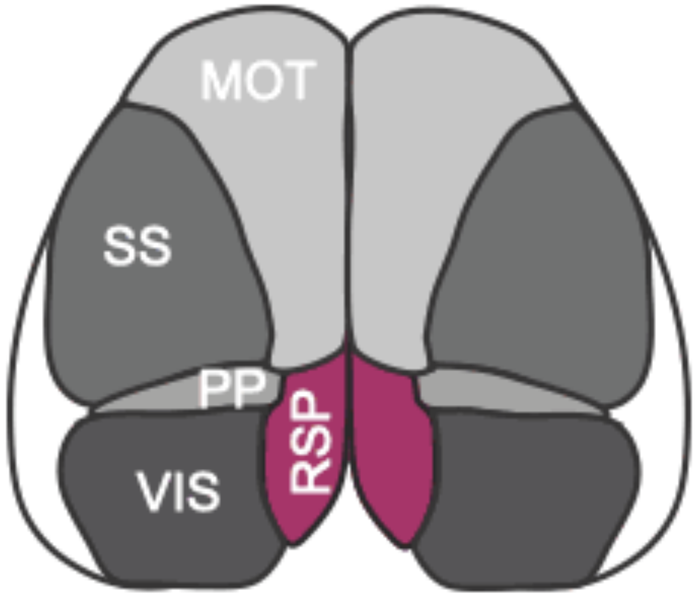

Allen*, Kauvar* et al., *Neuron* (2017)

# Multiregional widefield imaging of cortex after drug administration

Saline



Brain region map




Vesuna*, Kauvar* et al., *Nature* (2020)

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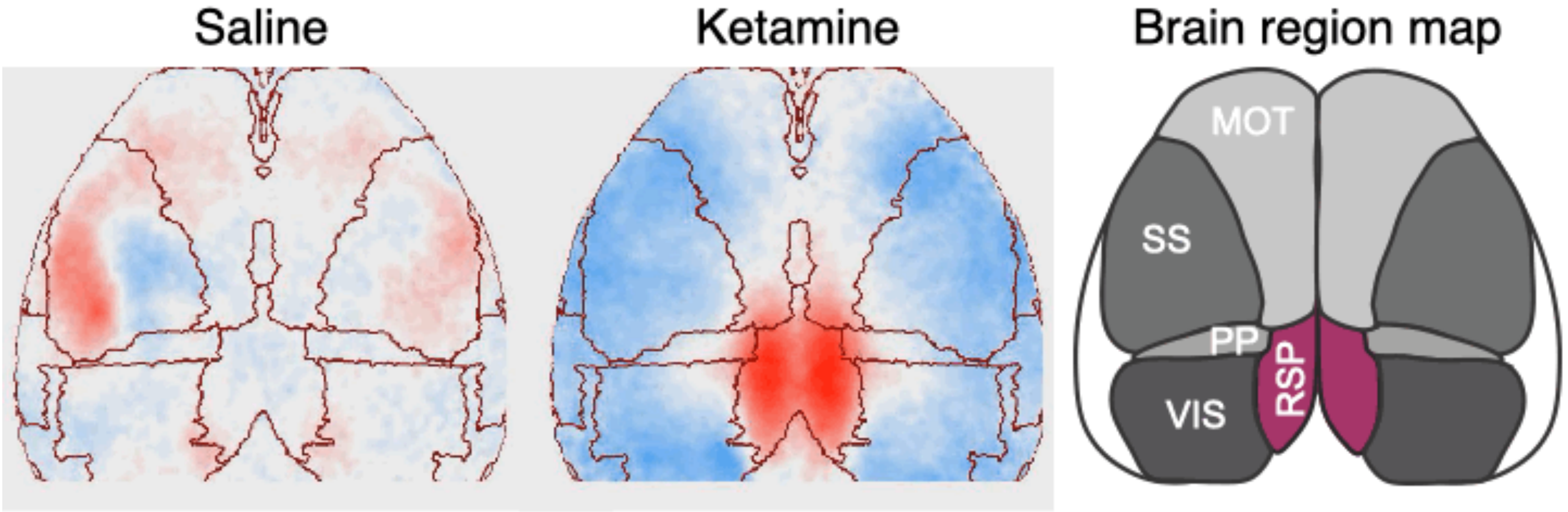
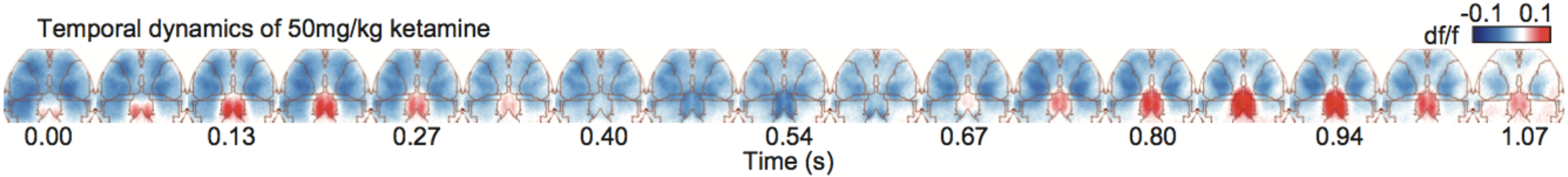



Vesuna*, Kauvar* et al., *Nature* (2020)

# Ketamine induces a retrosplenial-localized rhythm

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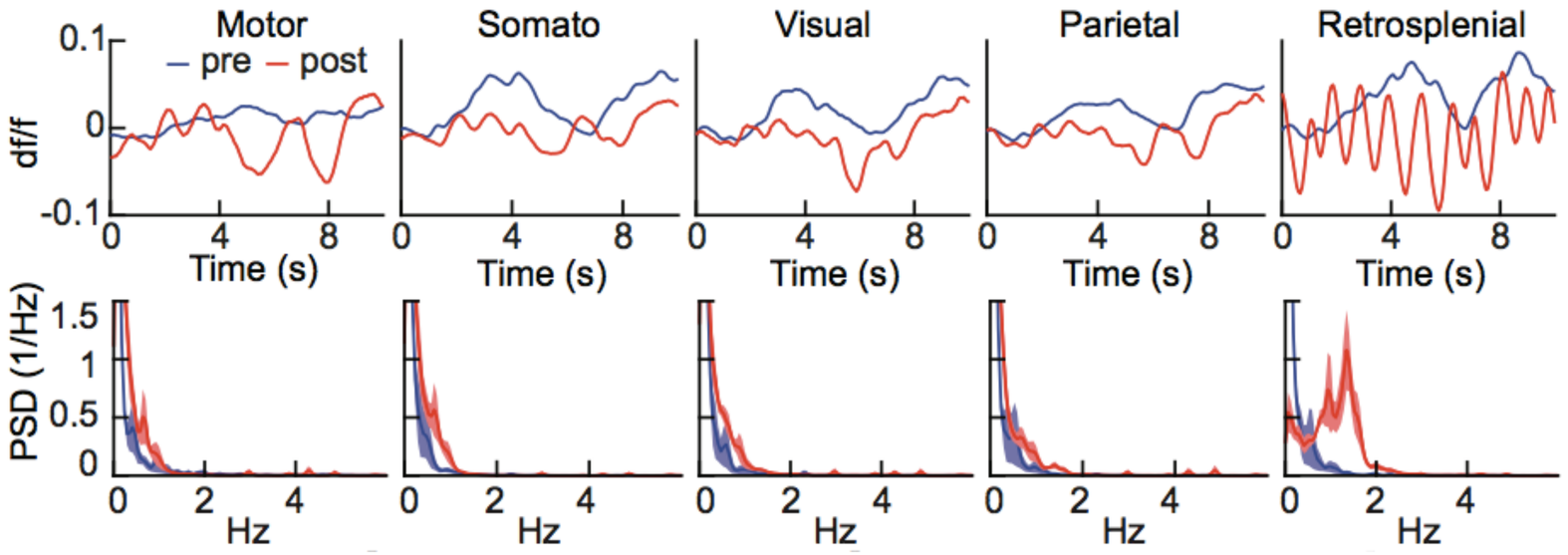

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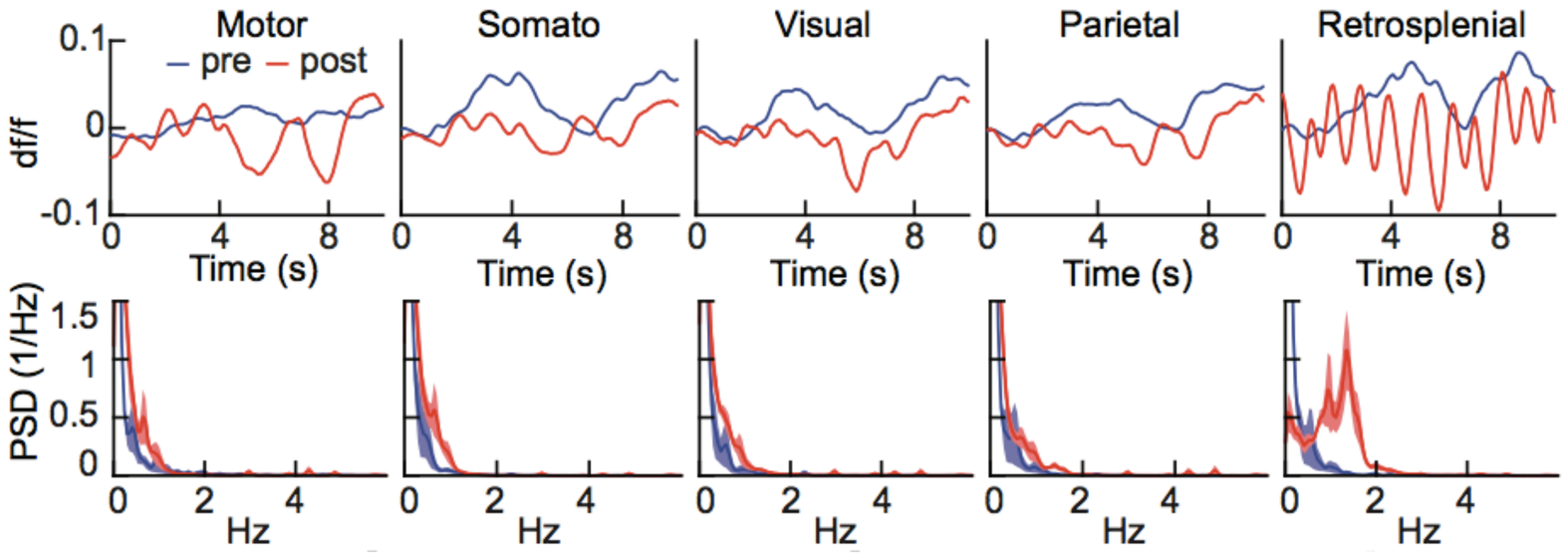
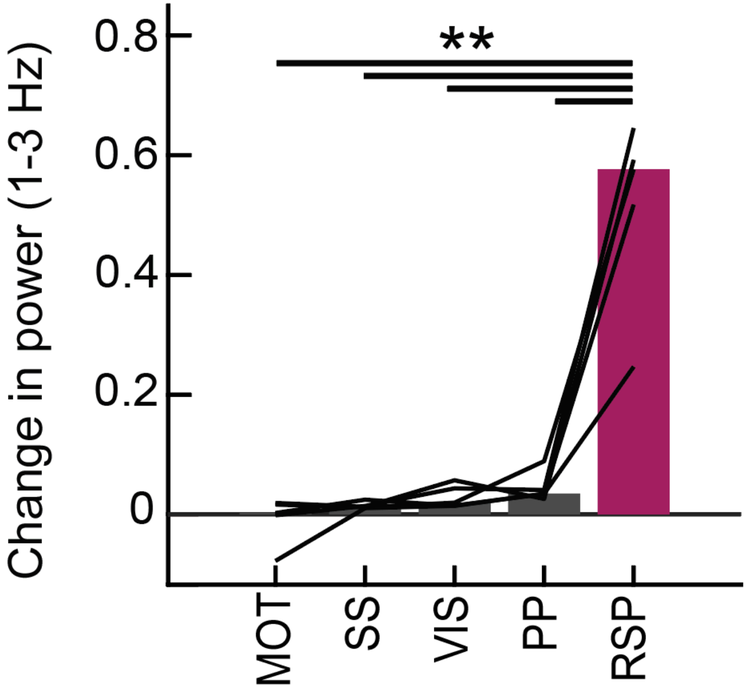
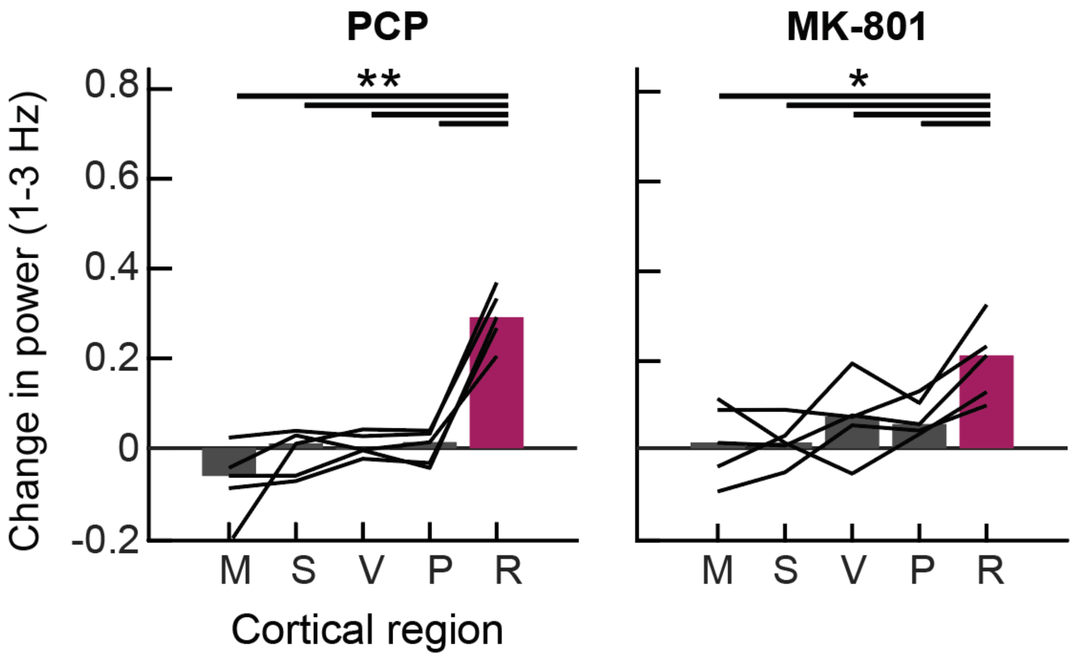


# Similar NMDA antagonists also induce a retrosplenial-localized rhythm



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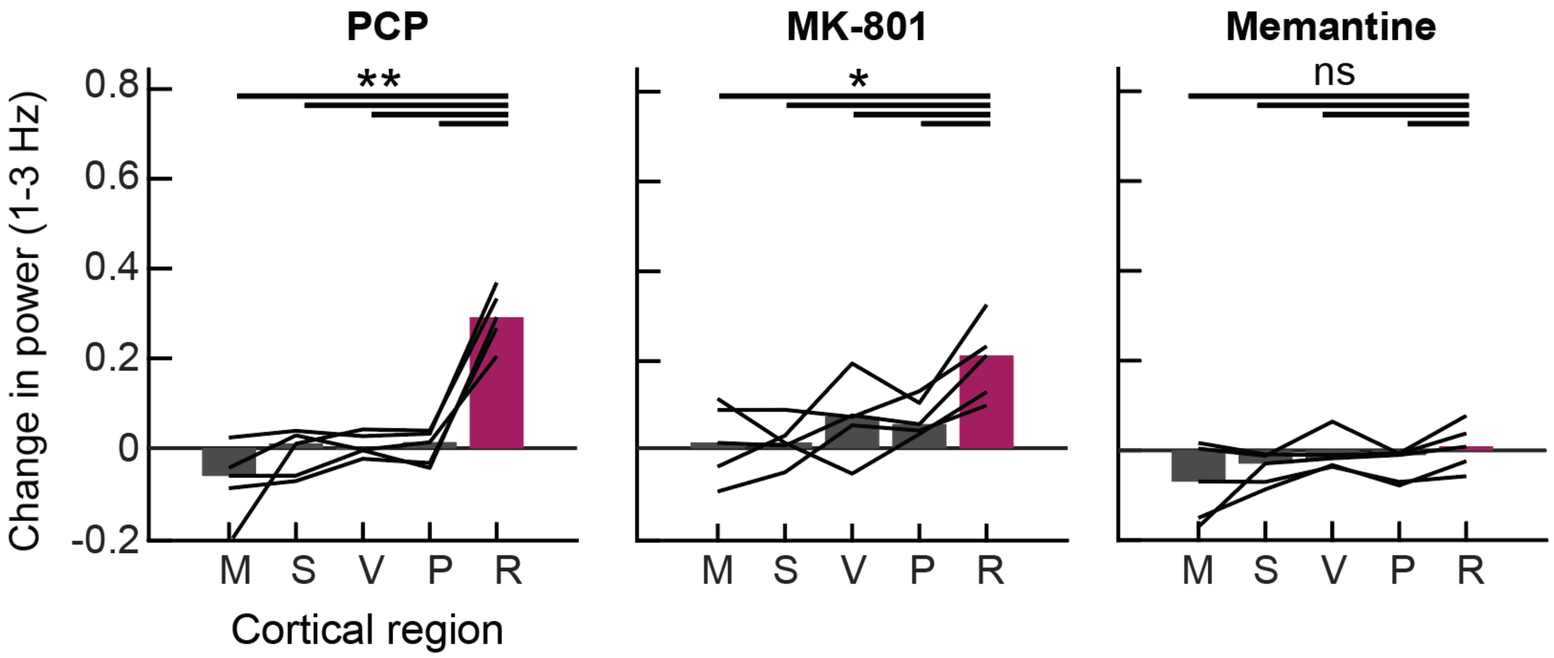

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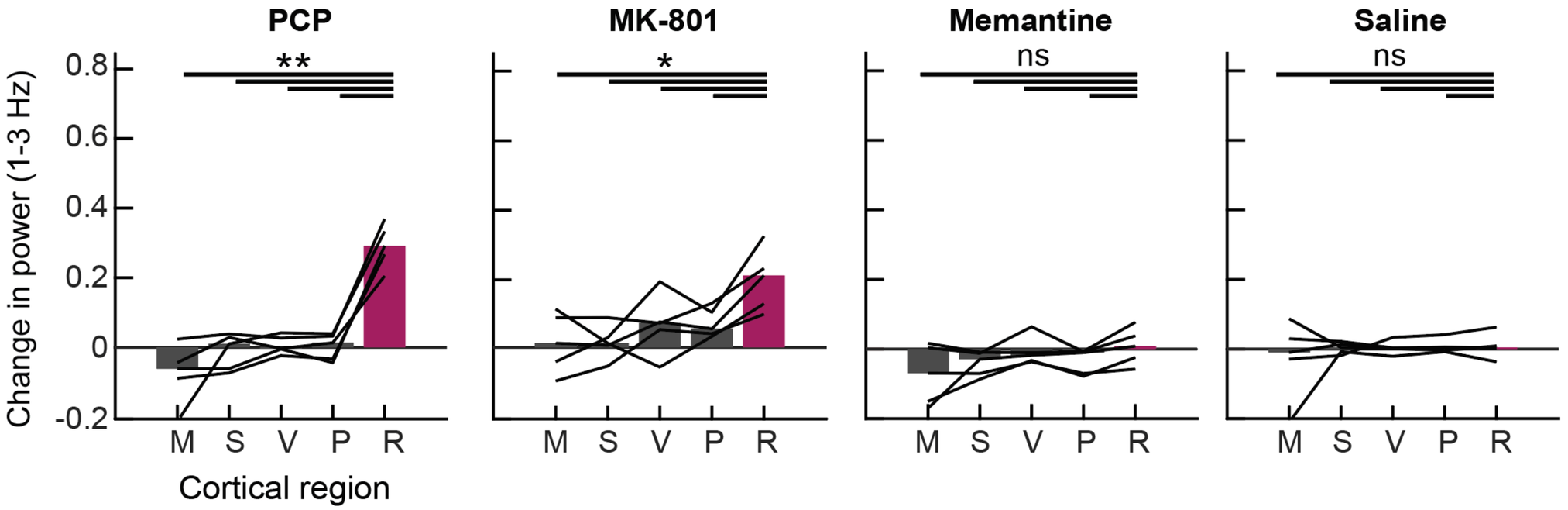

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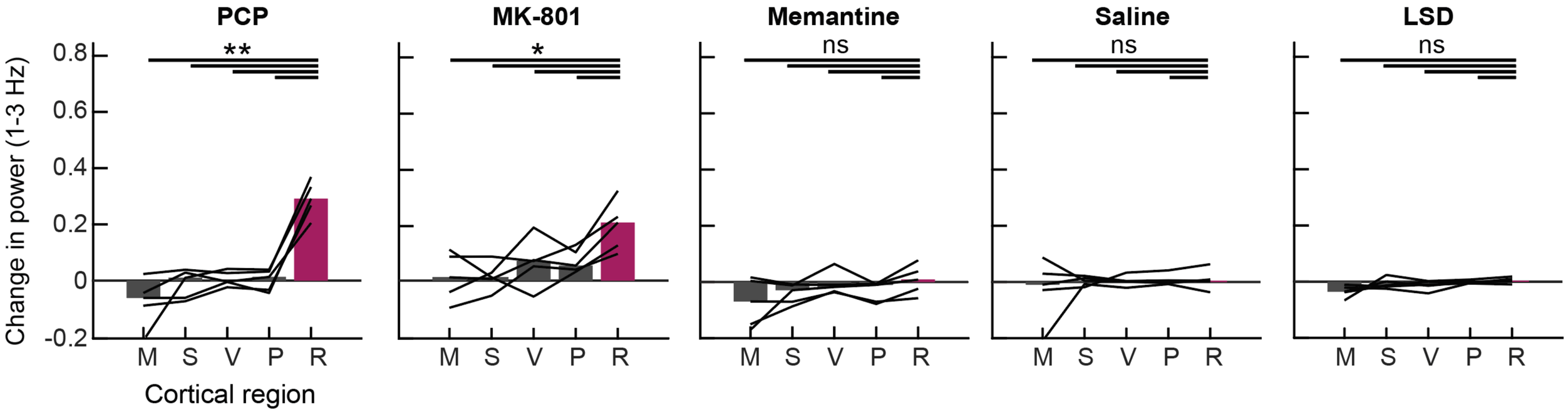
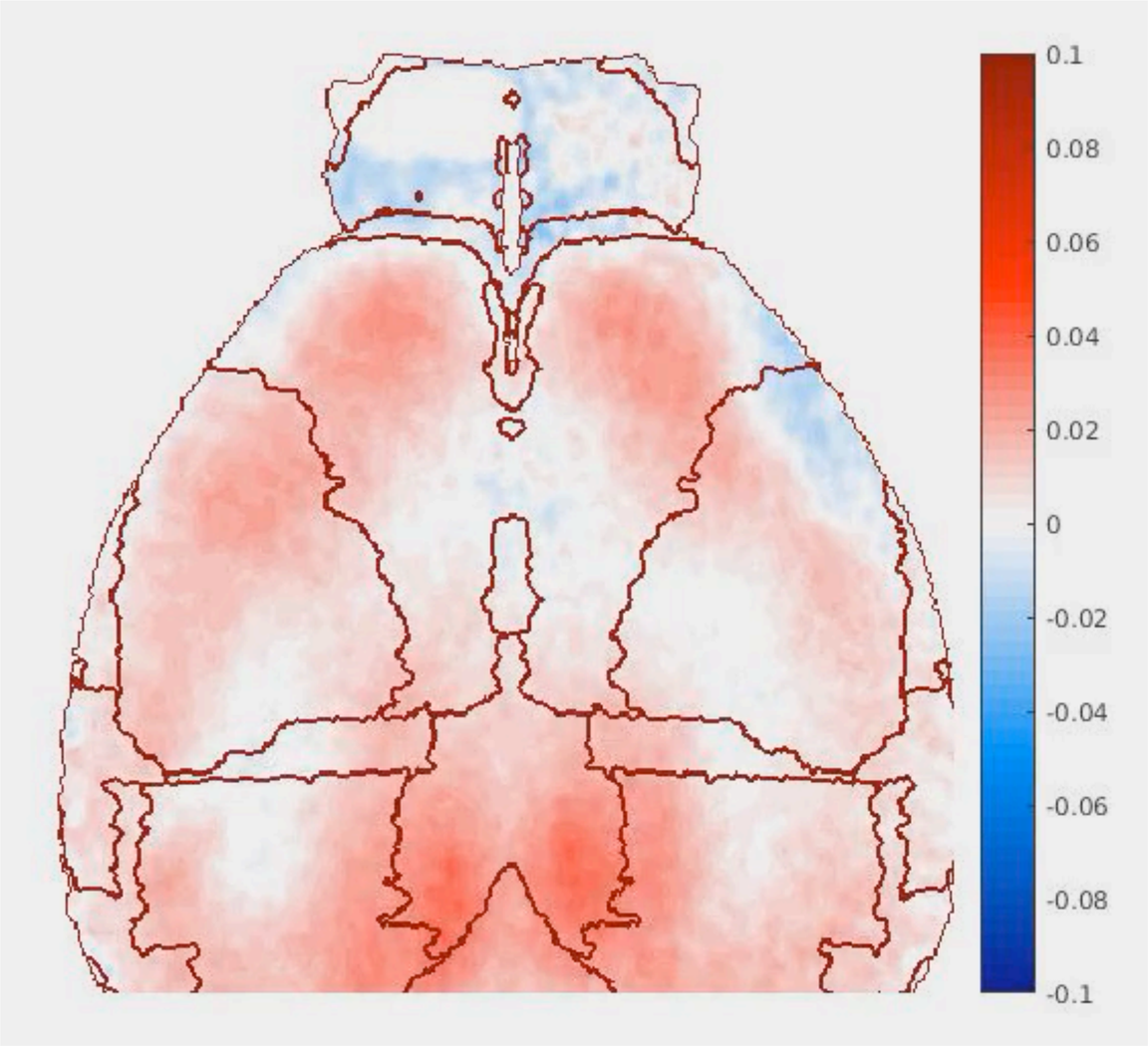


# Anesthetics do not induce a *localized* rhythm

Post-injection of anesthetic

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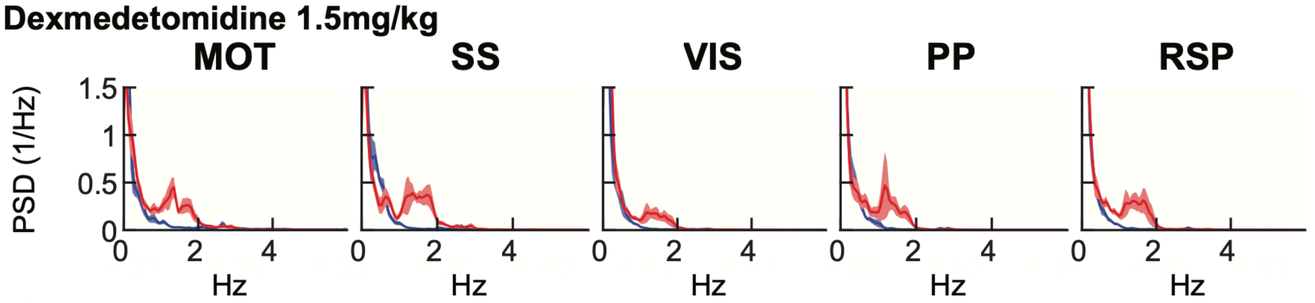
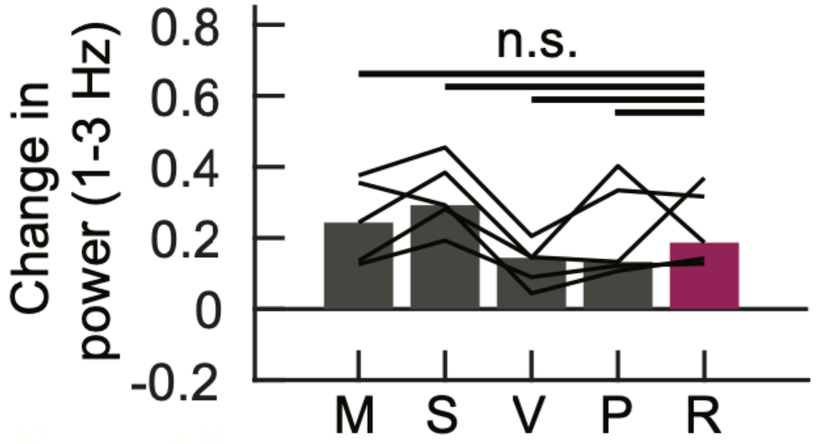
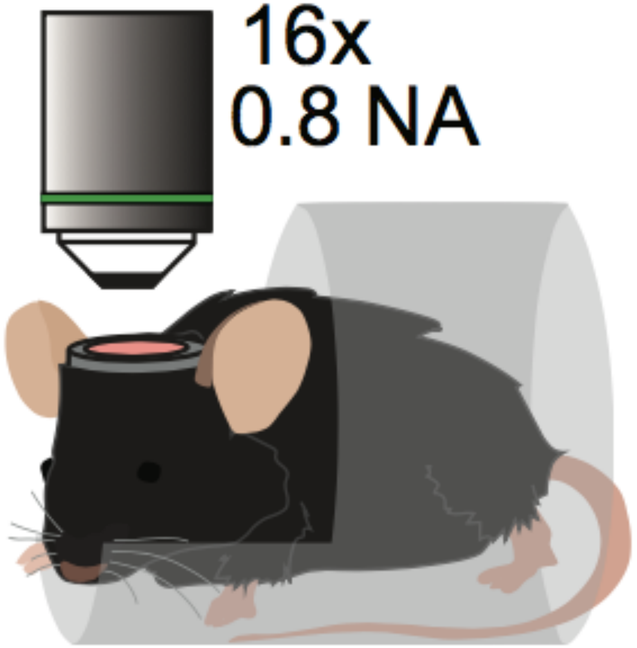
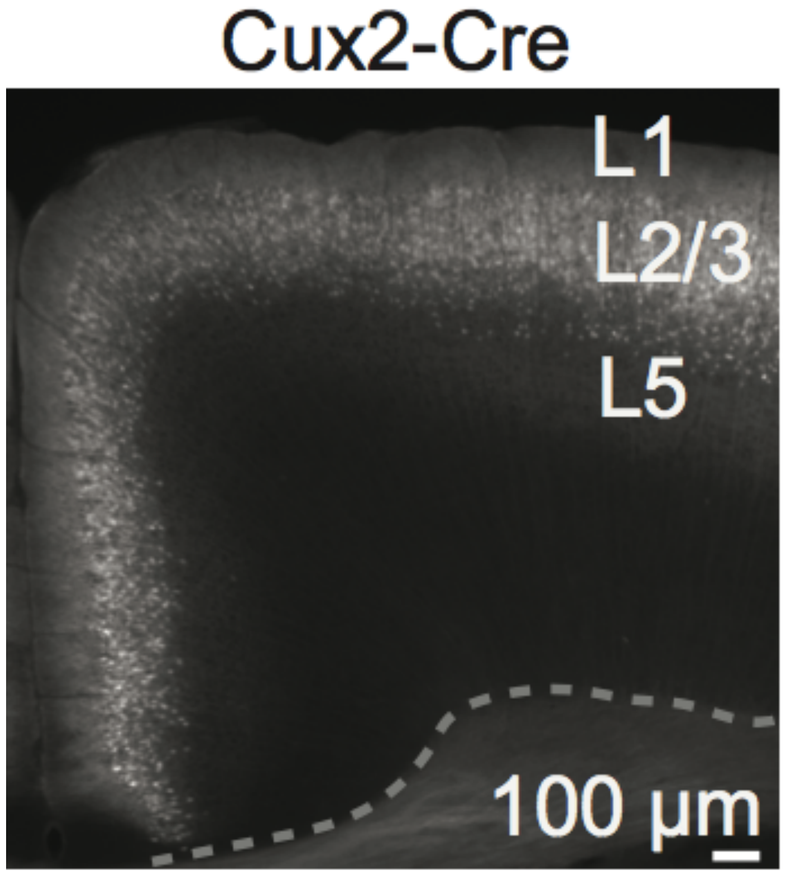
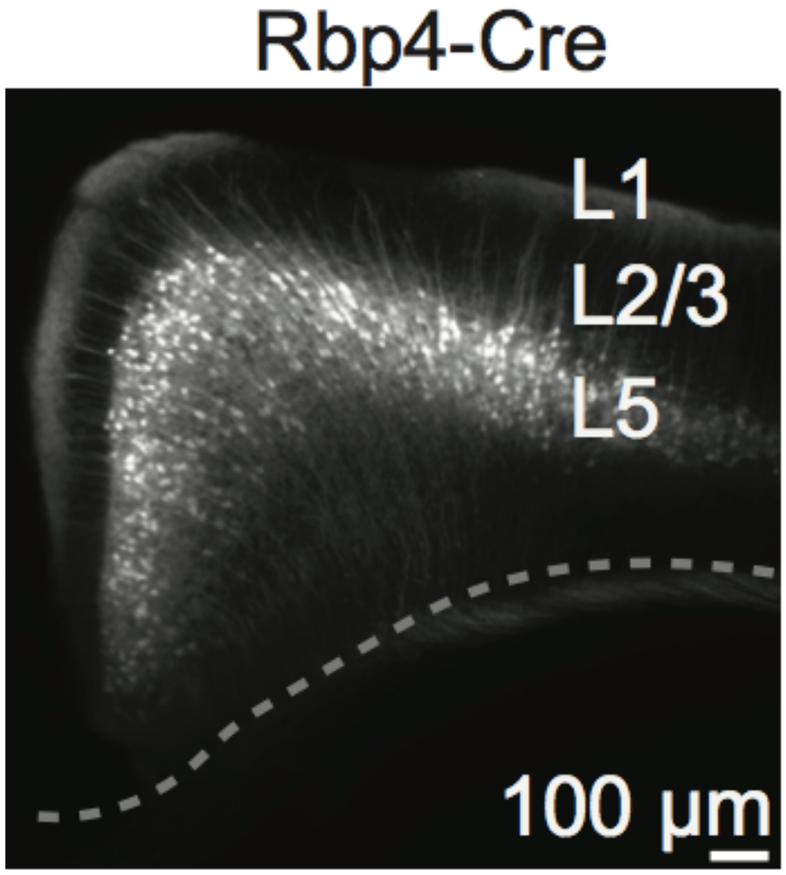


# Is there layer specificity to the ketamine-induced rhythm?

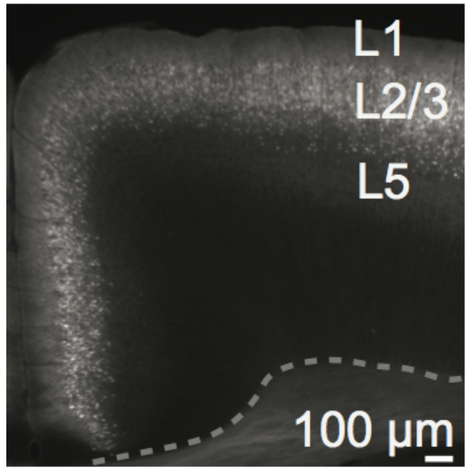


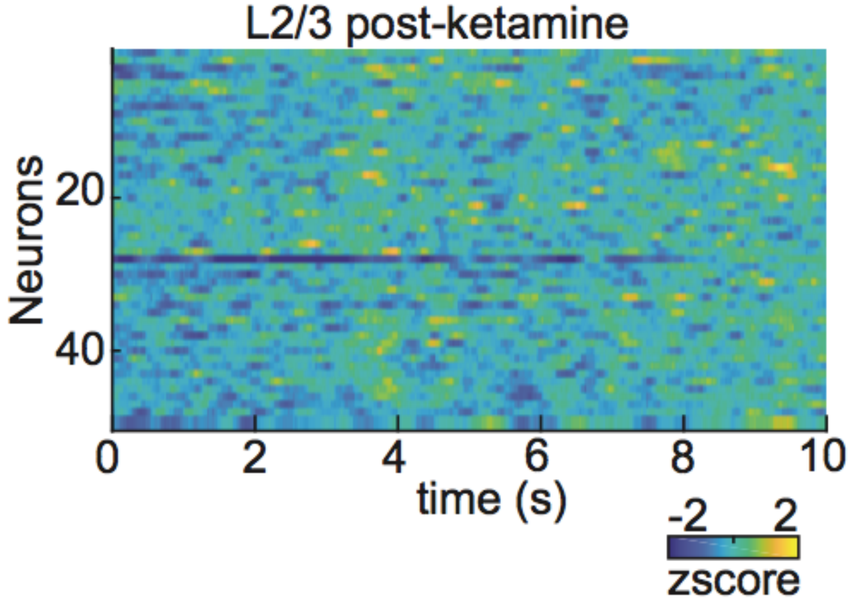



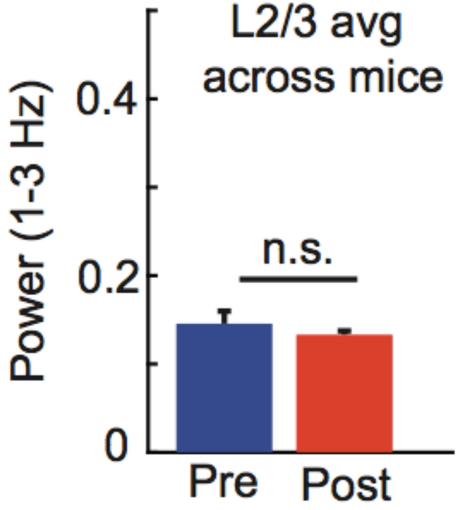



# Ketamine induced oscillation is restricted to layer 5

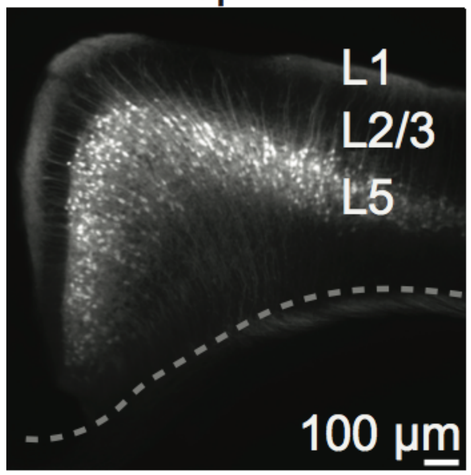
Cux2-Cre

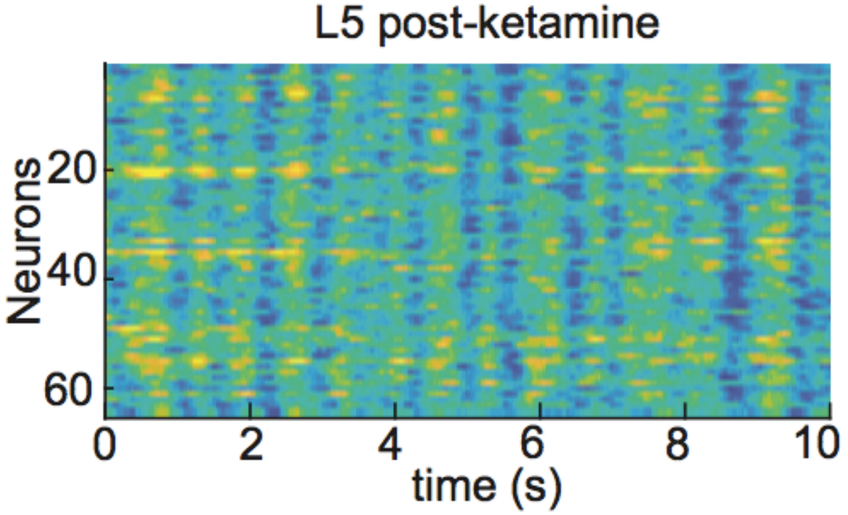


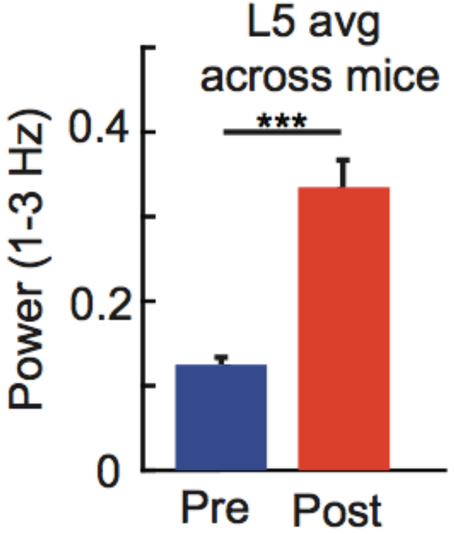




Rbp4-Cre

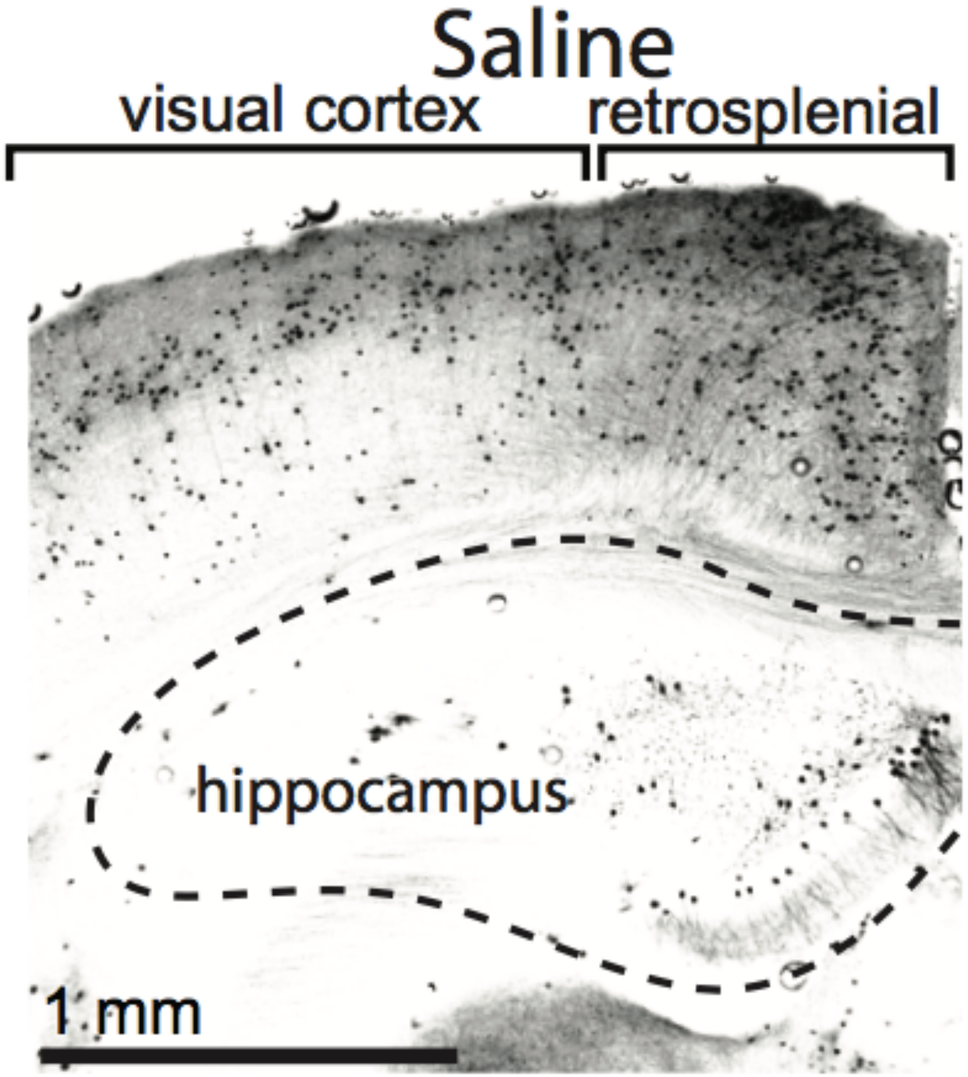


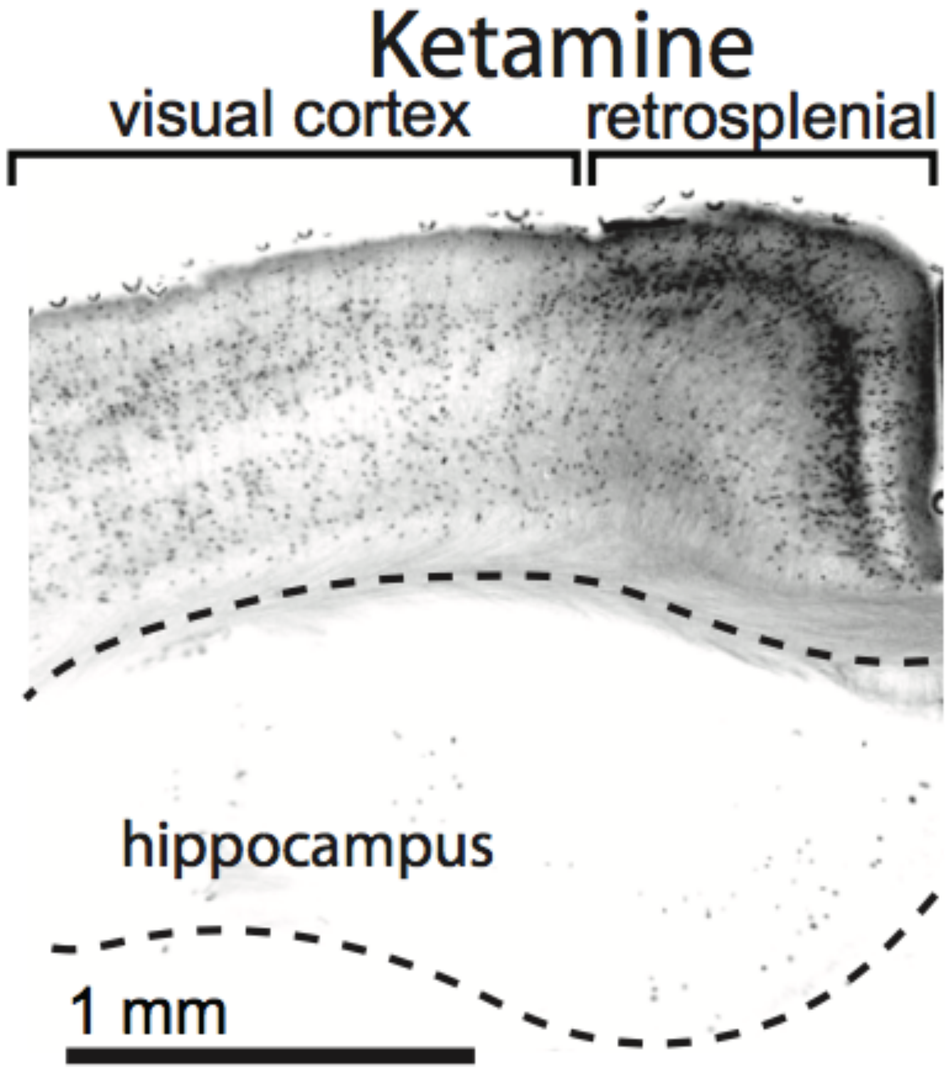



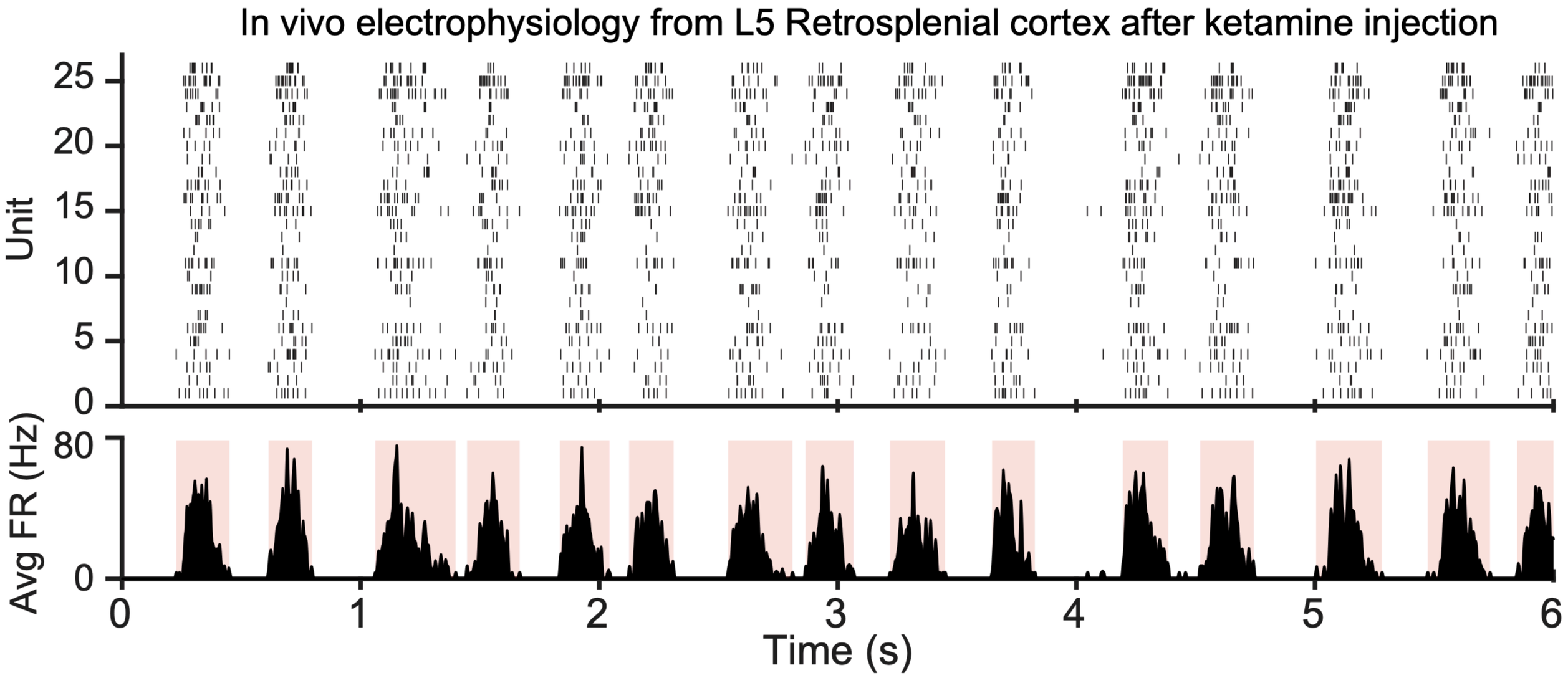
# Ketamine induced oscillation is restricted to layer 5

**Using TRAP2-Ai14 to label active neurons**



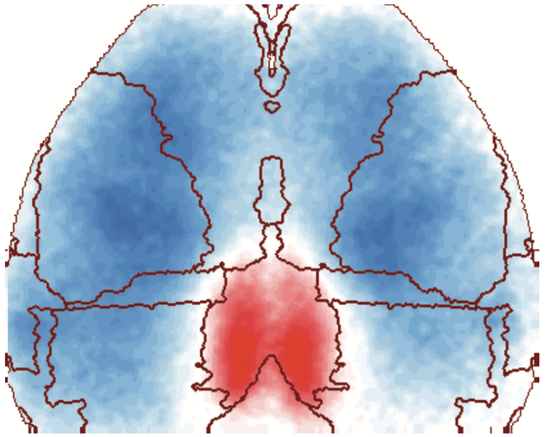



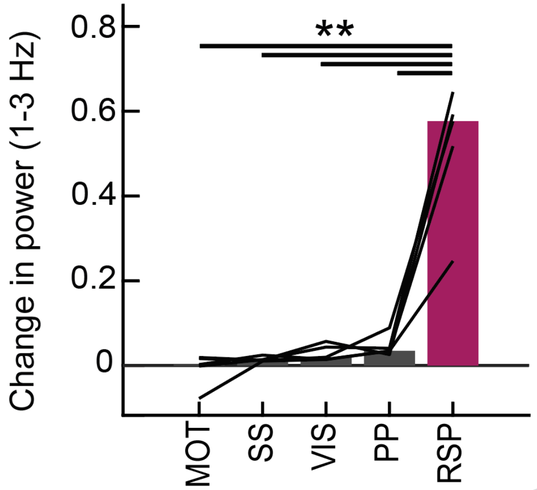
# In vivo electrophysiology of ketamine-induced activity



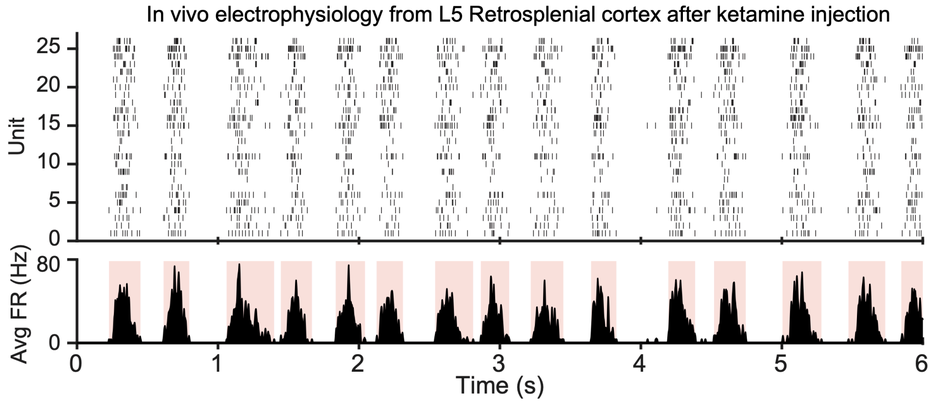
# Probing this rhythm with multiple lines of evidence

## Multi-region imaging

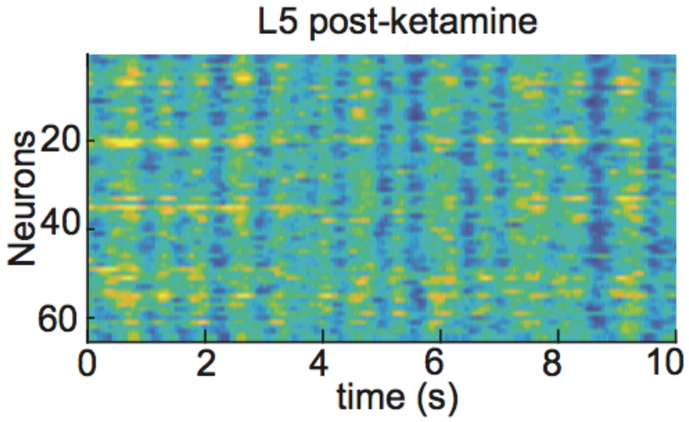


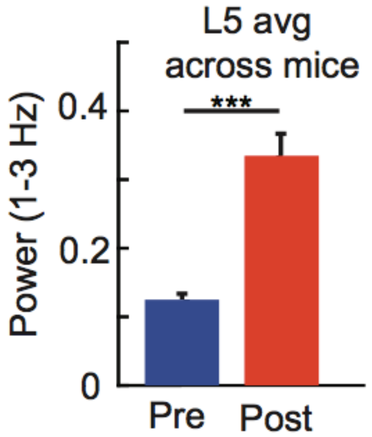



## Electrophysiology

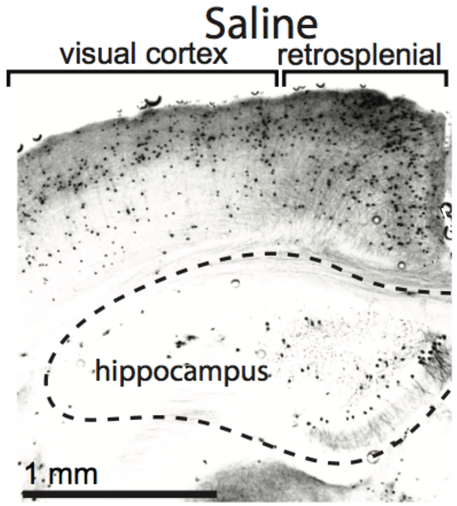


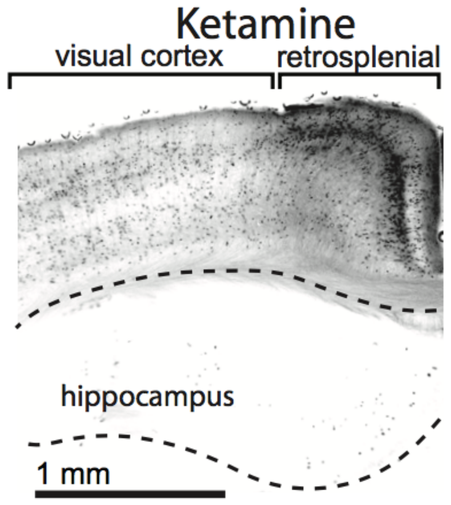

## High-magnification imaging




## Activity-dependent genetics



# A behavioral panel to measure dissociation-like behavior

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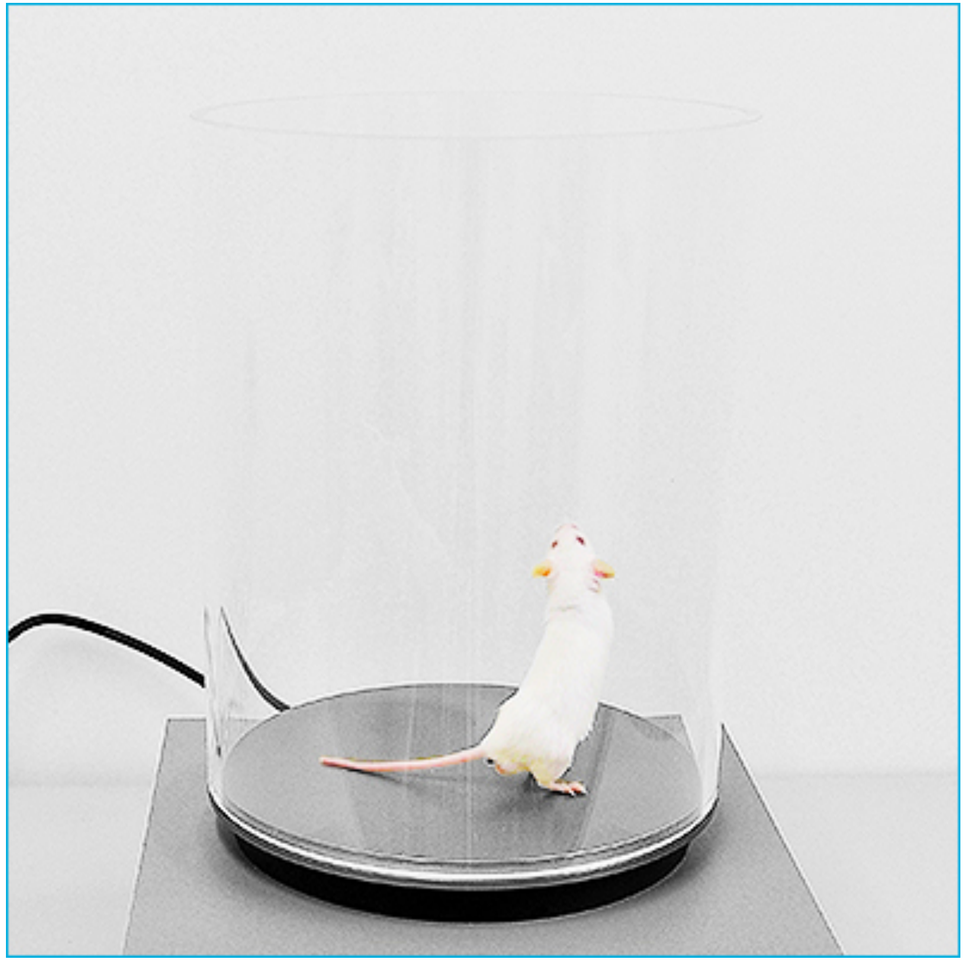

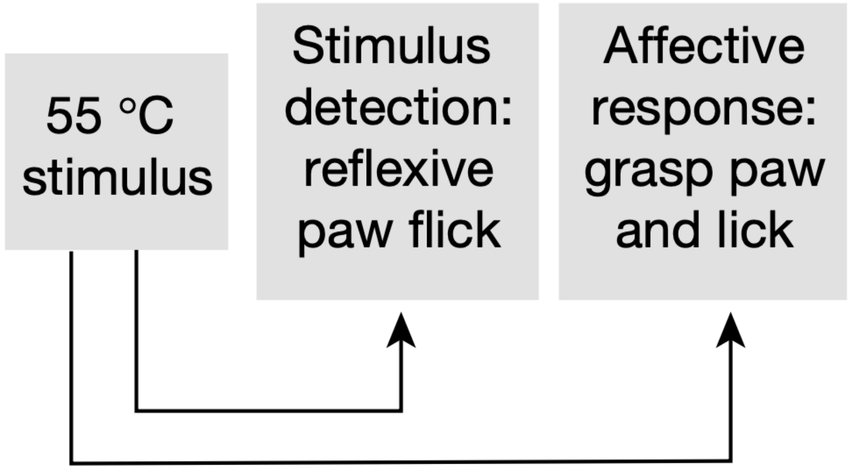

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Foot Flicks

Paw Licks

Time-to-jump

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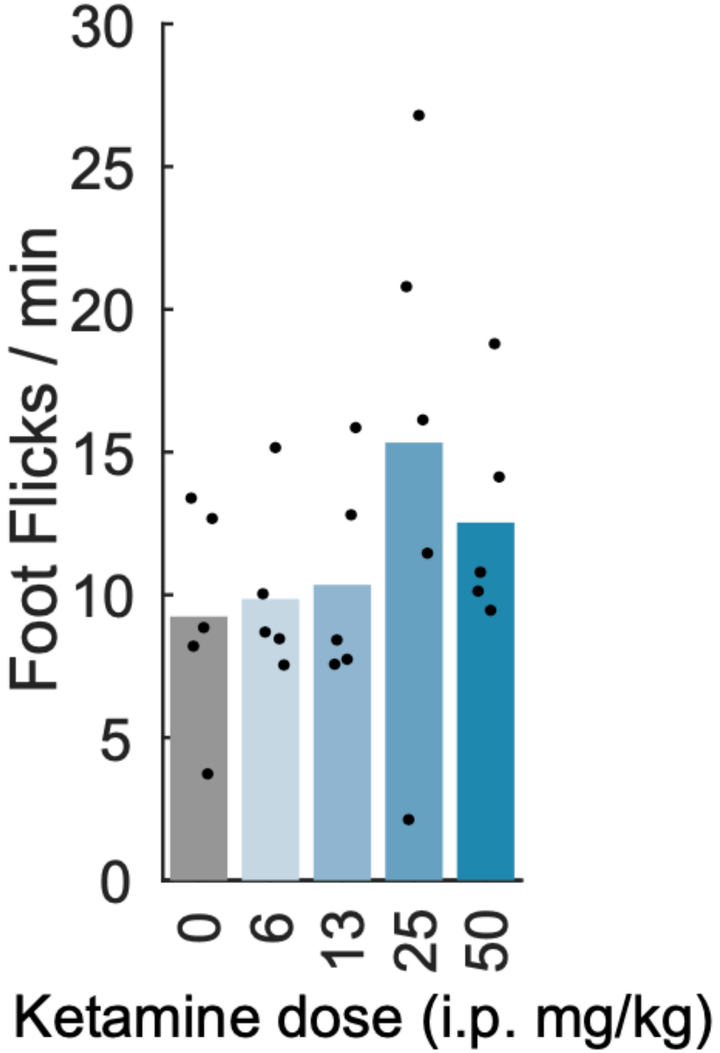
Time-to-jump



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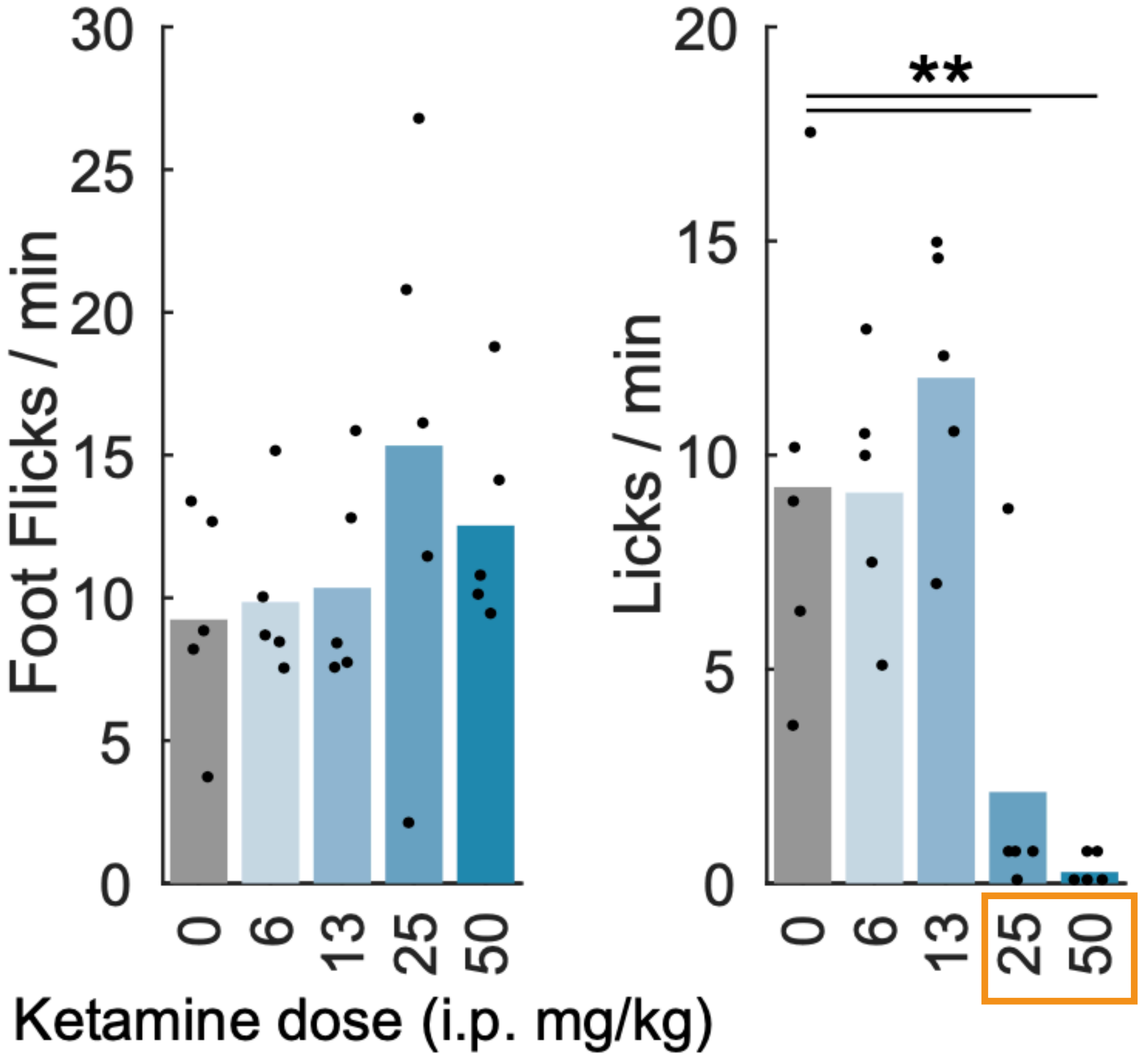
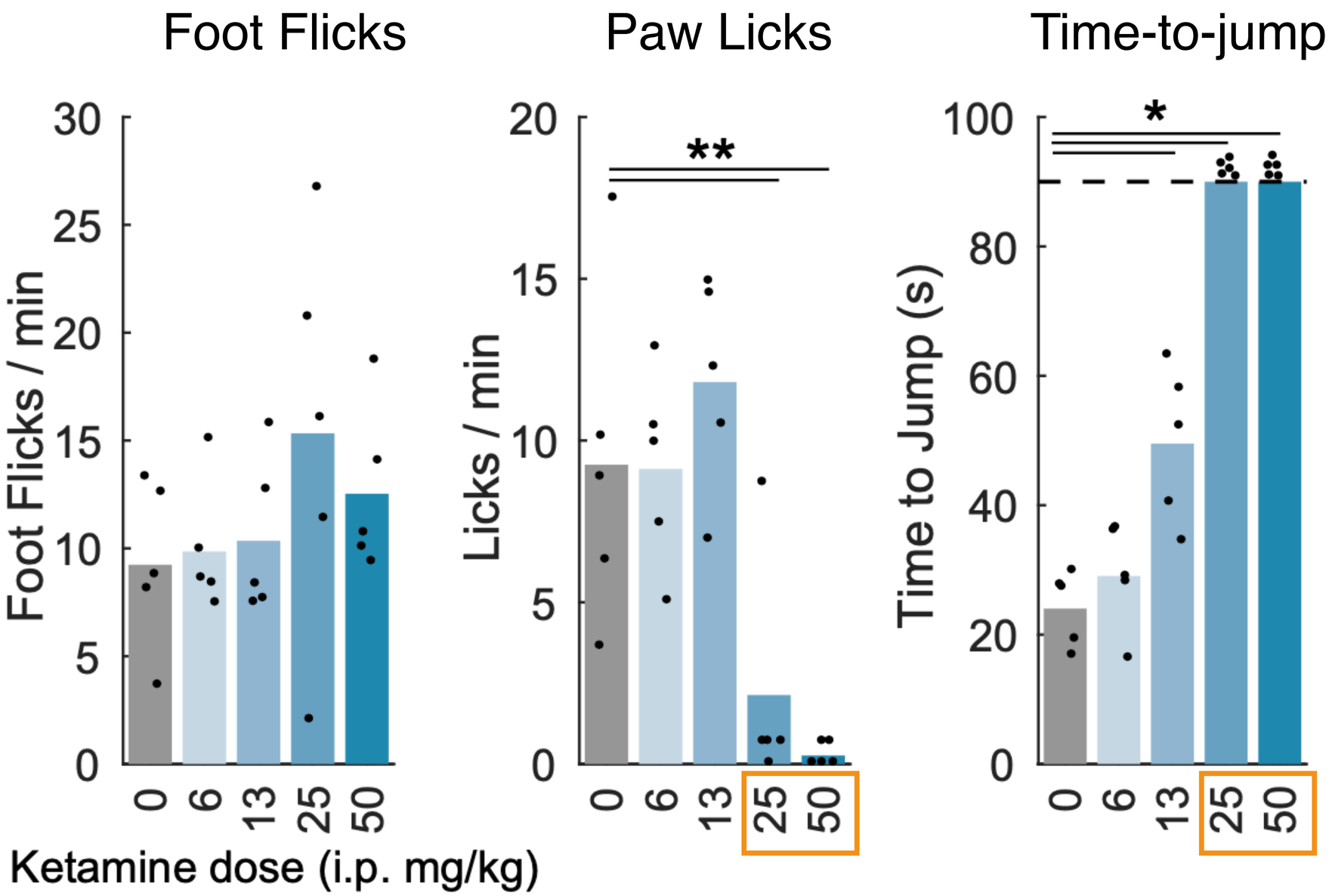
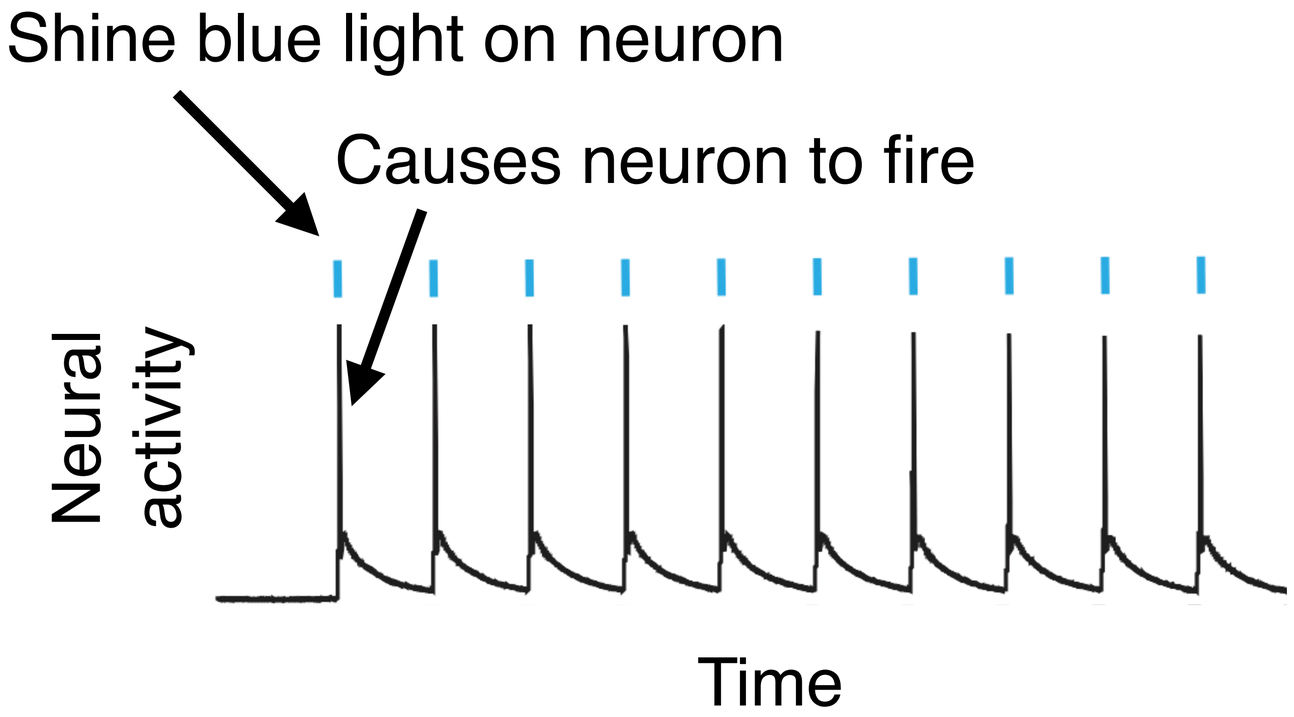


# A behavioral panel to measure dissociation-like behavior



# Can the rhythm cause dissociation-like behavior?

# Optogenetics

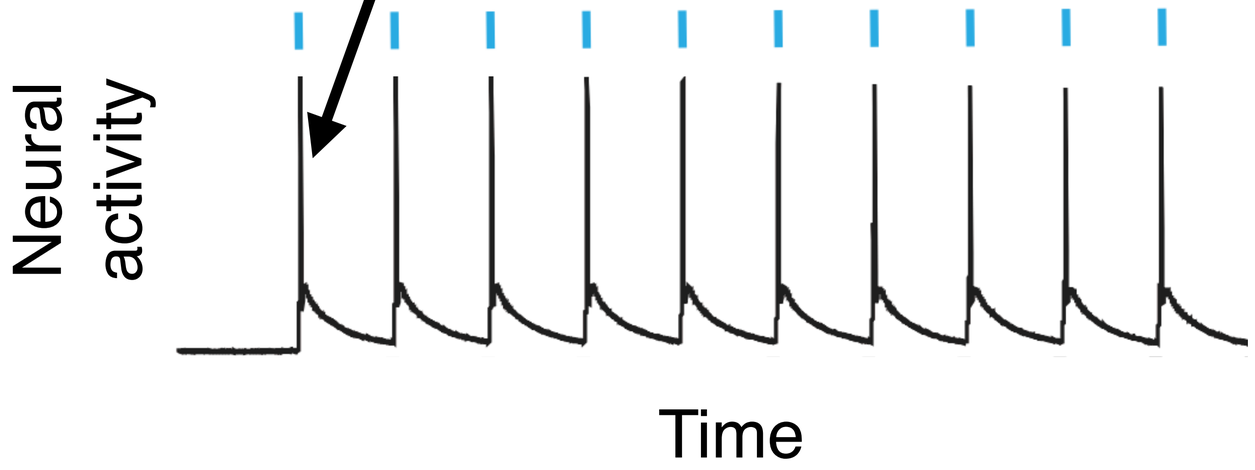



Boyden, et al. 2005, Zhang, et al. 2007

# Optogenetics

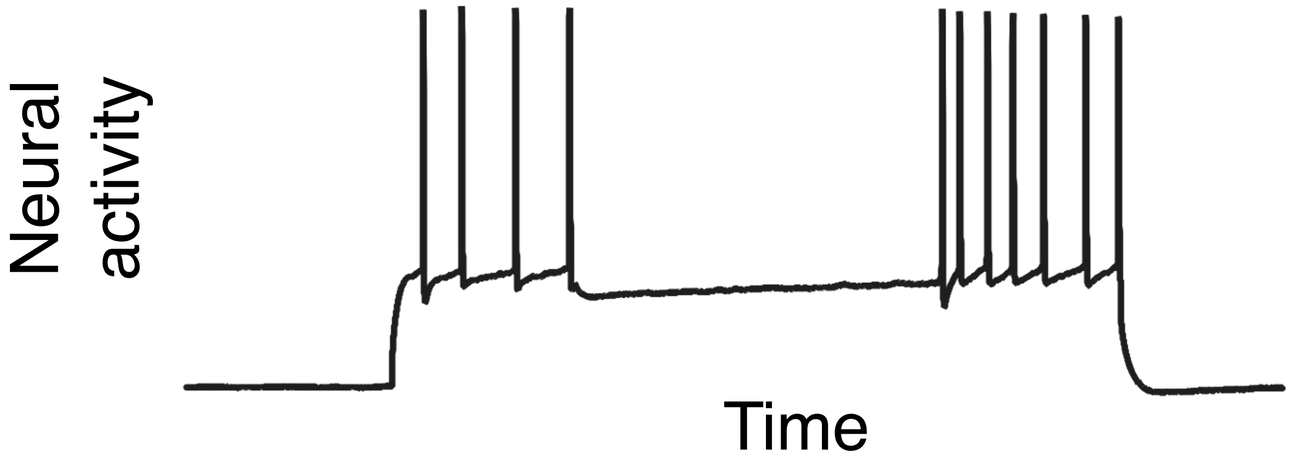
Shine blue light on neuron

Causes neuron to fire



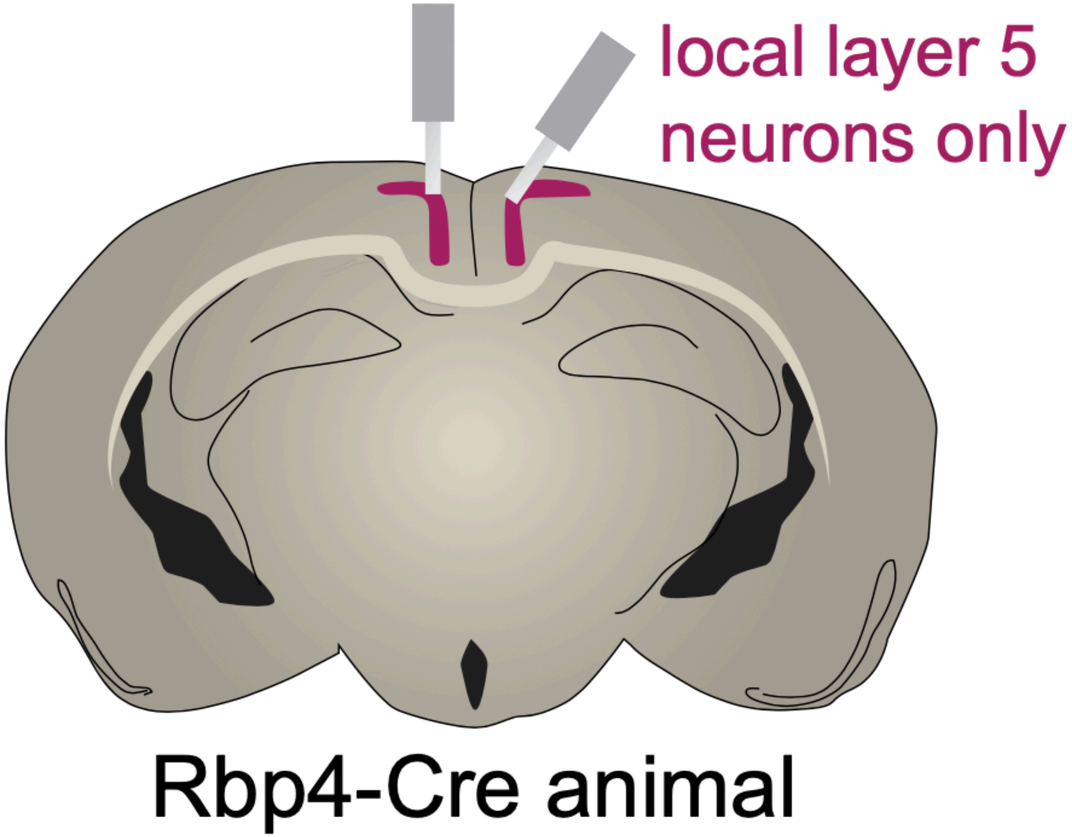

Shine yellow light on neuron

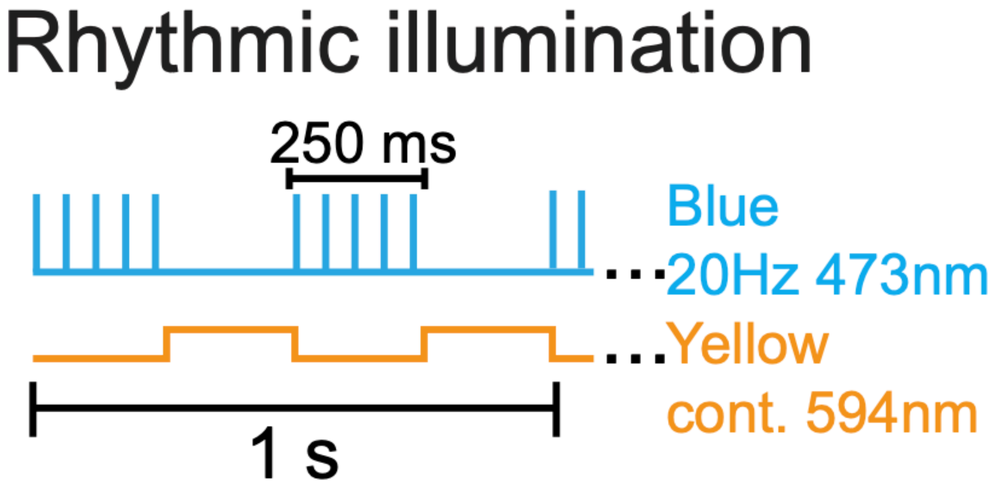
Stops neuron from firing




Boyden, et al. 2005, Zhang, et al. 2007

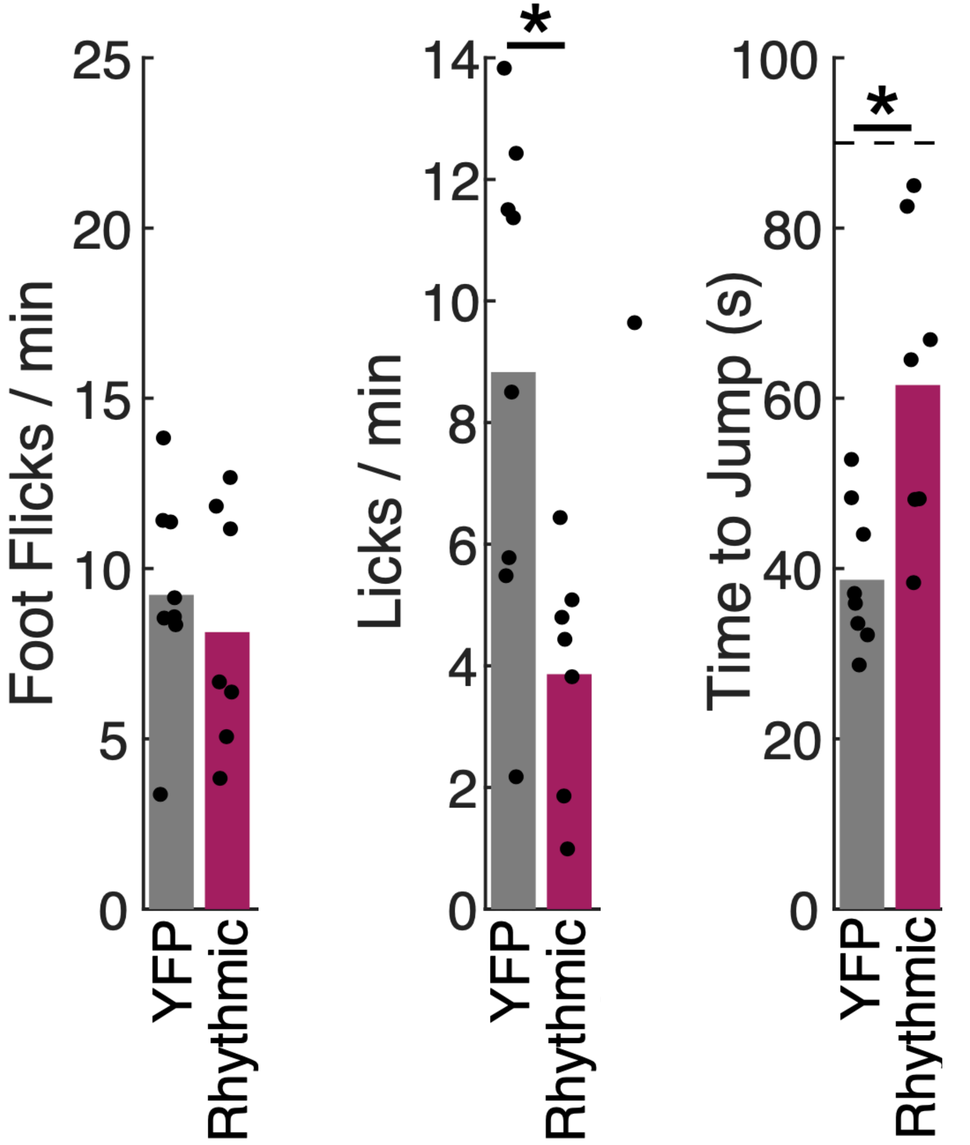
# Optogenetic recapitulation of dissociation-like behavior



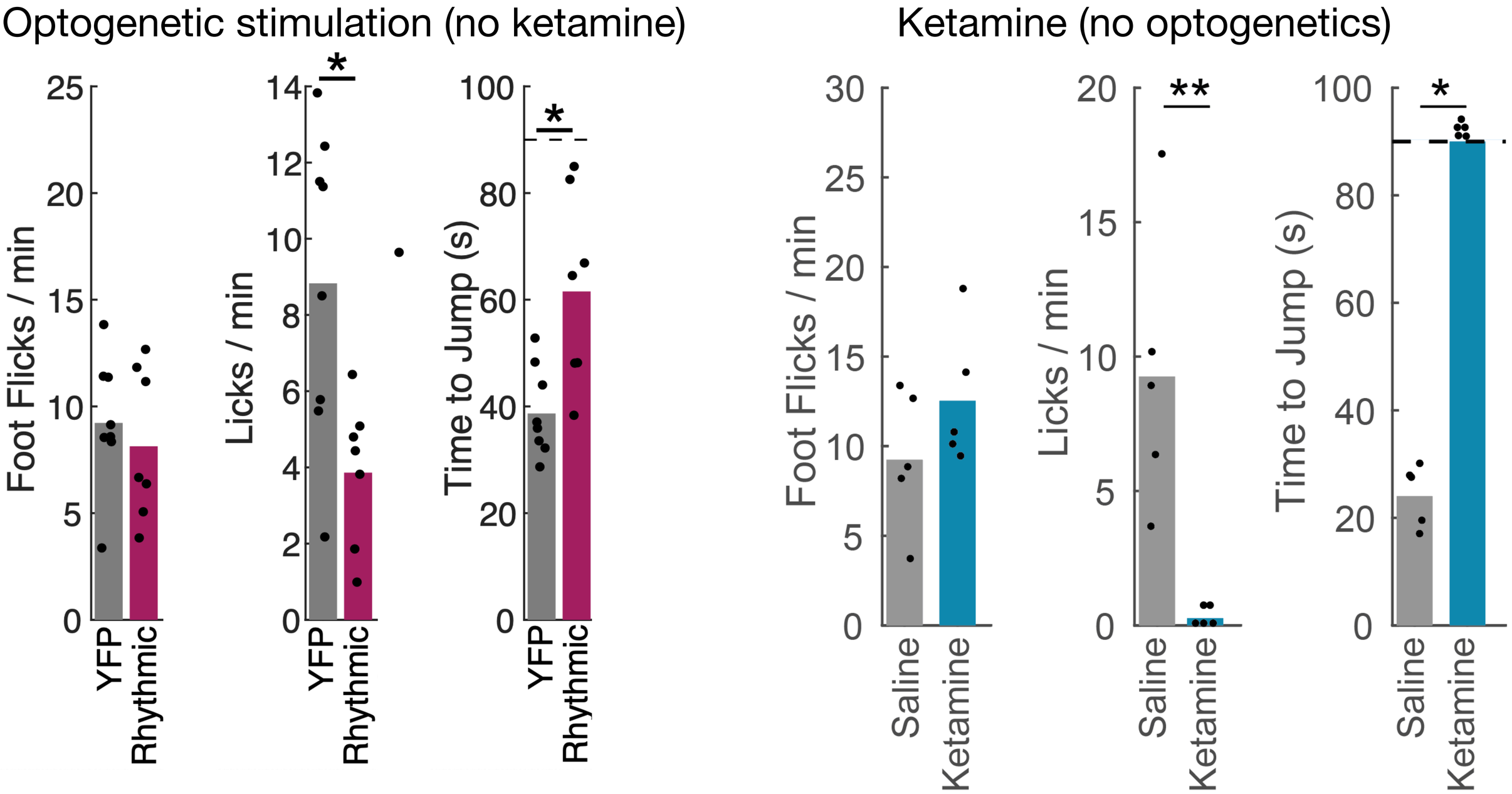



# Optogenetic recapitulation of dissociation-like behavior

Optogenetic stimulation (no ketamine)

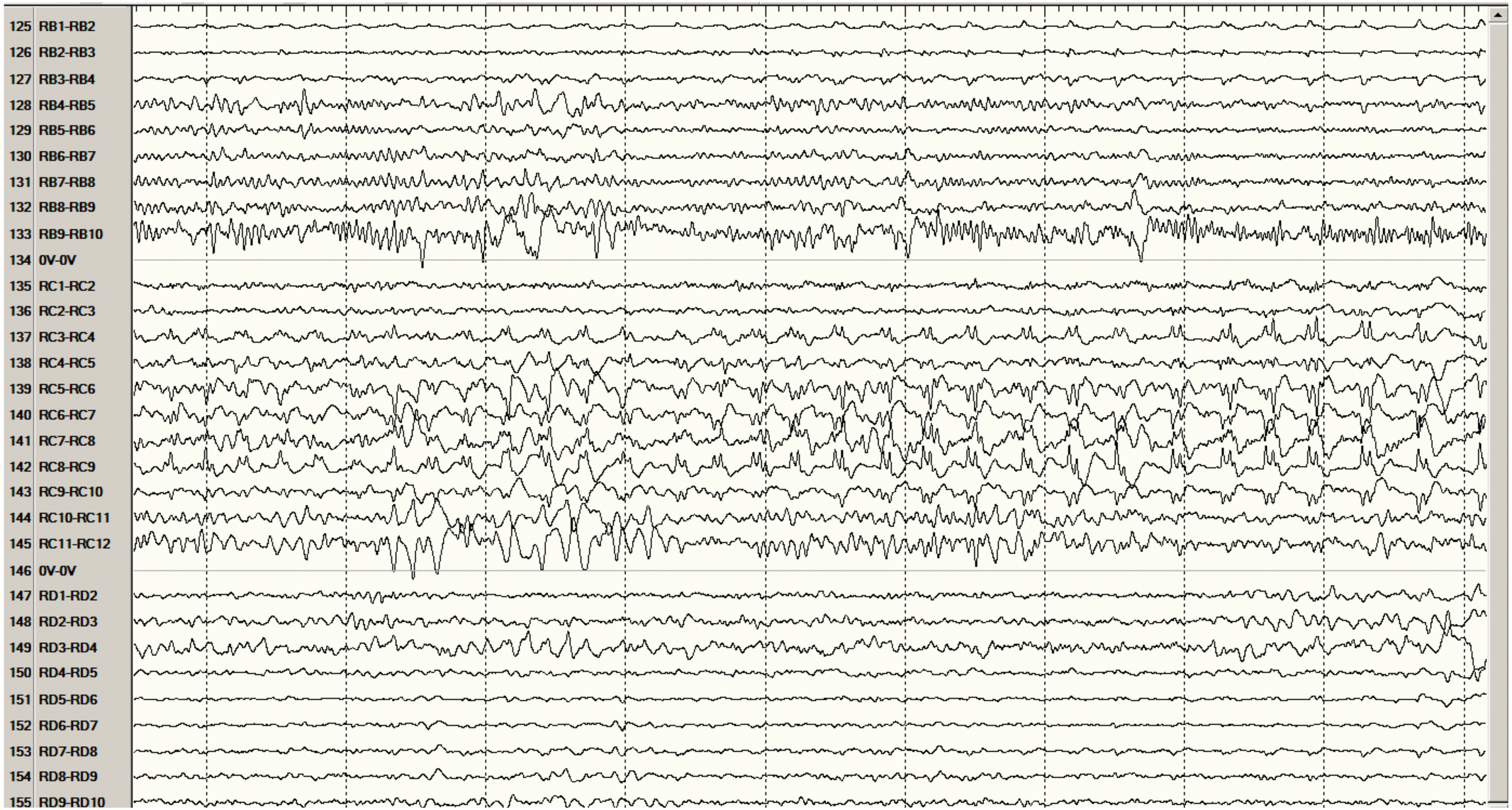


# Optogenetic recapitulation of dissociation-like behavior



# Mice are cool…but what about humans?

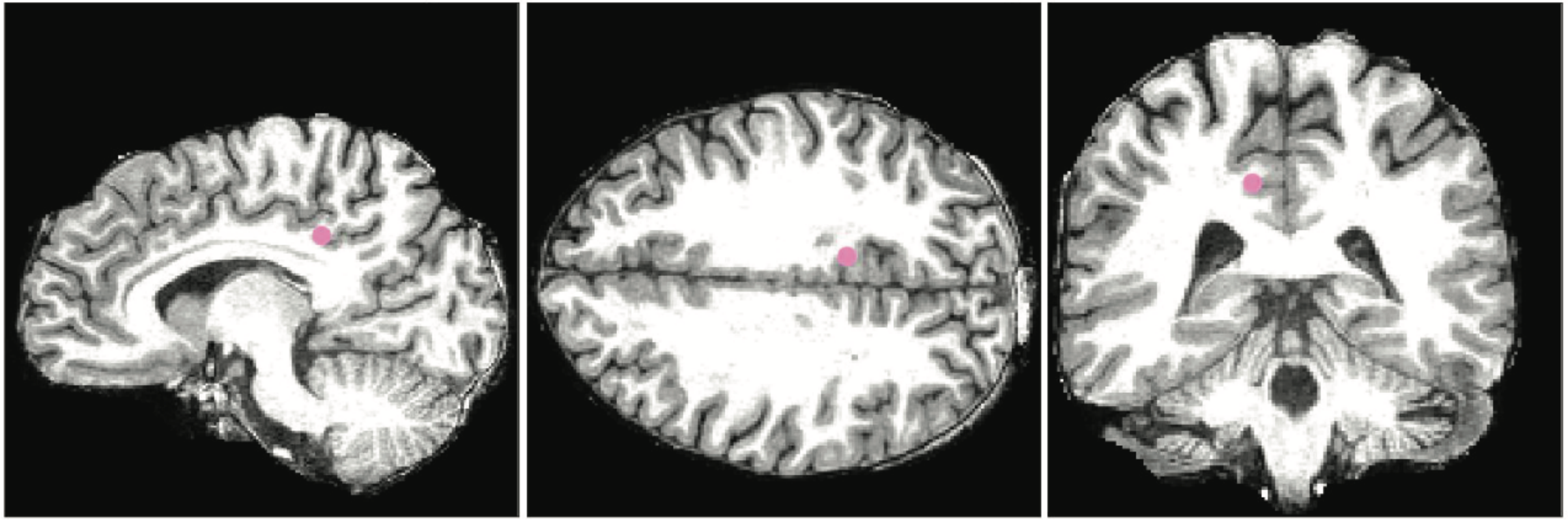
# The raw recording during pre-seizure period



# The raw recording during pre-seizure period

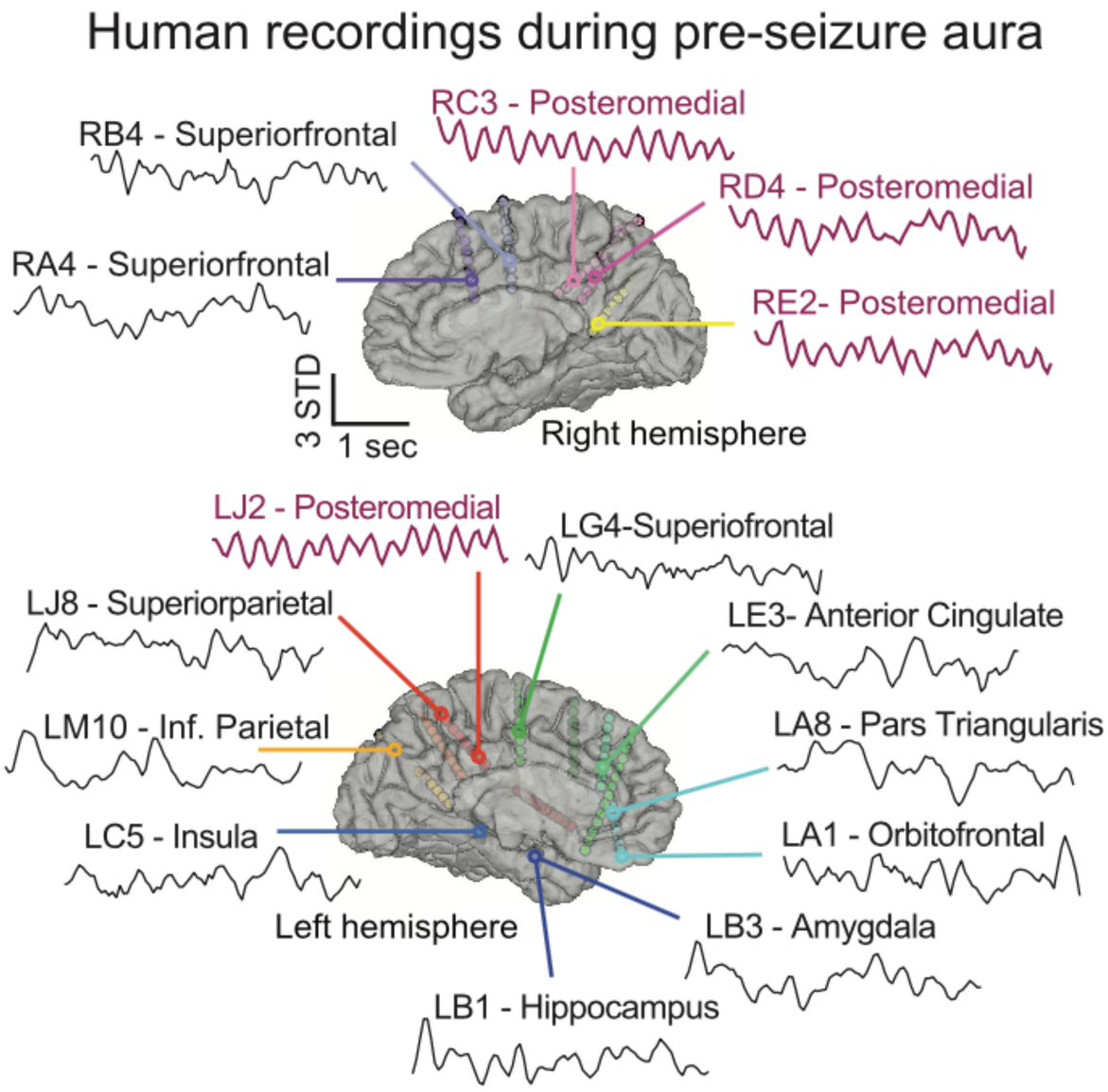
**The seizure is localized to posteromedial cortex**

Posteromedial cortex (R)



**Human-equivalent of mouse retrosplenial cortex**

# Posteromedial oscillations during epilepsy-induced dissociation



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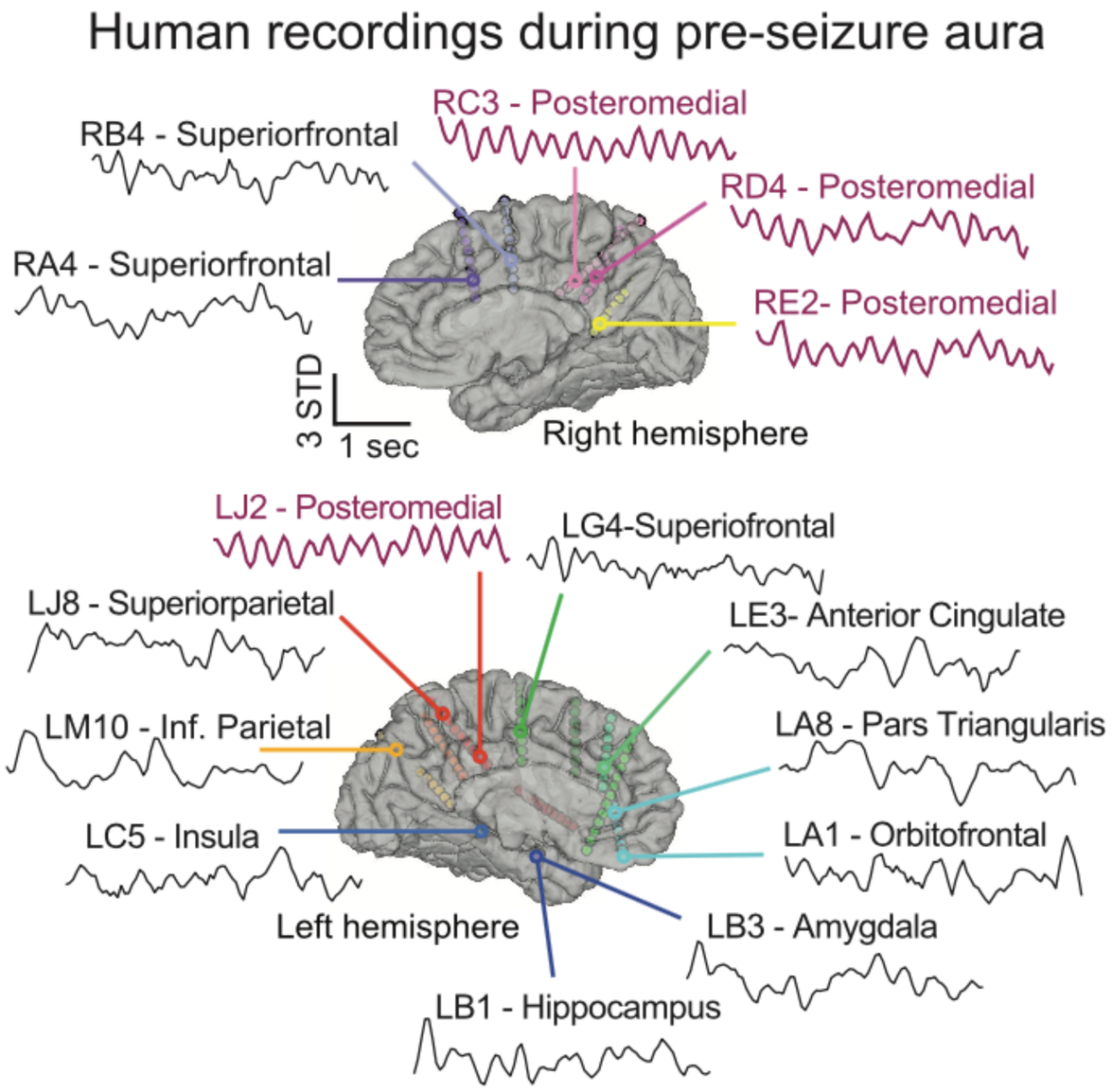
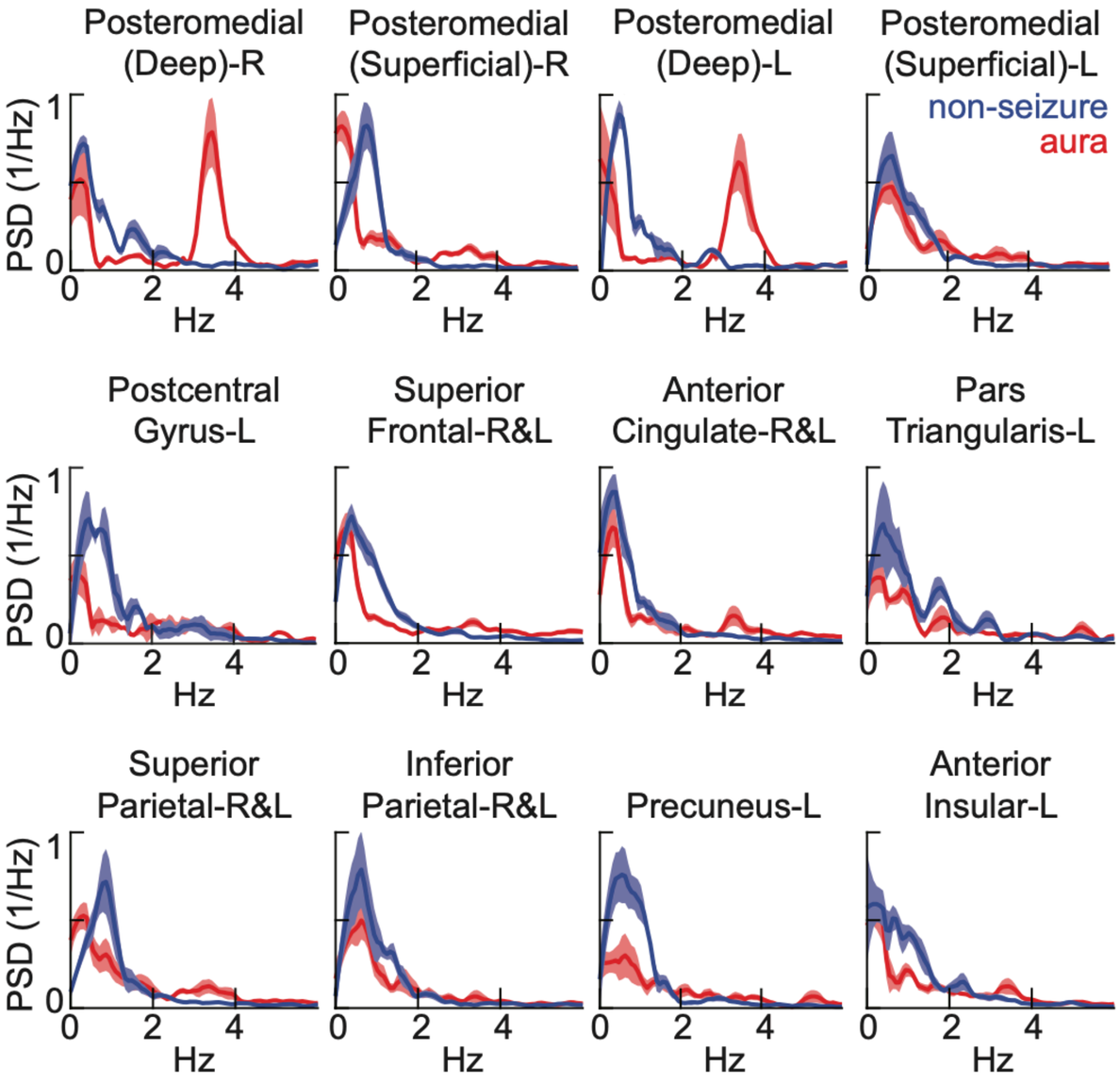
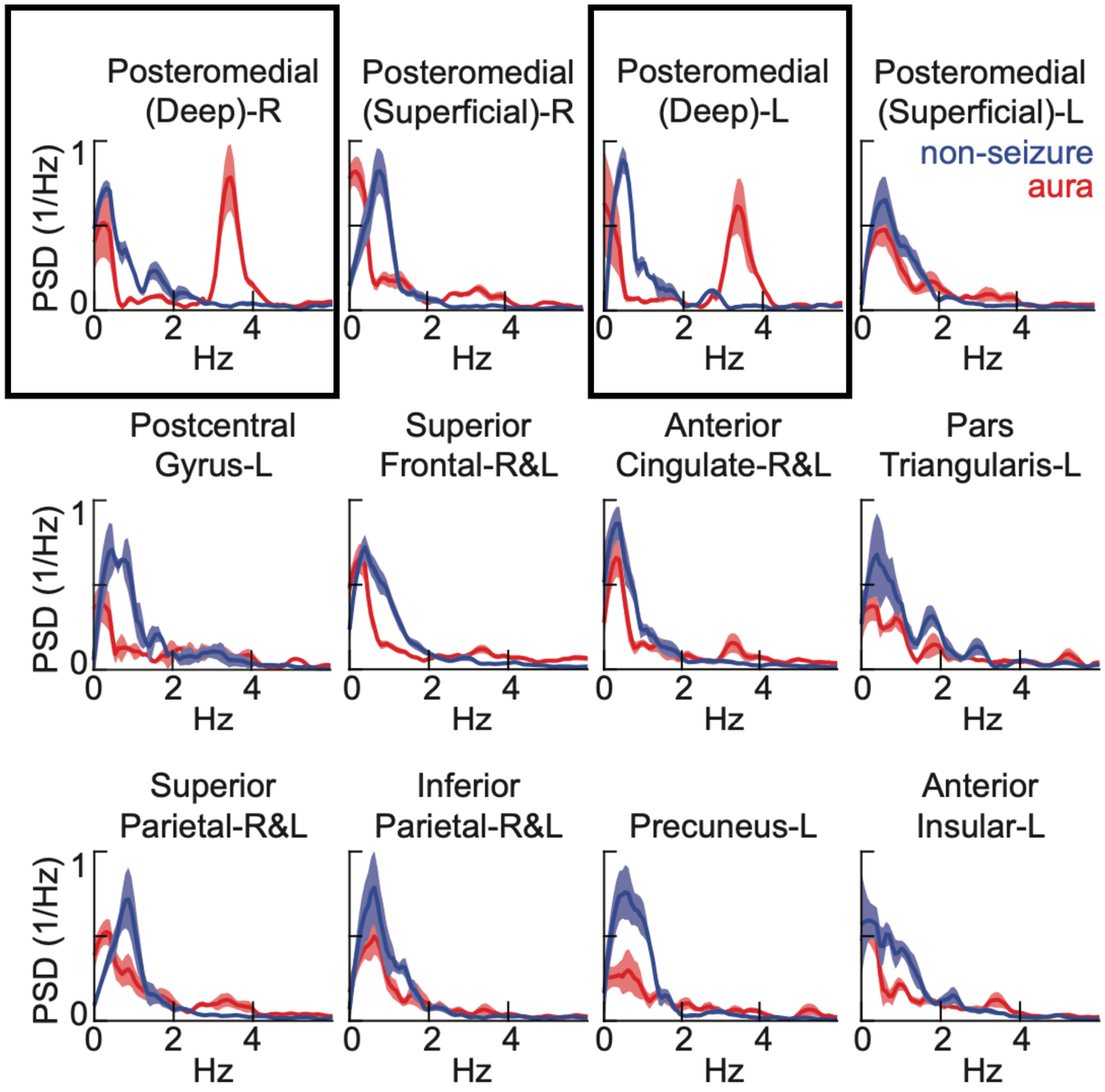



"I was aware that I was listening to two parts of my brain speak to each other in a way that a third part of my brain, which I considered to be me, was able to listen..."

# Posteromedial oscillations during epilepsy-induced dissociation



# Posteromedial oscillations during epilepsy-induced dissociation



# Electrical stimulation of posteromedial cortex induces dissociation

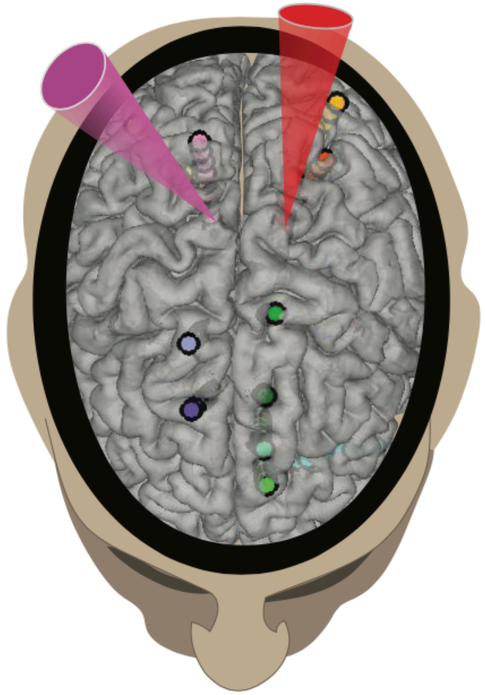
## Stimulation-evoked dissociative experiences

**Right Posteromedial Cortex Stimulation Responses**

(I) “felt similar to the seizure beginning.”

(II) “this is aura-like”

(III) “It’s like I’m about to have a seizure.”




**Left Posteromedial Cortex Stimulation Responses**

(IV) “this feeling of being disconnected from something... that was a little pleasant...”

(V)“...its like being weightless in your own mind as a personality...”

# Electrical stimulation of posteromedial cortex induces dissociation

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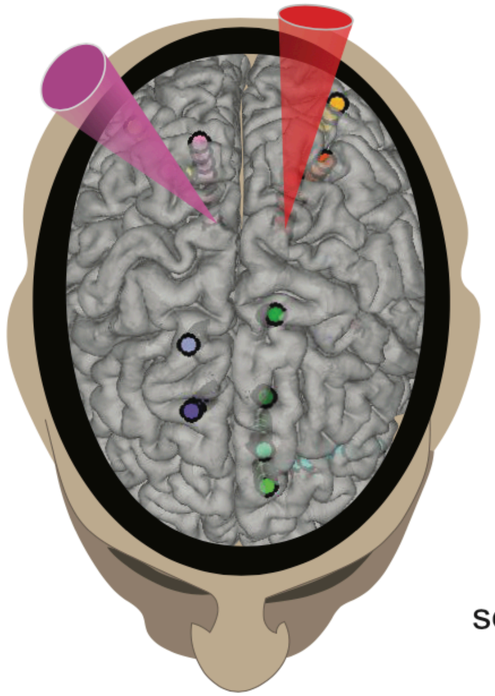


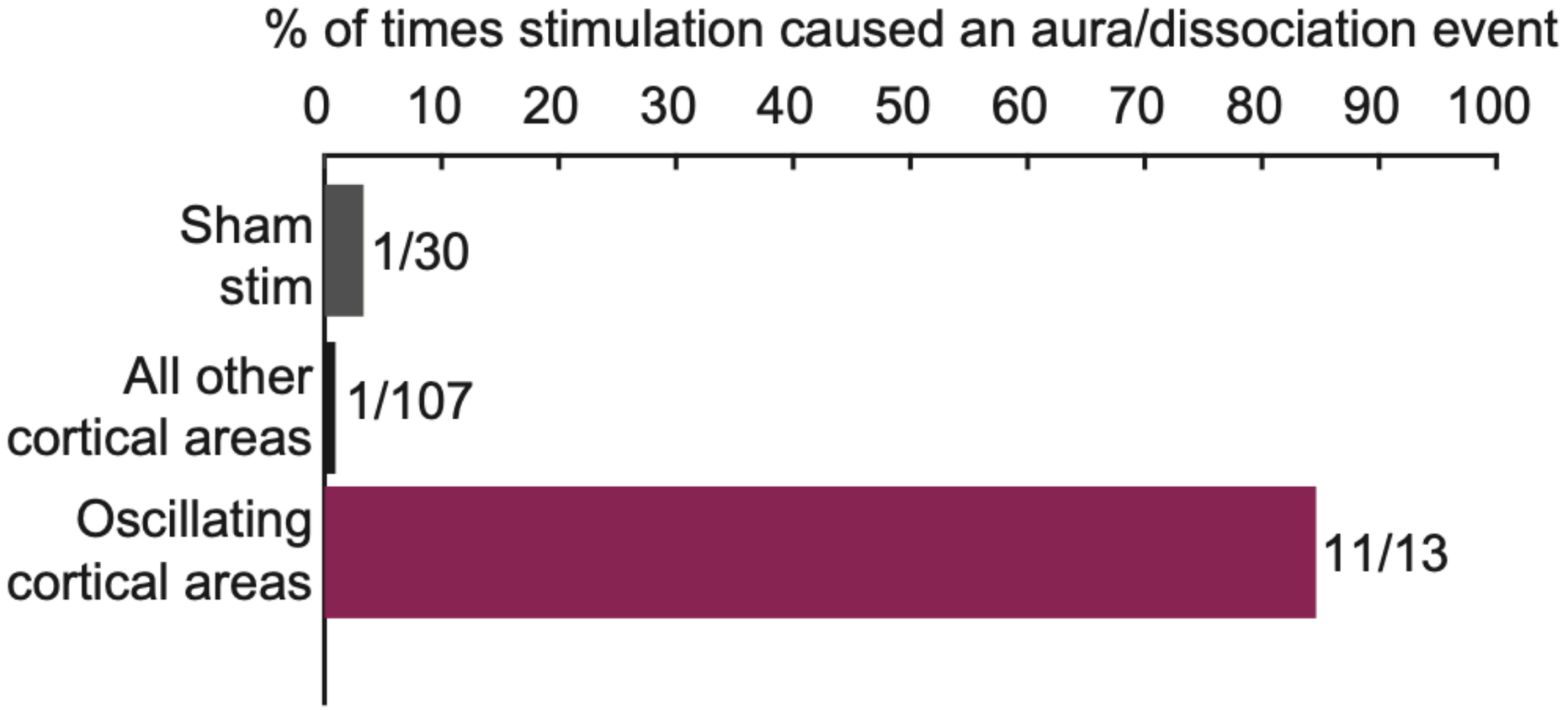

**Left Posteromedial Cortex Stimulation Responses**

(IV) "this feeling of being disconnected from something... that was a little pleasant..."

(V)"...its like being weightless in your own mind as a personality..."

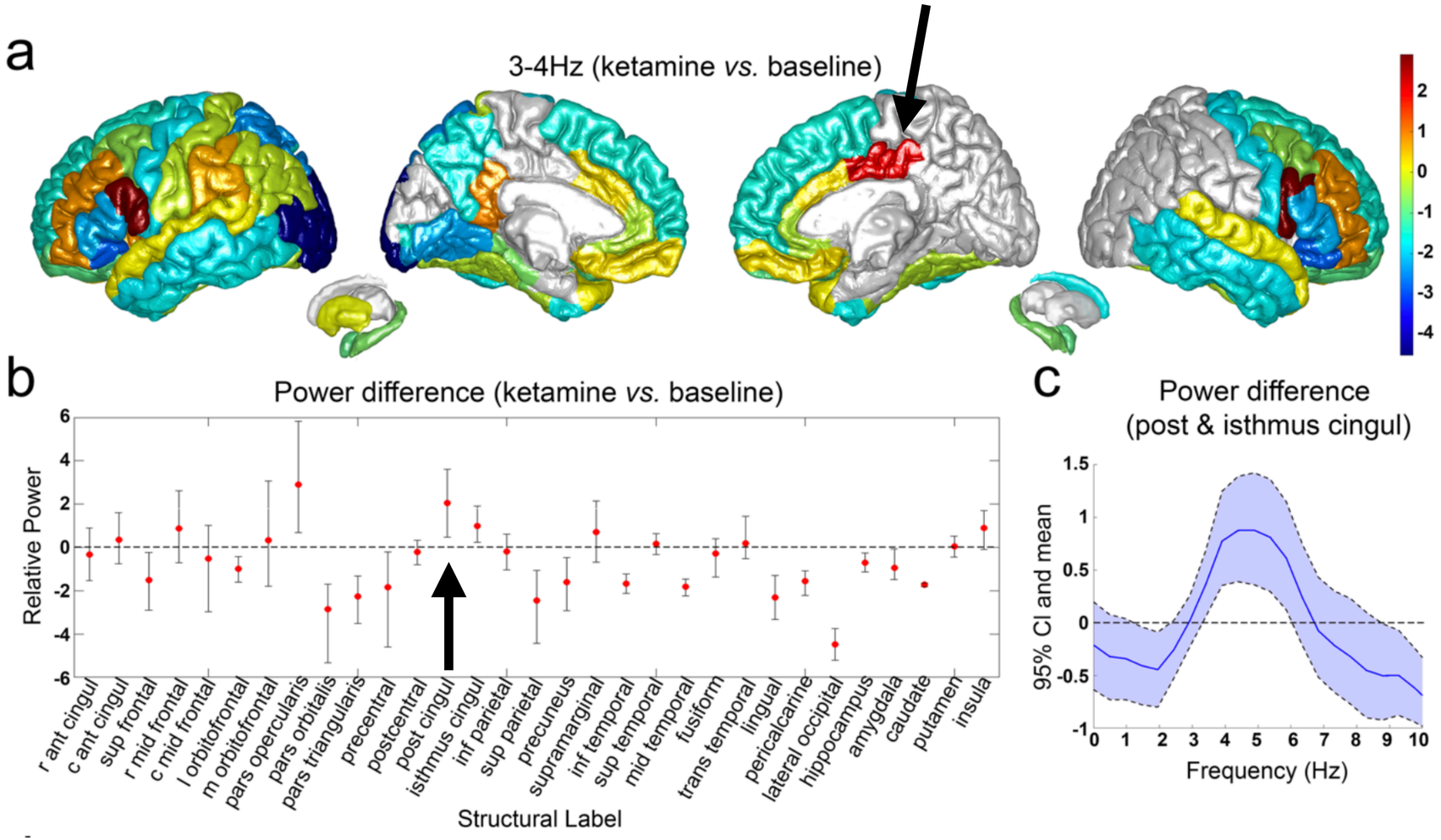
(VI) "...created that separation...the same way a pilot can lose control of a plane. They can be forced out of the cockpit or forced to not control...but still see what's happening to the whole plane, that's kinda just what happened I got pulled out of...the pilot's chair, but I could still see all the gauges...you can see the information flowing--you can't control it, but you can see it."

# Electrical stimulation of posteromedial cortex induces dissociation



# Characterizing brain dynamics during ketamine-induced dissociation and subsequent interactions with propofol using human intracranial neurophysiology

Fangyun Tian, Laura D. Lewis, David W. Zhou, Gustavo A. Balanza, Angelique C. Paulk, Rina Zelmann, Noam Peled, Daniel Soper, Laura A. Santa Cruz Mercado, Robert A. Peterfreund, Linda S. Aglio, Emad N. Eskandar, G. Rees Cosgrove, Ziv M. Williams, R. Mark Richardson, Emery N. Brown, Oluwaseun Akeju, Sydney S. Cash & Patrick L. Purdon



# Takeaways

- Unbiased imaging screen of drug-induced brain states revealed a **dissociative-induced 1-3 Hz oscillation** in mouse retrosplenial cortex

- **Optogenetic mimicking of the oscillation** elicited dissociation-like behavioral effects, in the absence of ketamine

- **An epilepsy patient exhibited a ~3 Hz oscillation** in posteromedial cortex corresponding to experiences of dissociation

**The experience of dissociation**

| Dissociative disorder | Ketamine | Posteromedial oscillation |
| --- | --- | --- |
| “if my mind is a car, I’m in the passenger seat, **looking at myself driving…**” | “if you’re in the audience… **as if you could watch the movie of your life**” | “The same way a pilot can lose control of a plane….**forced out of the cockpit**” |

Andy Warhol
Self-portrait (1978)

# Acknowledgements

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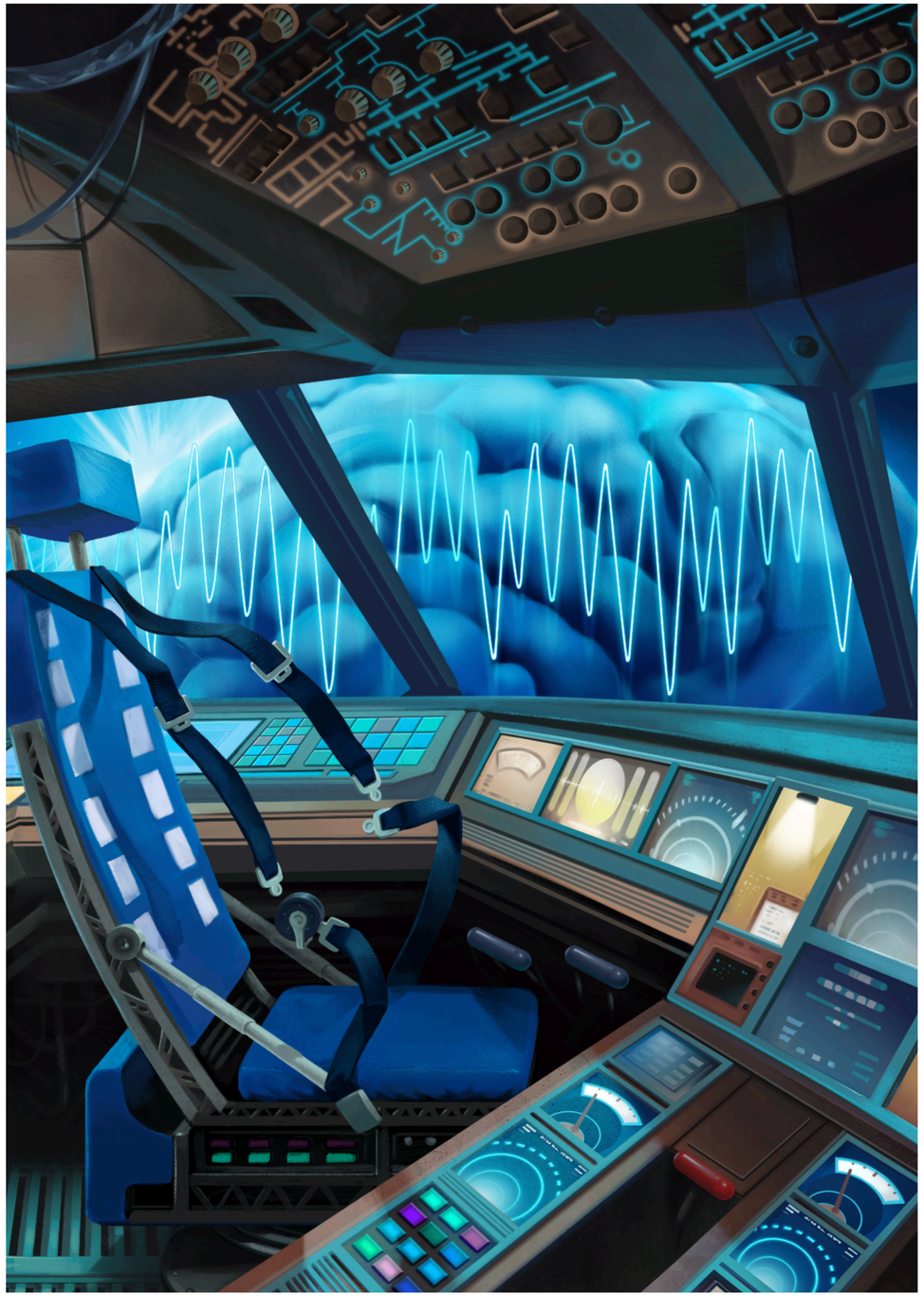
John Kochalka
Emily Sylwestrak
Xulu Sun
Yiming Chen
Santos Franco
Jan Hsi Lui
Kei Masuda
Lisa Giocomo

# Questions?

Isaac
Kauvar

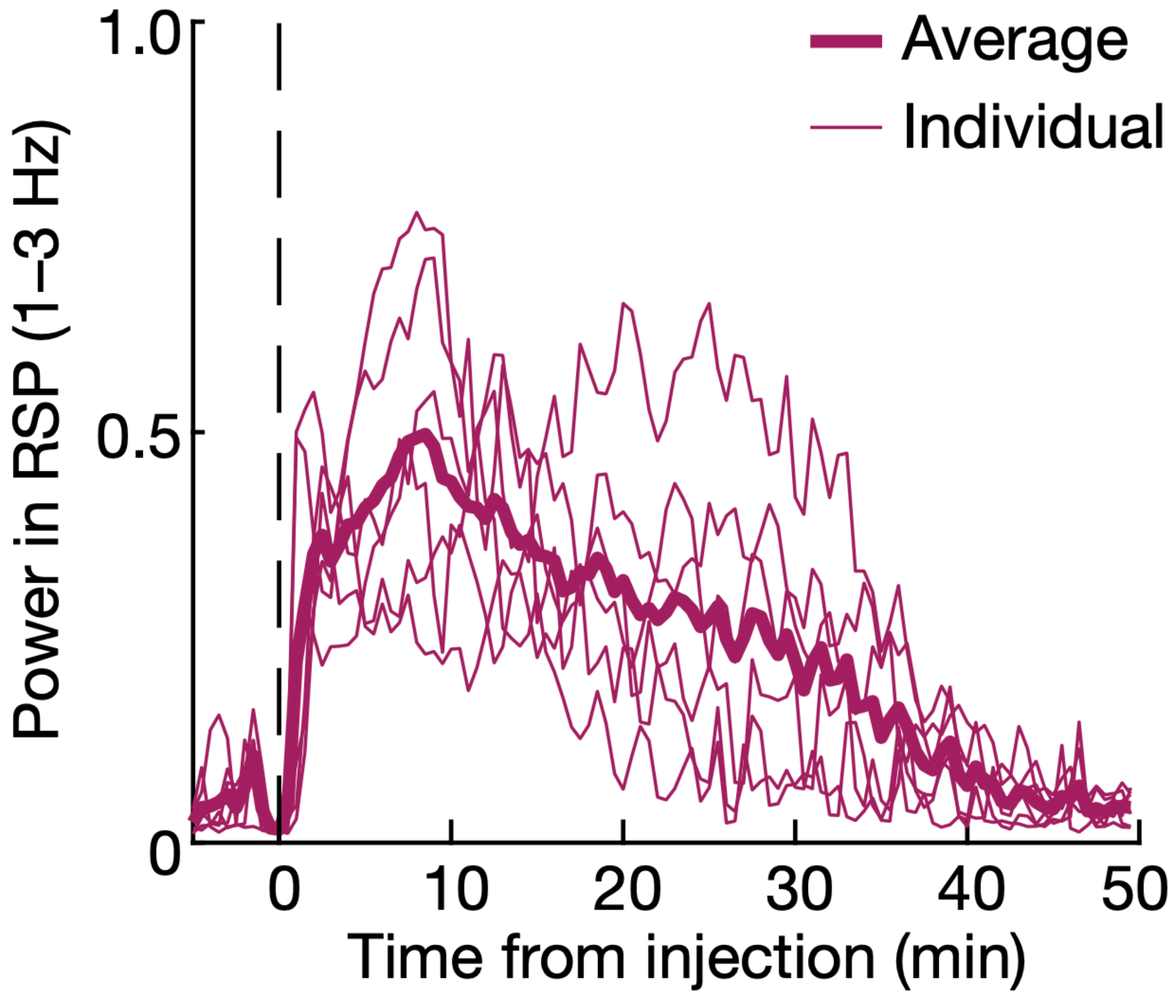
Stanford
University

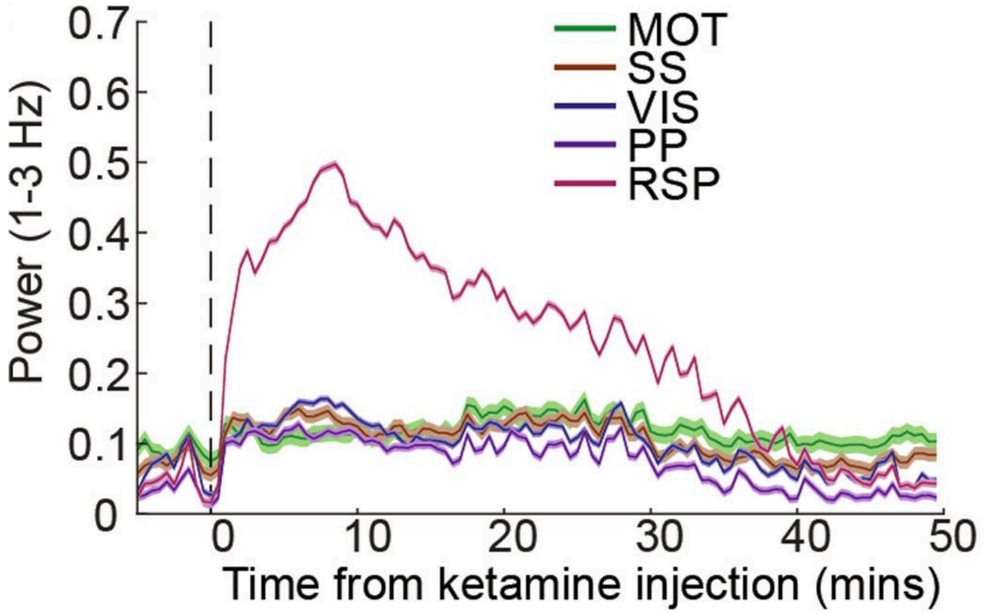
www.ivk.io



# Extra slides

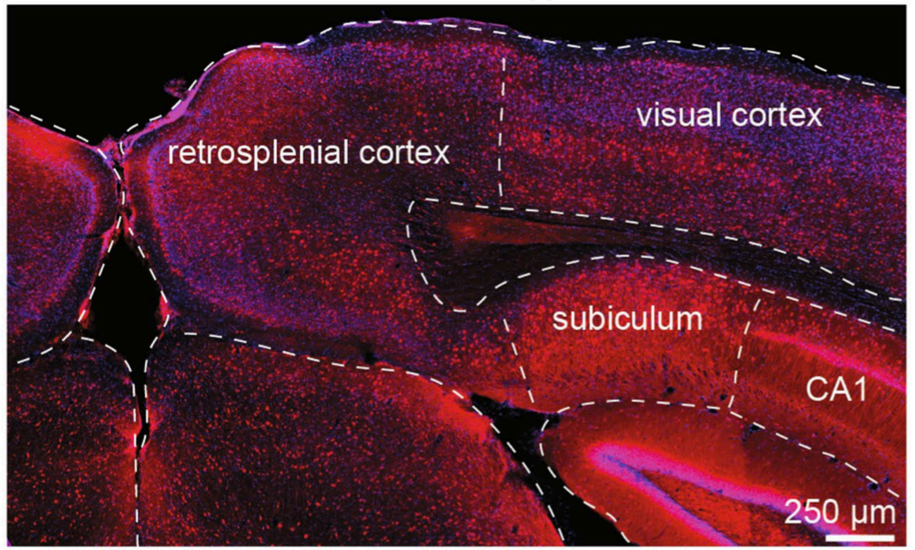
# Oscillation timecourse



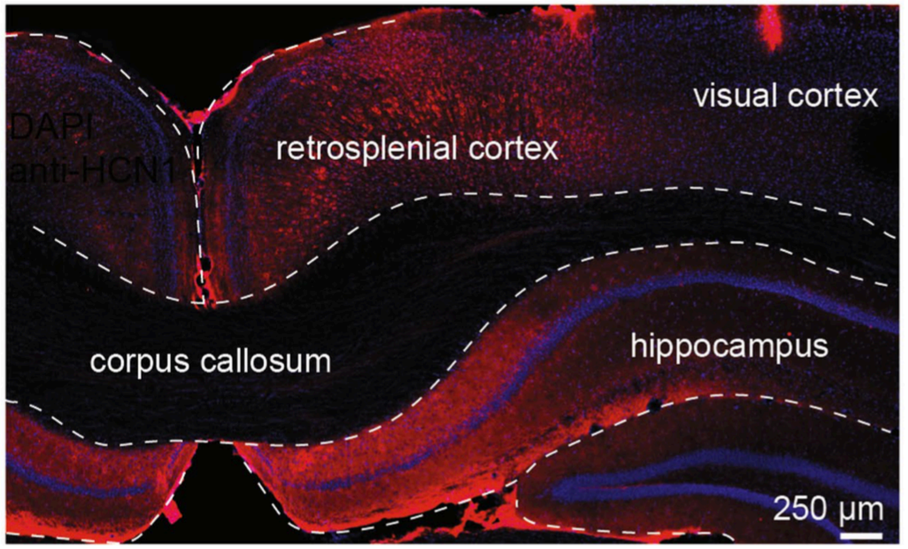



# HCN1 channels are localized to deep retrosplenial

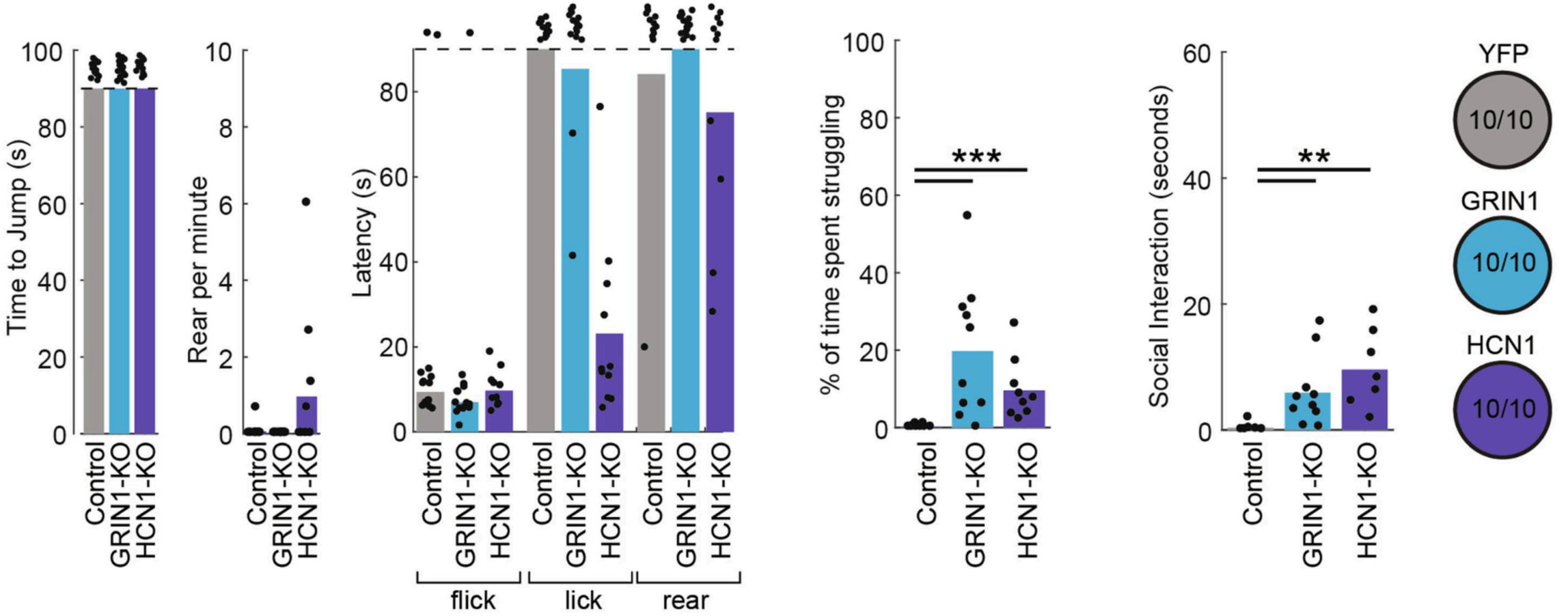
anti-GRIN in wild-type brain



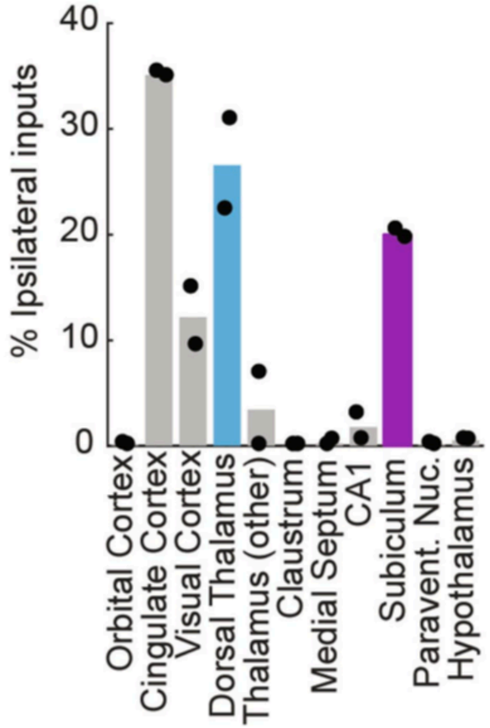

anti-HCN1 in wild-type brain

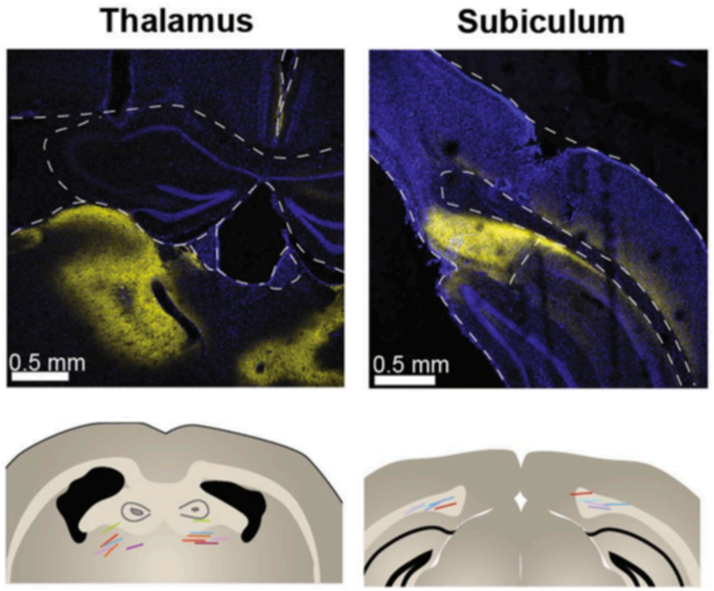


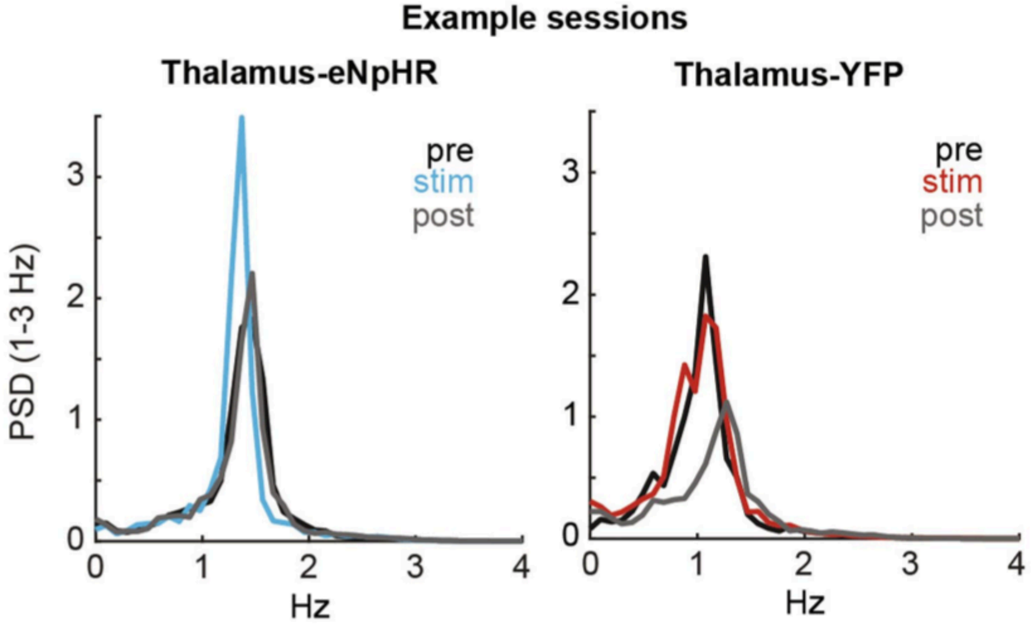
# Additional HCN1 results



# Monosynaptic inputs to retrosplenial layer 5



# Additional optogenetics results