Engineering neurons with light, chemicals, and sound.

Valerio Zerbi

Assistant Professor

UNIVERSITÉ DE GENÈVE

20 November 2024

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What is the ultimate goal in neuroscience?

What is the ultimate goal in neuroscience?

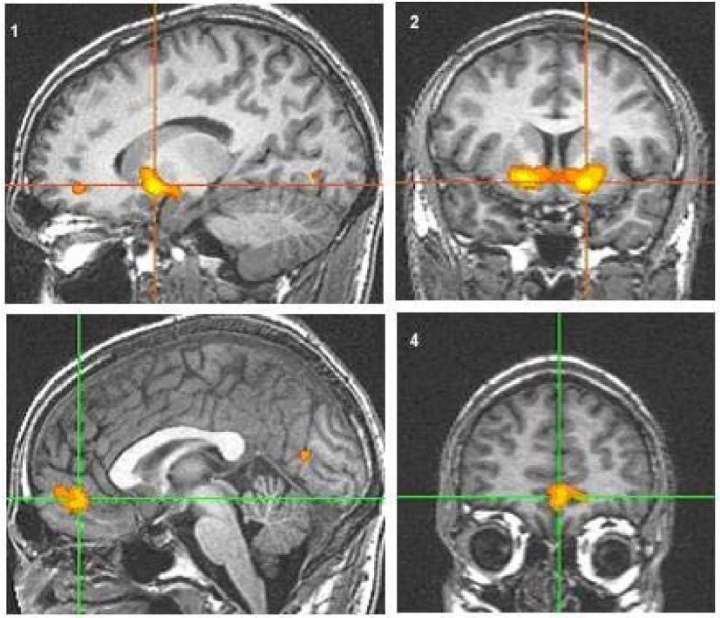
The ultimate goal in neuroscience is to understand how the brain works in its entirety—how neural circuits and networks process information, generate behavior, and underpin cognition, emotions, and consciousness. This encompasses understanding the molecular, cellular, and systems-level mechanisms of brain function, as well as how these processes are altered in diseases and disorders.

Achieving this goal could lead to transformative advancements in treating neurological and psychiatric conditions, improving mental health, and even enhancing cognitive abilities. It would also open new avenues for neurotechnology, brain-machine interfaces, and other applications that could have profound implications for human health, society, and the understanding of our consciousness.

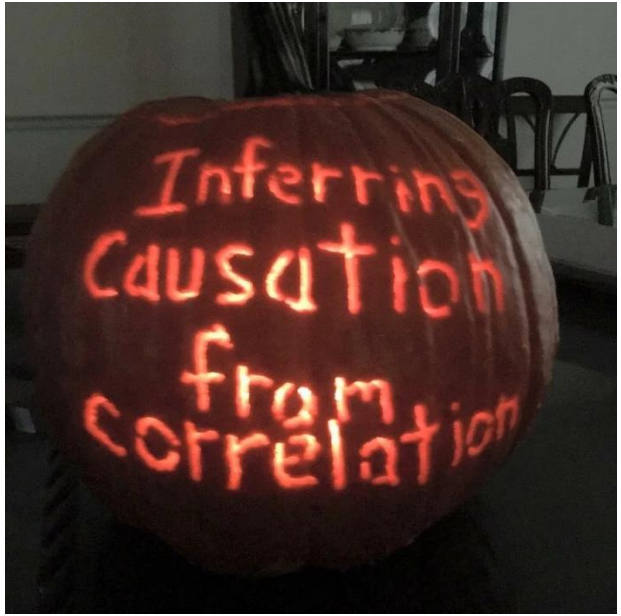
What is the ultimate goal in neuroscience?

However, I do feel that the varied, irregular and disjointed terrain of this field is merely a product of our *present* (very limited) knowledge of the brain. We don't have enough knowledge to see how a cohesive theory of the brain could arise from all our disparate branches of research. Of course if we did reach a full understanding of how the brain works, it would cover all possible levels and serve any purpose. Our knowledge of the computational, algorithmic, and physical workings of Alzheimer's and the brain areas involved with it, for instance, would make the production of treatments straight-forward. The field will be united. But for now, we are all working on separate chunks of a puzzle who's end picture none of us knows for certain. The best we can do is try to add one more piece onto our chunk in the hopes that they"ll all come together some day. However, for now, I think the goal of neuroscience will continue to vary from lab to lab, from researcher to researcher, and maybe even from day to day. Until we've all worked hard enough to realize that we're working on the same thing.

Brain – behaviour interactions



Petersen et al., 2005



Monetary Reward > Expectations

But…

Brain – behaviour interactions

Valerio Zerbi

nature

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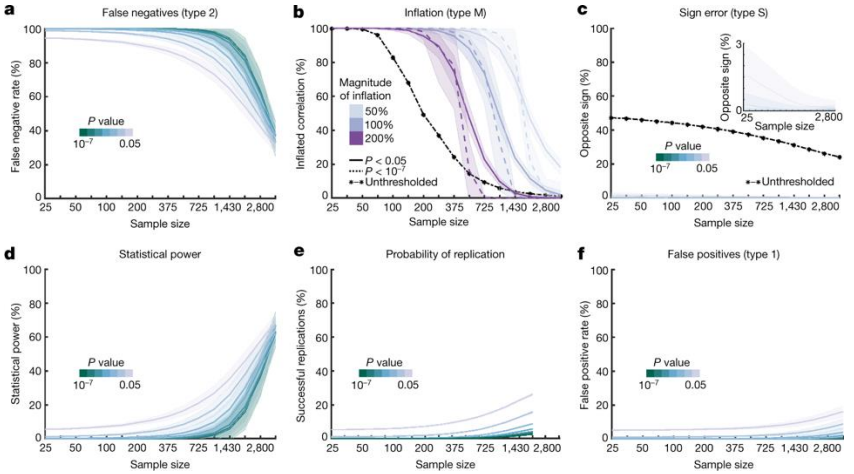
Reproducible brain-wide association studies require thousands of individuals

Scott Marek, Brenden Tervo-Clemmens, Finnegan J. Calabro, David F. Montez, Benjamin P. Kay, Alexander S. Hatoum, Meghan Rose Donohue, William Foran, Ryland L. Miller, Timothy J. Hendrickson, Stephen M. Malone, Sridhar Kandala, Eric Feczko, Oscar Miranda-Dominguez, Alice M. Graham, Eric A. Earl, Anders J. Perrone, Michaela Cordova, Olivia Doyle, Lucille A. Moore, Gregory M. Conan, Johnny Uriarte, Kathy Snider, Benjamin J. Lynch, James C. Wilgenbusch, Thomas Pengo, Angela Tam, Jianzhong Chen, Dillan J. Newbold, Annie Zheng, Nicole A. Seider, Andrew N. Van, Athanasia Metoki, Roselyne J. Chauvin, Timothy O. Laumann, Deanna J. Greene, Steven E. Petersen, Hugh Garavan, Wesley K. Thompson, Thomas E. Nichols, B. T. Thomas Yeo, Deanna M. Barch, Beatriz Luna, Damien A. Fair & Nico U. F. Dosenbach — Show fewer authors

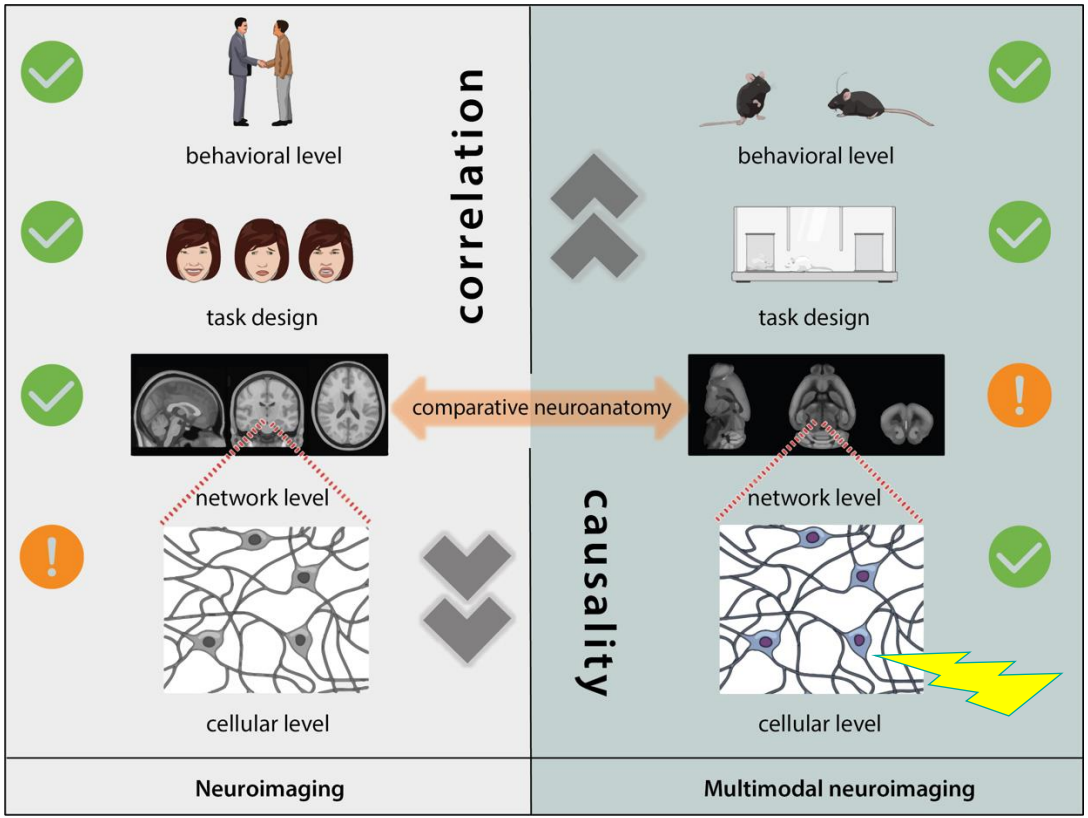
Nature **603**, 654–660 (2022) | Cite this article

64k Accesses | **277** Citations | **1511** Altmetric | Metrics

"A primary challenge has been replicating associations between inter-individual differences in brain structure or function and complex cognitive or mental health phenotypes (brain-wide association studies (BWAS))"



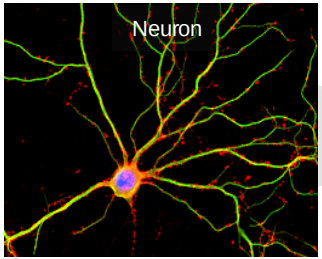
TOP-down vs BOTTOM-up approach

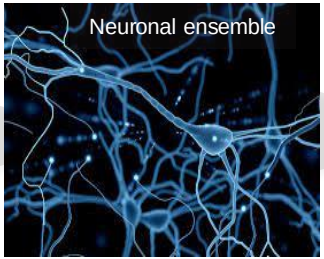


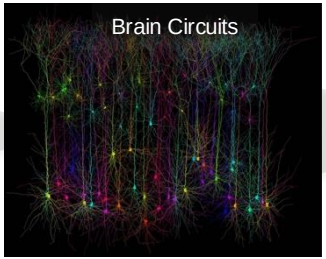
Grimm, Balsters, Zerbi. The Neuroscientist, 2020

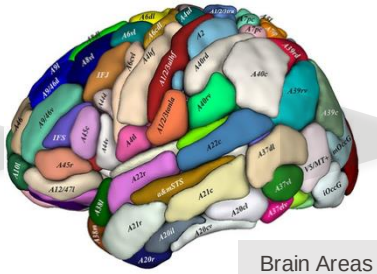
TOP-down vs BOTTOM-up approach

What to target?





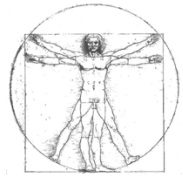




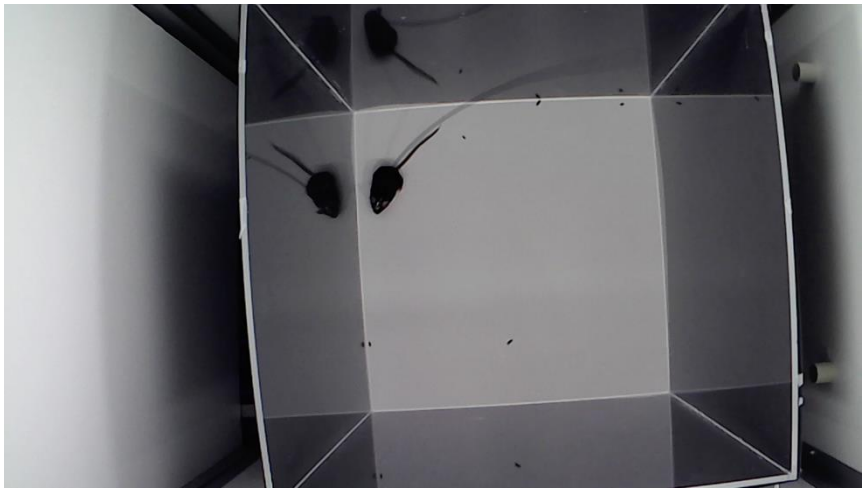
Brain Areas

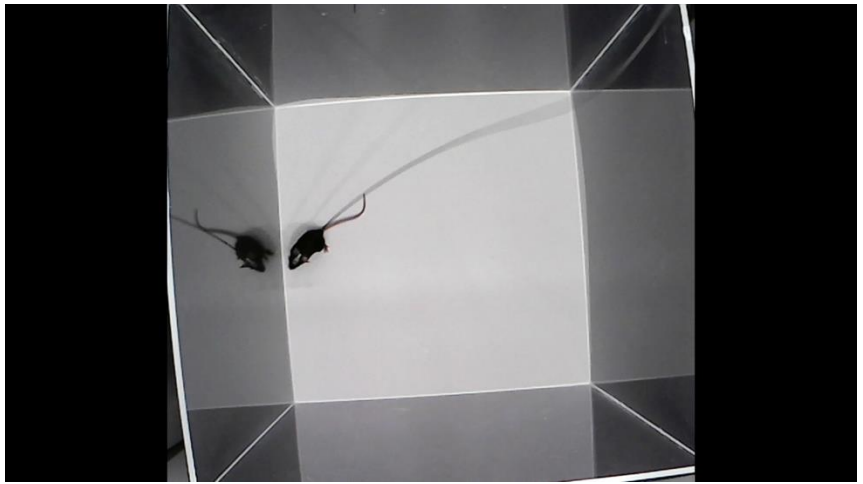
Behavior

In which species?

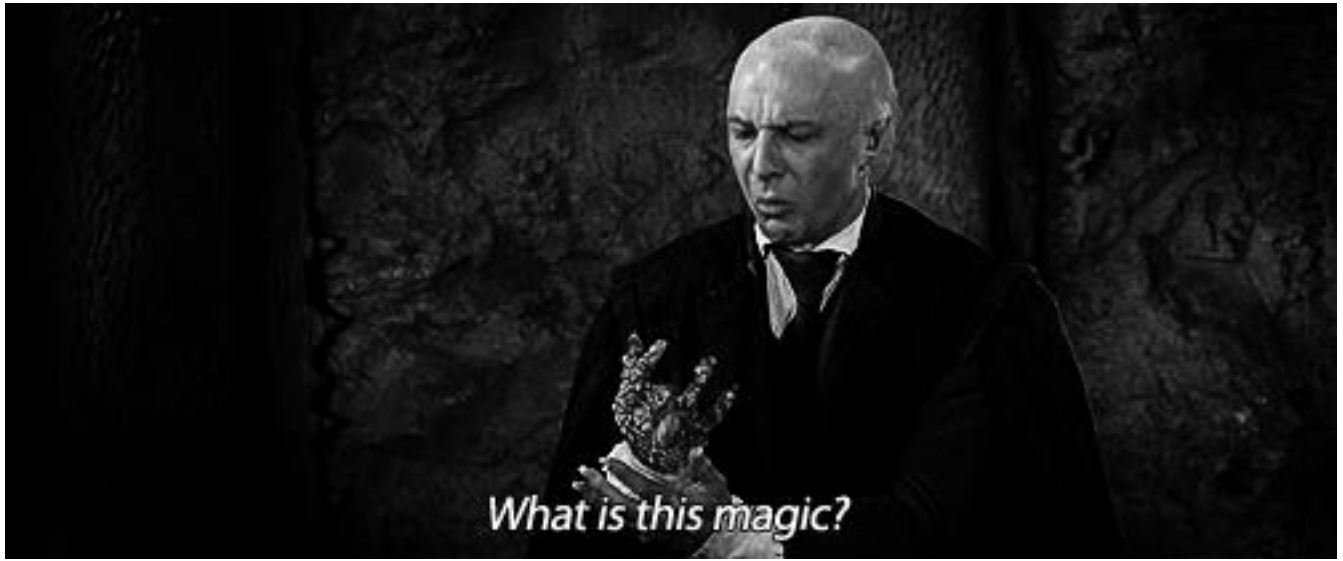


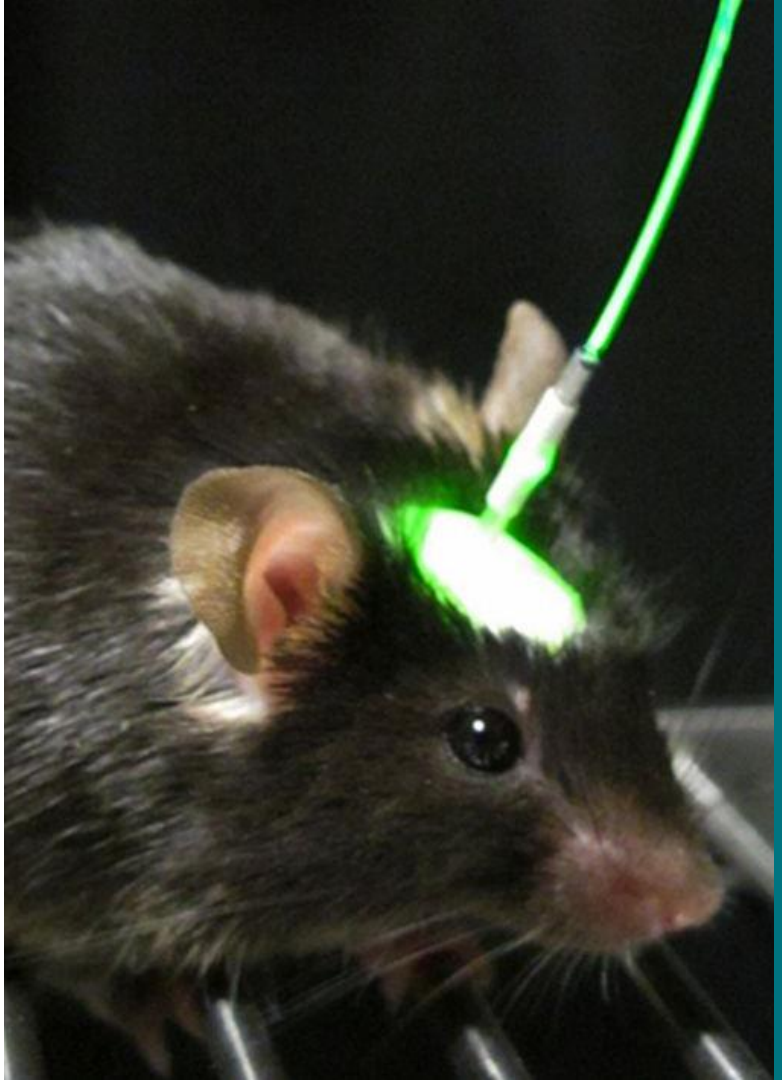
If you control brain-circuit activity, you control behavior





Grimm et al., Cell Reports, 2021


What is this magic?

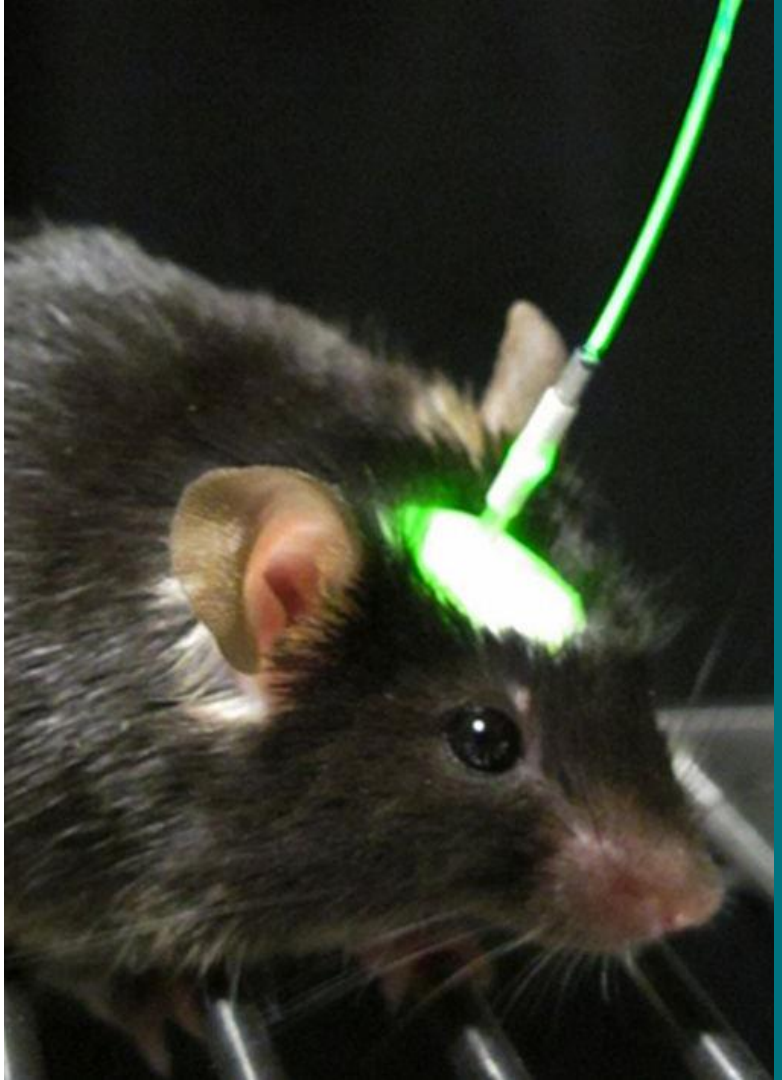


OUTLINE

1. Neural activity and action potentials
   - Generation
   - Transmission
   - Propagation
   - The synapsis

2. Engineering neural activity
   - Optogenetics
   - Chemogenetics
   - Sonogenetics

3. Some cool examples



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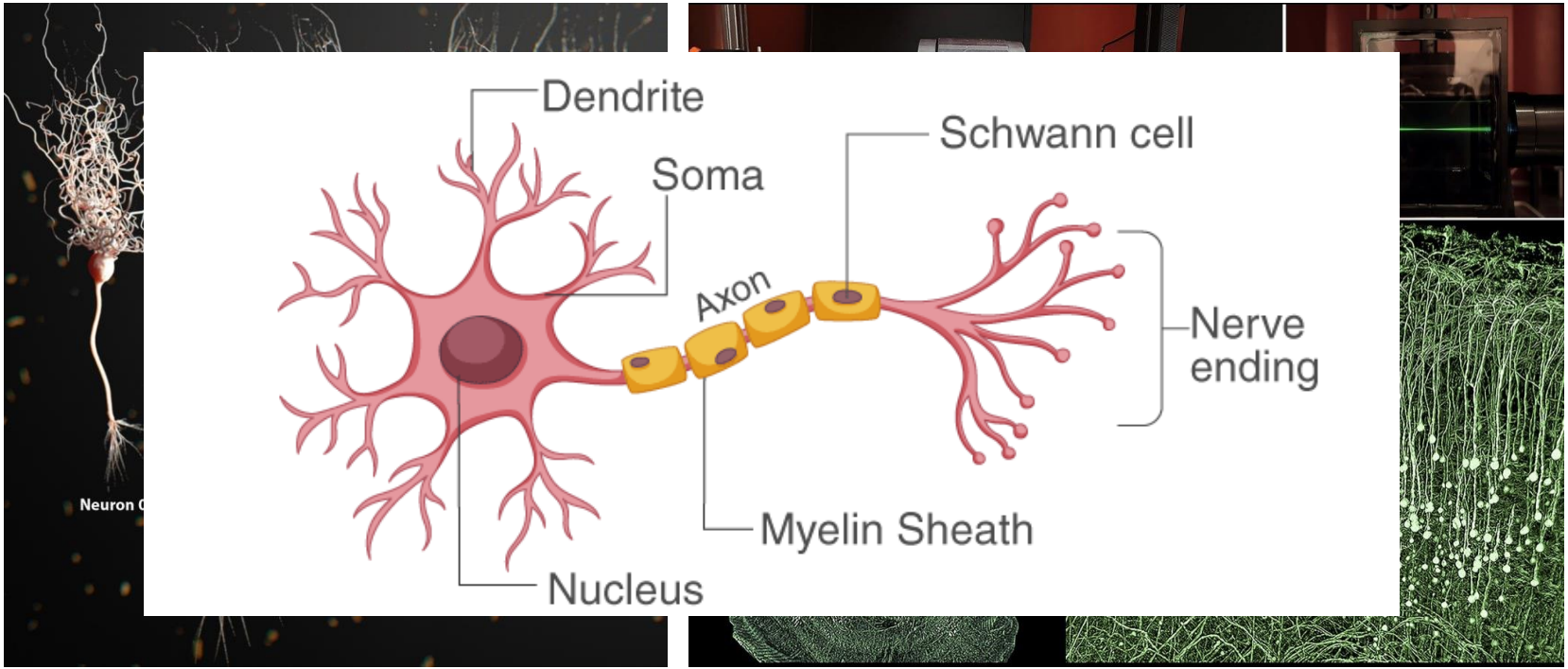
Neural activity and action potentials

Valerio Zerbi

The Neuron



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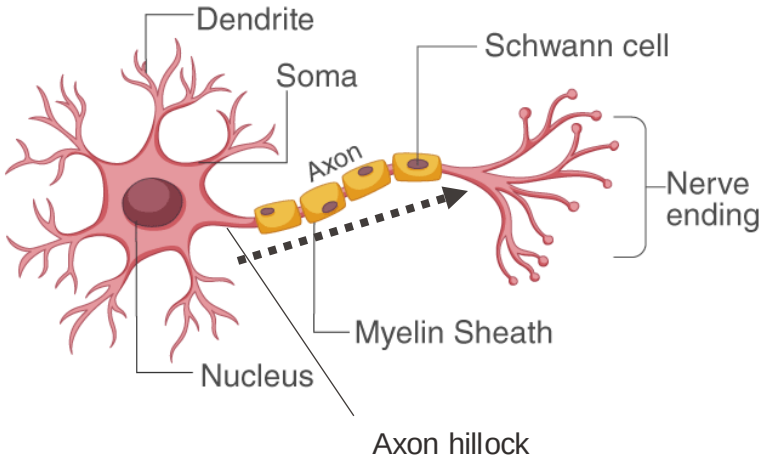
Neural activity and action potentials

The Neuron

Key proprieties

- ✓ Their function is to transmit information (in a single direction, dendrite → axons)
- ✓ Asymmetric. They communicate between each other at the start or end (synapse)
- ✓ Neurons are highly polarised cells



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Neural activity and action potentials

Polarization or resting potential (unexcited neuron)

1.Membrane Potential

The voltage difference across the neuron's membrane, known as "membrane potential," is comparable to a capacitor, typically resting at around -70mV, representing a polarized state

2.Na+ /K+ pumps

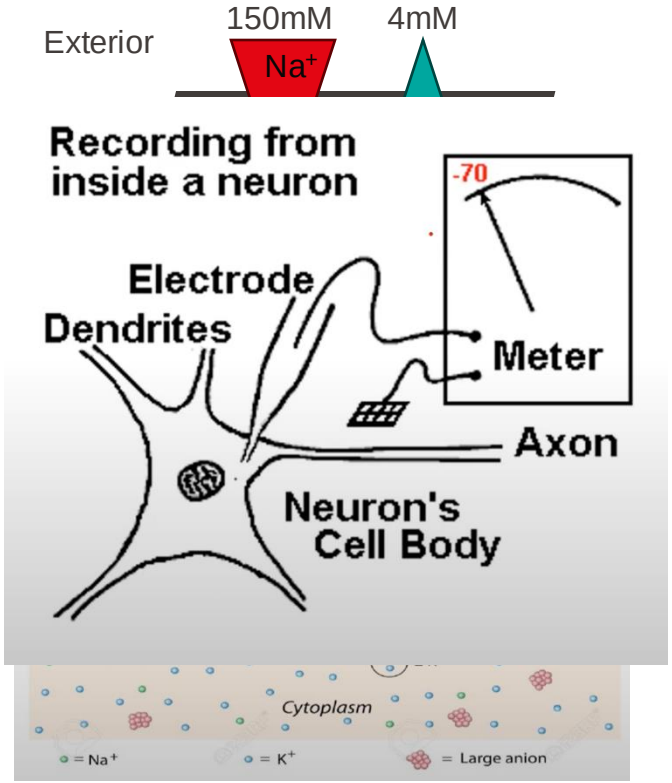
Neurons expend energy to maintain ion concentration gradients, allowing for electrical signalling. ATP is converted to ADP to actively transport 3 Na^+ ions out of the cell and pump 2 K^+ ions inside

3.Anions

Inside the cell there are large anions, which are negatively charged

4.Leaky channels

Diffusion of the Na^+ and K^+ across channels helps maintaining the resting potential across the membrane



Molecular Cell Biology, Seventh Edition. W.H. Freeman and Company

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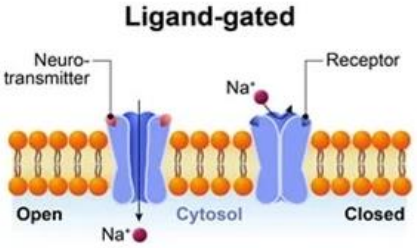
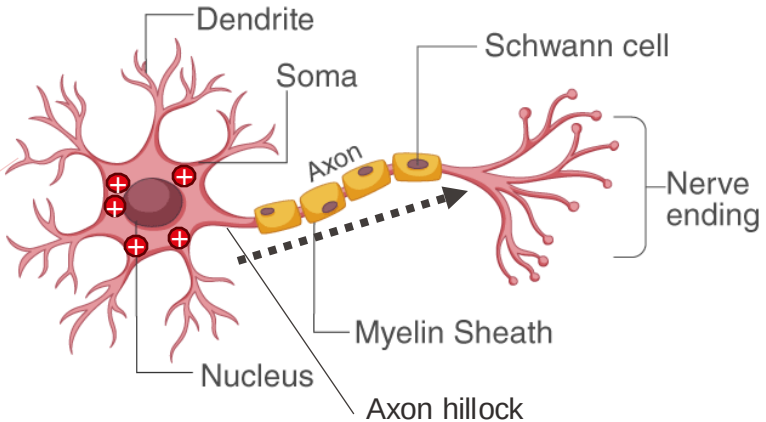
Neural activity and action potentials

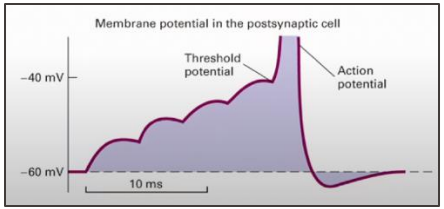
It all starts in the dendrites

Ligand-gated ion channels: allow positive or negative ions (eg. Na+) to flow into the cell following a chemical signalling (eg. Serotonin)
→ Transient change of membrane potential



Example: excitatory synapse





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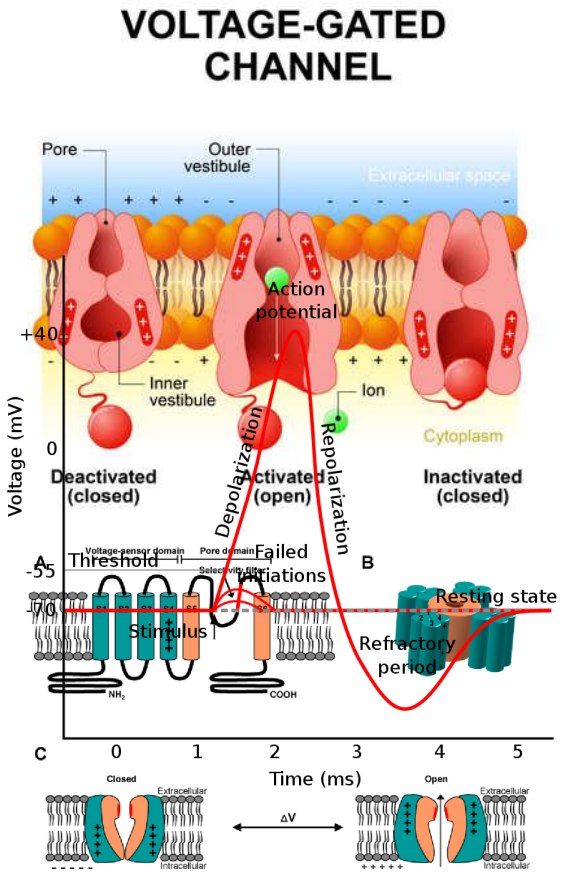
Neural activity and action potentials

The Action Potential (AP)

Voltage-Gated Na^+ channels
Open at -55mV and close at +40mV.
Sodium ions (Na+) rapidly enter the neuron through these channels, causing a swift change in membrane potential and depolarizing the membrane.
These channels physically block after 0.5-1ms, impeding more Na^+ to enter

Depolarization and K^+
Open at +40mV and close at -80mVAs
As the depolarization progresses, voltage-gated potassium (K+) channels also open, allowing **potassium ions to flow out** of the neuron. This potassium efflux helps repolarize the membrane quickly, restoring the negative resting membrane potential.



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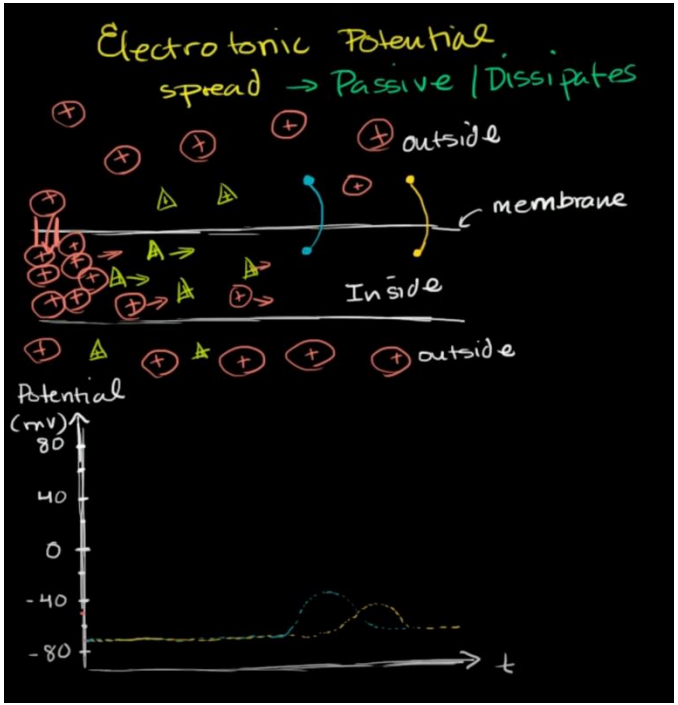
Neural activity and action potentials

Action potential is a traveling wave of ions



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Neural activity and action potentials

Action potential is a traveling wave of ions

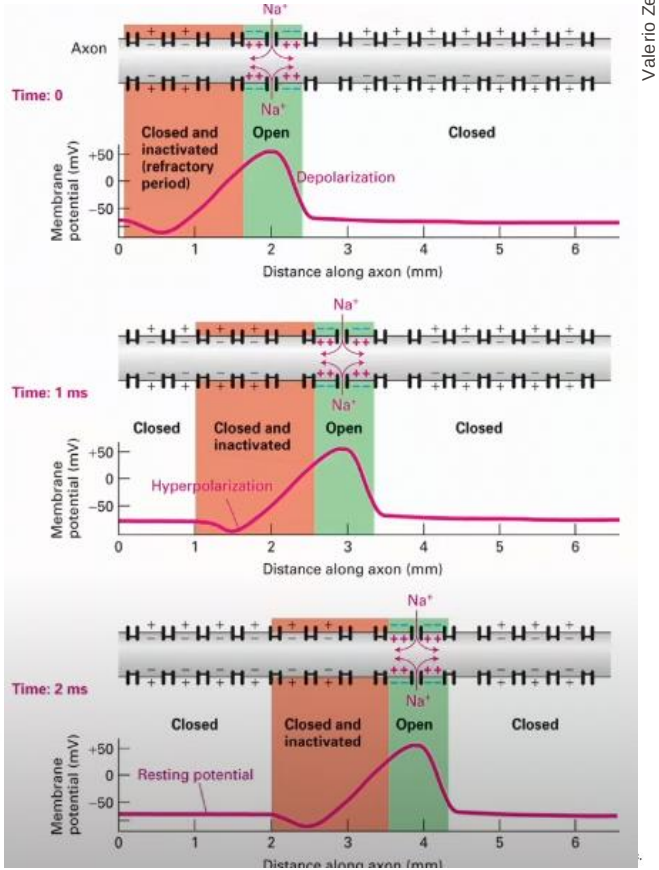
Traveling Wave

• Action potentials act as traveling waves, ensuring information travels in one direction along the neuron.

• Because the Na^+ voltage-gated channels close after 0.5-1ms, the AP can't travel backwards

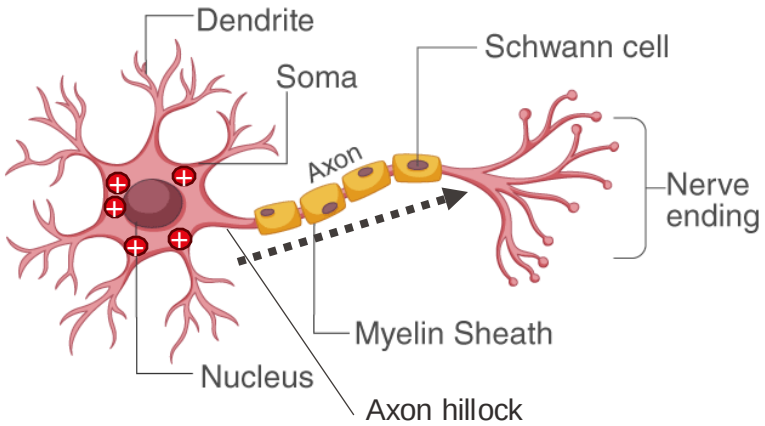
• In Myelinated axons the speed of conduction is up to 100fold faster transmission of the signal (speed) AP is jumping from node to node

• Disease like Multiple Sclerosis affects the myelin sheet (slow down AP, impact in the network communication)



Neural activity and action potentials

Synaptic transmission



Neural activity and action potentials

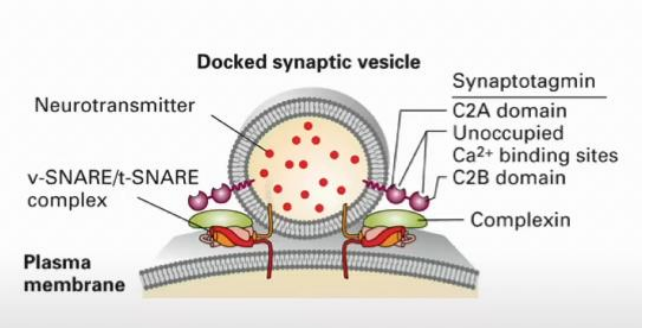
Synaptic transmission

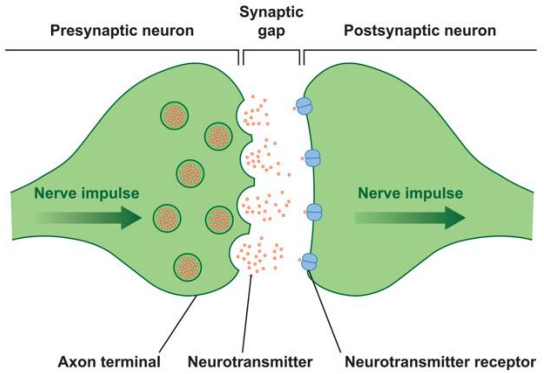
At the end of the axon, the synapsis contains vesicles that are docked at the plasma membrane and contain neurotransmitters

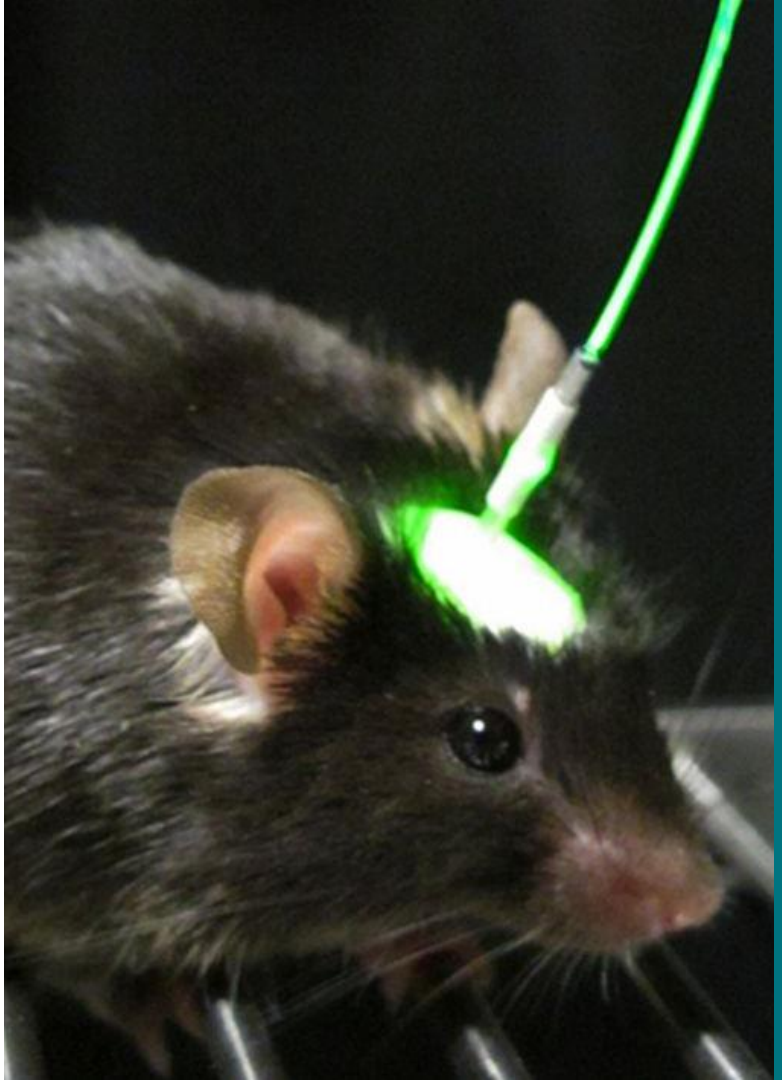
Fusion Trigger: Synaptic vesicle fusion is initiated by an increase in intracellular Ca2+ levels, which occurs upon receiving an action potential.

Neurotransmitter Release: This fusion process leads to the release of neurotransmitters into the synaptic cleft.

Signal Termination: The signal is terminated by re-absorption or re-uptake in the presynapse, a target for certain drugs like SSRI antidepressants, which are re-uptake inhibitors.







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3. Some cool examples

OPTOGENETICS

Opto? Genetics?

Integration of optics and genetics that allows for experimental control of events within a specific cell

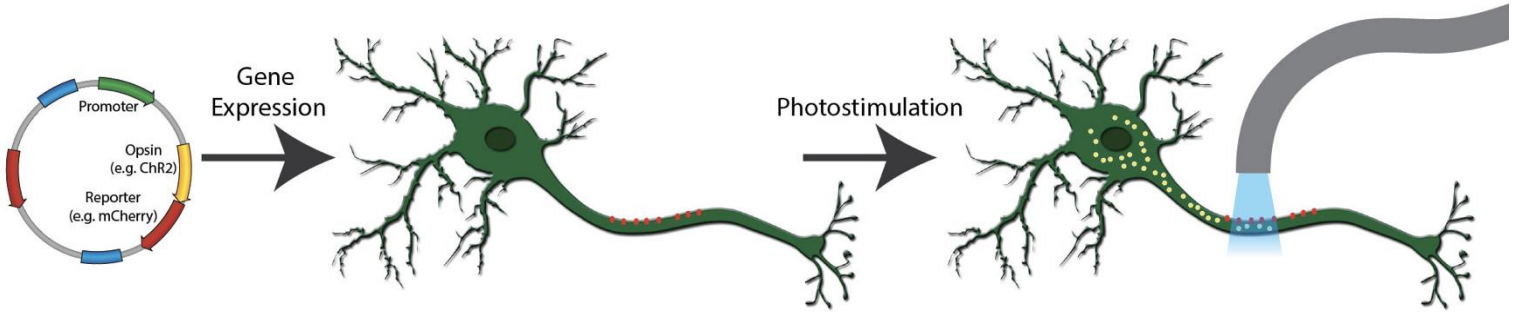
Valerio Zerbi

OPTOGENETICS

Building a tool to reach the ultimate goal in neuroscience

- If we could express a **light-activated ion channel** in a specific sub-population of neurons ..
- If we could then illuminate those neurons ..

✓.. we could influence behavior at the speed of light!



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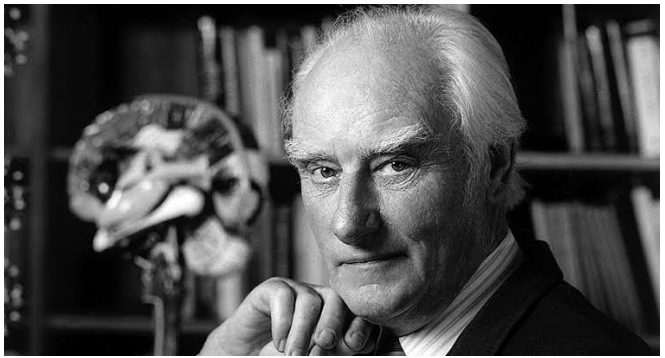
History

The possibility of using light to control neural activity (action potential) was first articulated by Francis Crick



THE ROYAL SOCIETY

The impact of molecular biology on neuroscience

Francis Crick, OM FRS

The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA

"One of the next requirements (as discussed above) is to be able to turn the firing of one or more types of neurons on and off in the alert animal in a rapid manner. The ideal signal would be light, probably at an infrared wavelength to allow the light to penetrate far enough. This seems rather farfetched but it is conceivable that molecular biologists could engineer a particular cell type to be sensitive to light in this way."

Francis Crick (1999)

OPTOGENETICS

Recipe for success

In order to light-control neurons, you need few things:

1. Light-sensitive system (sensor)
2. Ability to influence cellular ion flow in response to light (actuator)
3. Potential for co-expression of these systems in neurons
4. A system that does all these things without harming the cell

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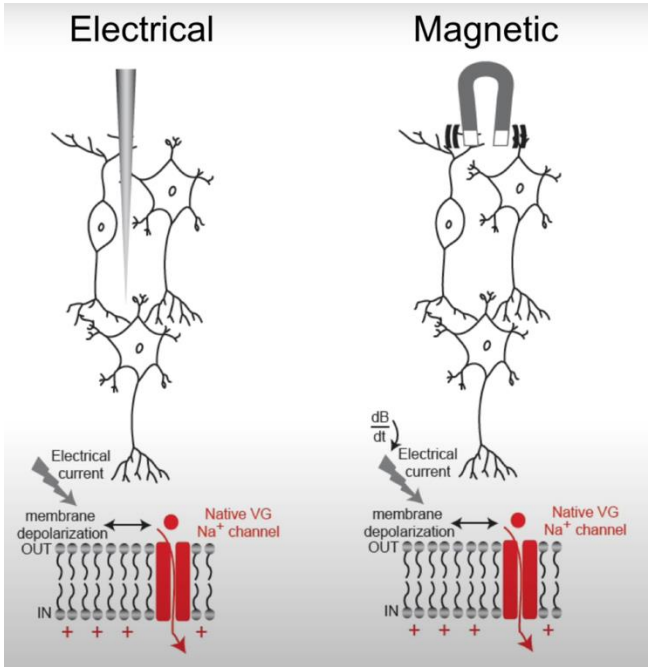
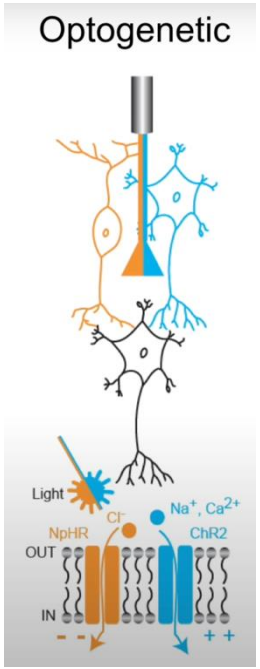
Basic Concepts



Non-specific



Cell-type-specific

OPTOGENETICS

Early developments: multi-component cocktails

> Neuron. 2002 Jan 3;33(1):15-22. doi: 10.1016/s0896-6273(01)00574-8.

Selective photostimulation of genetically chARGed neurons

Boris V Zemelman [1], Georgia A Lee, Minna Ng, Gero Miesenböck

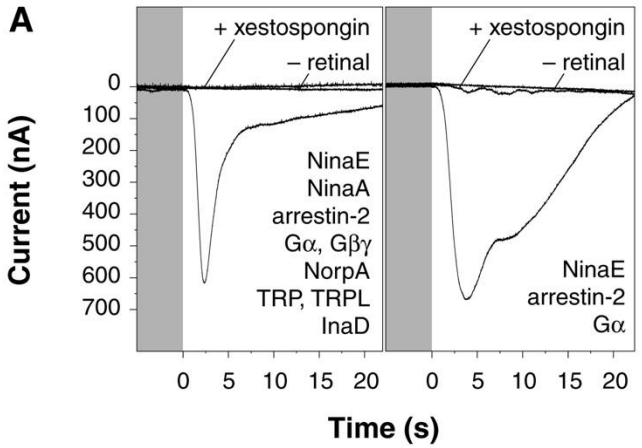
Affiliations + expand

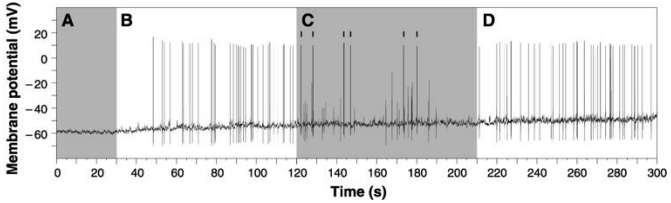
PMID: 11779476 DOI: 10.1016/s0896-6273(01)00574-8

Free article

Abstract

To permit direct functional analyses of neural circuits, we have developed a method for stimulating groups of genetically designated neurons optically. Coexpression of the Drosophila photoreceptor genes encoding arrestin-2, rhodopsin (formed by liganding opsin with retinal), and the alpha subunit of the cognate heterotrimeric G protein--an explosive combination we term "chARGe"--sensitizes generalist vertebrate neurons to light. Illumination of a mixed population of neurons elicits action potentials selectively and cell-autonomously in its genetically chARGed members. In contrast to bath-applied photostimulants or caged neurotransmitters, which act indiscriminately throughout the illuminated volume, chARGe localizes the responsiveness to light. Distributed activity may thus be fed directly into a circumscribed population of neurons in intact tissue, irrespective of the spatial arrangement of its elements.





OPTOGENETICS

Mayor Breakthrough: single component system

First demonstration of a single-component optogenetic system, beginning in cultured mammalian neurons using channelrhodopsin, a single-component light-activated cation channel from unicellular algae).

Prof. Karl Deisseroth

https://www.youtube.com/watch?v=MUGky_QaaV0&ab_channel=iBiologyScienceStories

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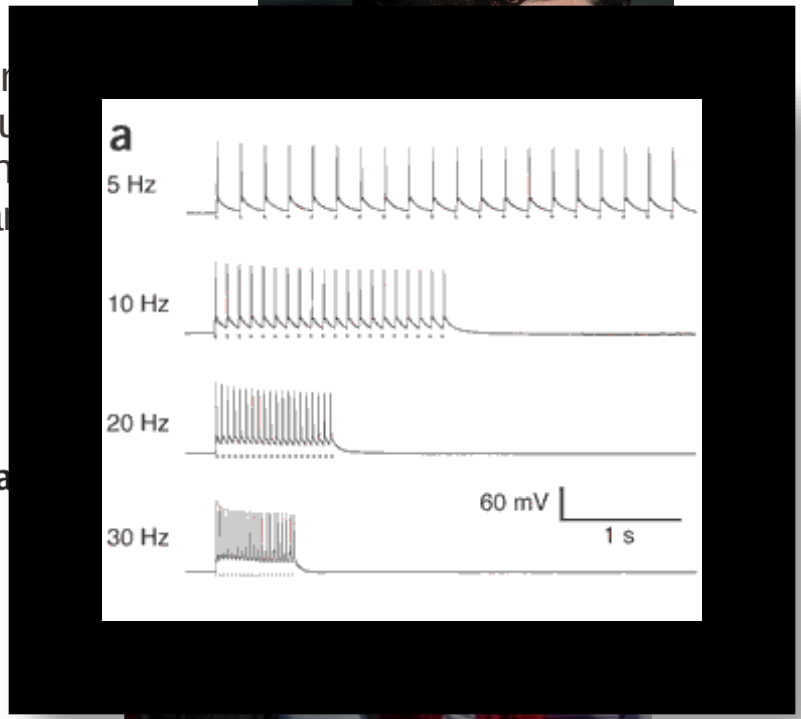

Comparative Study > Nat Neurosci. 2005 Sep;8(9):1263-8. doi: 10.1038/nn1525.
Epub 2005 Aug 14.

**Millisecond-timescale, genetically targeted optica
control of neural activity**

Edward S Boyden [1], Feng Zhang, Ernst Bamberg, Georg Nagel, Karl Deisseroth

Affiliations + expand

PMID: 16116447 DOI: 10.1038/nn1525

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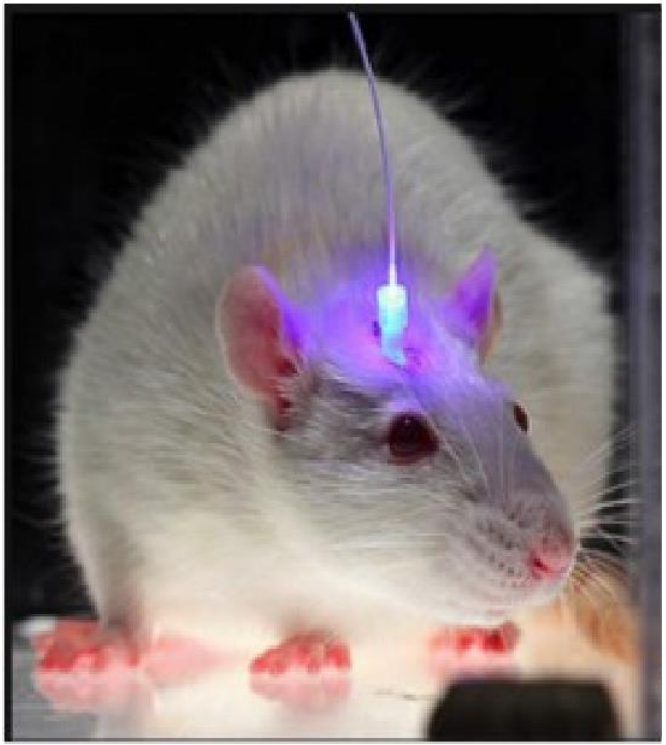
In six steps

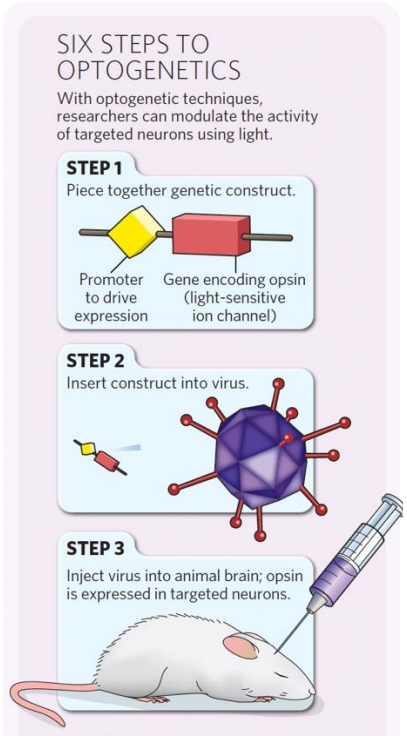


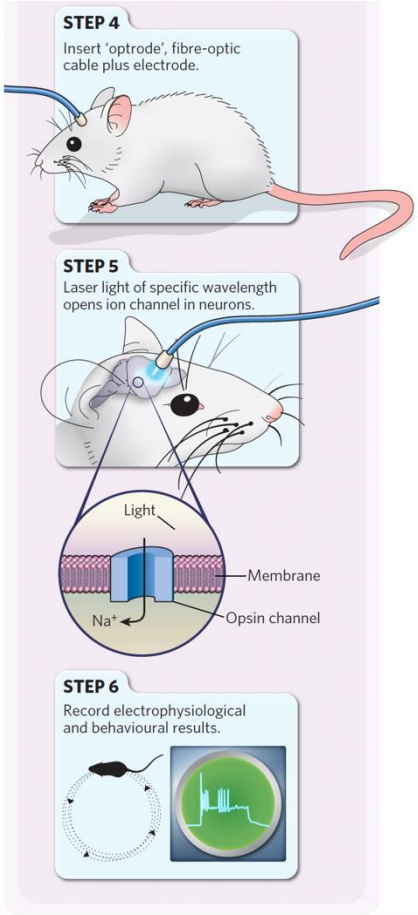
News Feature | Published: 05 May 2010

Neuroscience: Illuminating the brain

Lizzie Buchen

Nature **465**, 26–28 (2010) | Cite this article



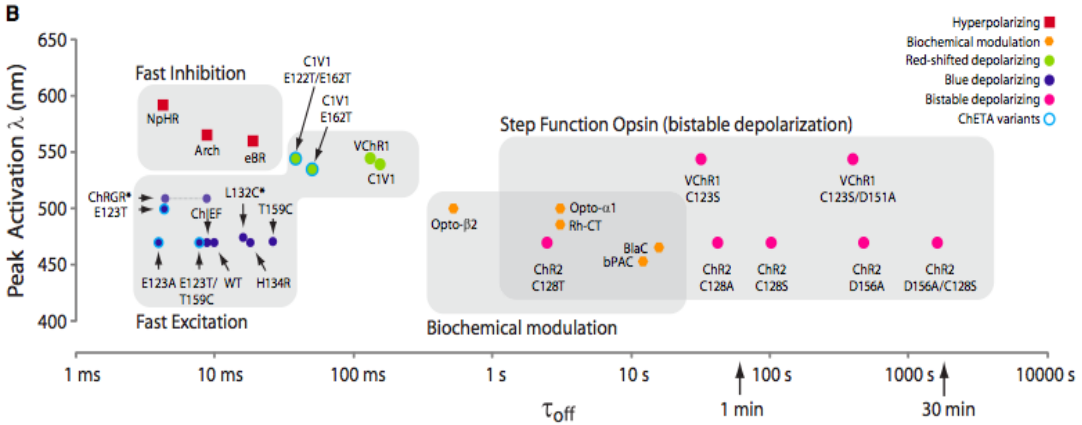


Valerio Zerbi

OPTOGENETICS

A diverse toolkit

- The optogenetic effect experienced by a cell will depend on many factors
  - The properties of single-component opsin being used
  - The efficiency of the expression of that opsin
  - The source/wavelength/intensity of the light
  - The location and density of the population of neurons being investigated



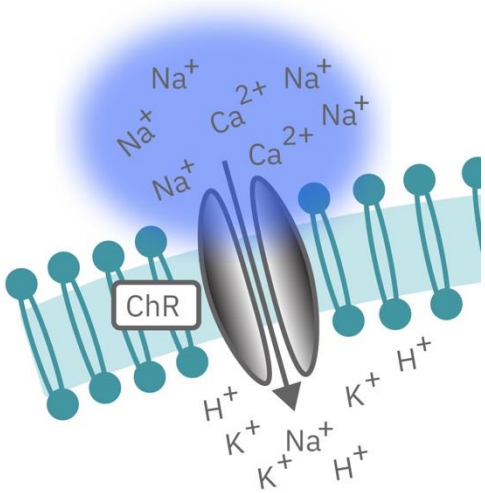
OPTOGENETICS

Valerio Zerbi

A diverse toolkit

Opsin	Mechanism	Peak Activation λ	Off Kinetics (τ, ms)*	Kinetics References
Blue/Green Fast Excitatory				
ChR2	Cation channel	470 nm	~10 ms	Boyden et al., 2005; Nagel et al., 2003
ChR2(H134R)	Cation channel	470 nm	18 ms	Nagel et al., 2005; Gradinaru et al., 2007
ChR2 (T159C)	Cation channel	470 nm	26 ms	Berndt et al., 2011
ChR2 (L132C)	Cation channel	474 nm	16 ms*	Kleinlogel et al., 2011
ChETAs: ChR2(E123A) ChR2(E123T) ChR2(E123T/T159C)	Cation channel	470 nm (E123A) 490 nm (E123T)	4 ms (E123A) 4.4 ms (E123T) 8 ms (E123T/T159C)	Gunaydin et al., 2010; Berndt et al., 2011
ChIEF	Cation channel	450 nm	~10 ms	Lin et al., 2009
ChRGR	Cation channel	505 nm	4-5 ms* (8-10ms)	Wang et al., 2009; Wen et al., 2010
Yellow/Red Fast Excitatory				
VChR1	Cation channel	545 nm	133 ms	Zhang et al., 2008
C1V1	Cation channel	540 nm	156 ms	Yizhar et al., 2011a
C1V1 ChETA (E162T)	Cation channel	530 nm	58 ms	Yizhar et al., 2011a
C1V1 ChETA (E122T/E162T)	Cation channel	535 nm	34 ms	Yizhar et al., 2011a

Fast excitation



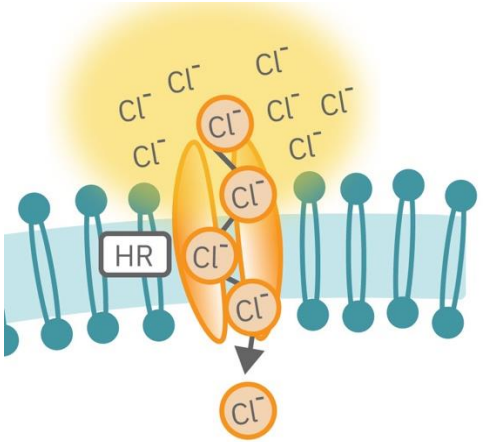
OPTOGENETICS

A diverse toolkit

Yellow/Red Inhibitory				
eNpHR3.0	Chloride pump	590 nm	4.2 ms	Gradinaru et al., 2010
Green/Yellow Inhibitory*				
Arch/ArchT	Proton pump	566 nm	9 ms	Chow et al., 2010
eBR	Proton pump	540 nm	19 ms	Gradinaru et al., 2010

Active pumps (slower)

Fast inhibition



Halorhodopsin

Valerio Zerbi

OPTOGENETICS

A diverse toolkit

- Product of molecular engineering
- Much slower deactivation rate
- Cation (or chloride) channels
- Larger disparity between activating wavelength and deactivating wavelength

Bistable Modulation				
ChR2-step function opsins (SFOs)	Cation channel	470 nm activation / 590 nm deactivation	2 s (C128T); 42 s (C128A) 1.7 min (C128S) 6.9 min (D156A) 29 min (128S/156A)	Berndt et al., 2009; Bamann et al., 2010 Yizhar et al., 2011a
VChR1-SFOs	Cation channel	560 nm activation / 390 nm deactivation	32 s (C123S) 5 min (123S/151A)	

Step Function Opsins (SFOs)

OPTOGENETICS

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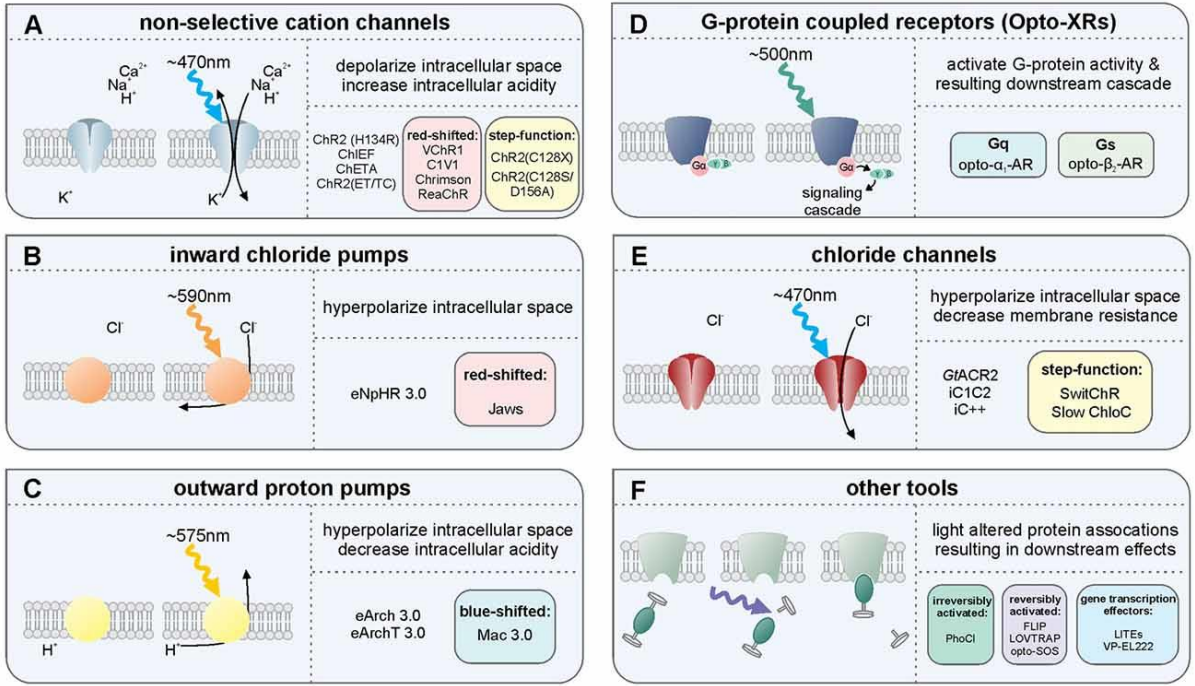
A diverse toolkit



Wick, Krook-Magnuson 2018

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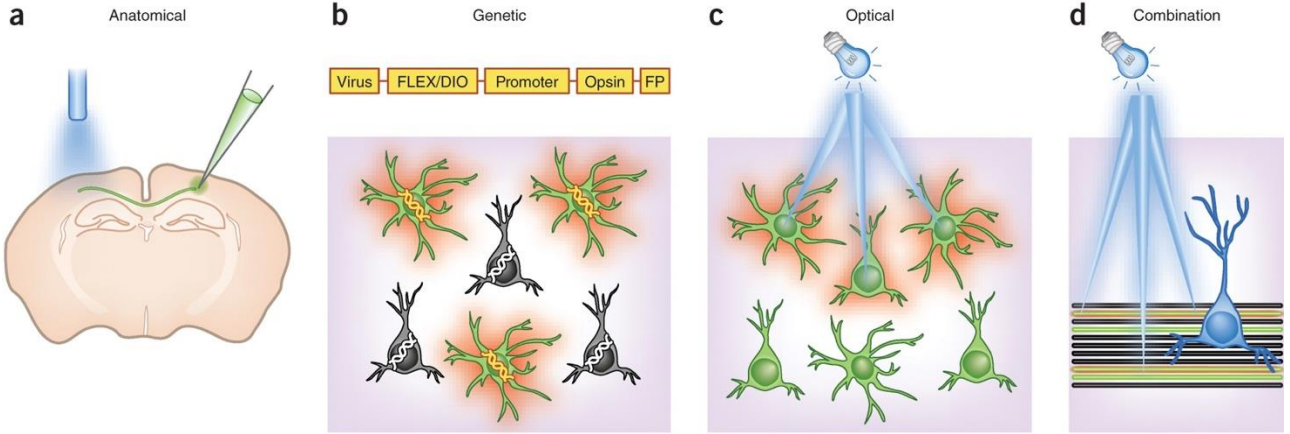
OPTOGENETICS

Targeting neurons with opsins

1. Anatomical Coordinates (injection & light)
2. Viral vector (Lenti (LV), Adeno-associated (AAV), canine, rabies, ..)
3. Viral promoter (CamKIIa, Syn1, …)
4. Transgenic mouse lines that are under recombinase-dependent control
5. Spatiotemporal targeting (Birthdate of cells , specific layer, …)
6. Light delivery



OPTOGENETICS

Light delivery (1)

Assuming you are expressing the correct opsin in the desired cell population, you now need to somehow get light to those cells.

There are several facets to consider, and the best choice will depend on your experiment

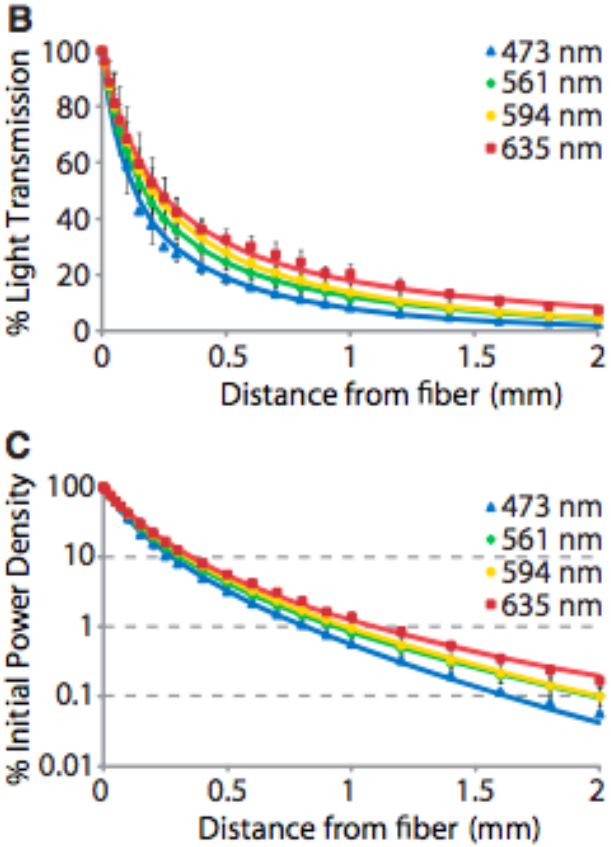
- ✓ Excitation vs inhibition vs bistable
- ✓ Wavelength
- ✓ Intensity
- ✓ Duration

OPTOGENETICS

Light delivery (2)

Brain tissue scatters and absorbs light

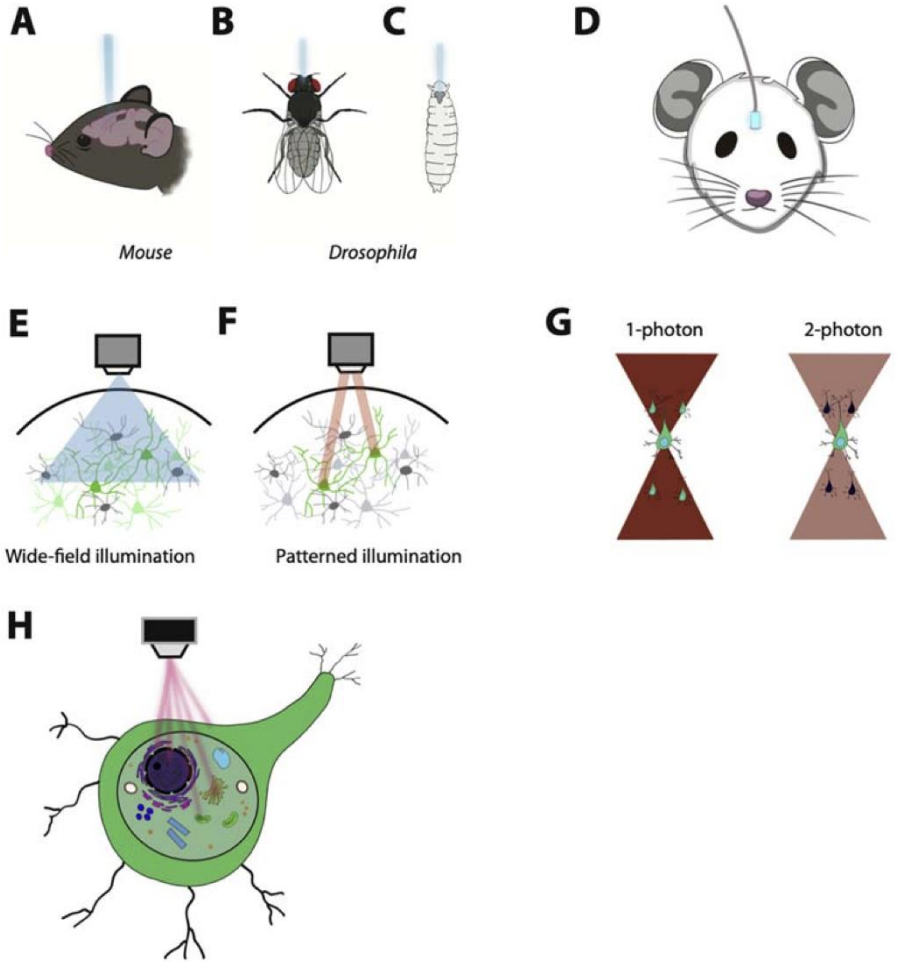
Different wavelengths of light penetrate brain tissue better than others



OPTOGENETICS

Advanced Tools

More than just an optic fiber ..



OPTOGENETICS

Recap

CHEMOGENETICS

What if..

Instead of proteins that are sensitive to light, can we engineer proteins that respond exclusively to synthetic compounds (designer drugs) and not endogenous ligands?

-> A step toward a translational tool (no optic fiber required)

CHEMOGENETICS

DREADDs

Designer
Receptors
Exclusively
Activated by
Designer
Drugs

Neuron. Author manuscript; available in PMC 2017 Feb 17.
Published in final edited form as:
Neuron. 2016 Feb 17; 89(4): 683–694.
doi: 10.1016/j.neuron.2016.01.040

DREADDs for Neuroscientists

Bryan L. Roth[1,*]

Prof. Bryan Roth

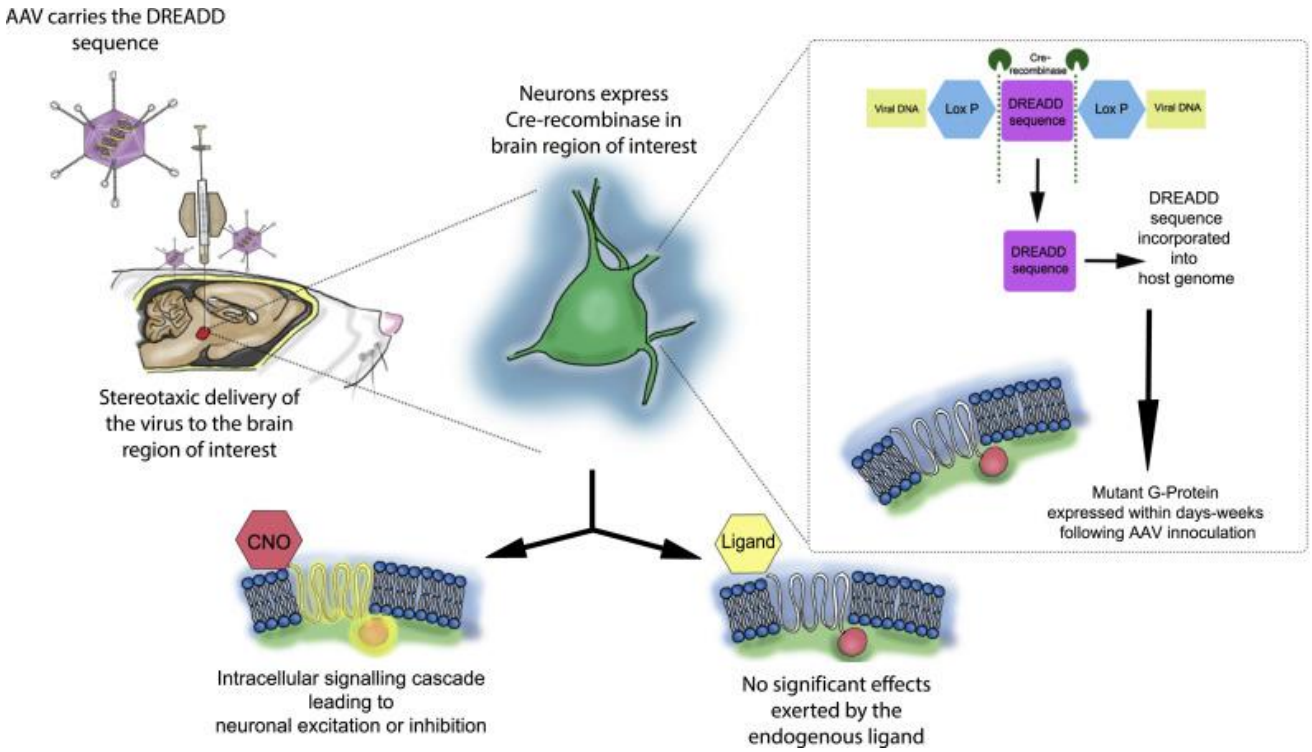
DREADDs were originally invented by modifying muscarinic acetylcholine receptors to be activated by the inert ligand clozapine-*N*-oxide (CNO) via directed molecular evolution in genetically engineered yeast (Armbruster et al., 2007)

https://www.youtube.com/watch?v=lfddjwrk6e8

CHEMOGENETICS

DREADDs

Designer
Receptors
Exclusively
Activated by
Designer
Drugs



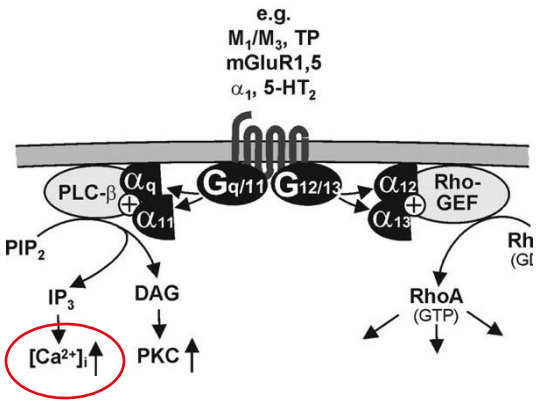
Sharma et al., 2018

CHEMOGENETICS

DREADDs

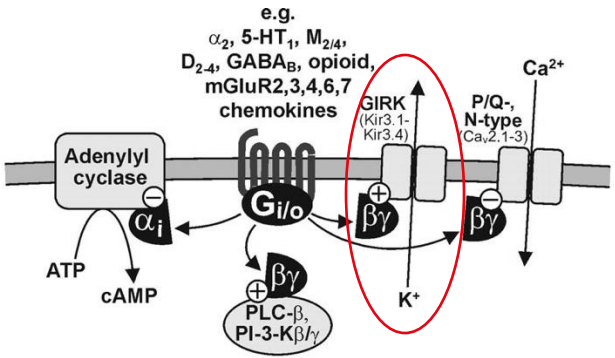
Designer
Receptors
Exclusively
Activated by
Designer
Drugs

hM3Dq



Neuronal excitation

hM4Di

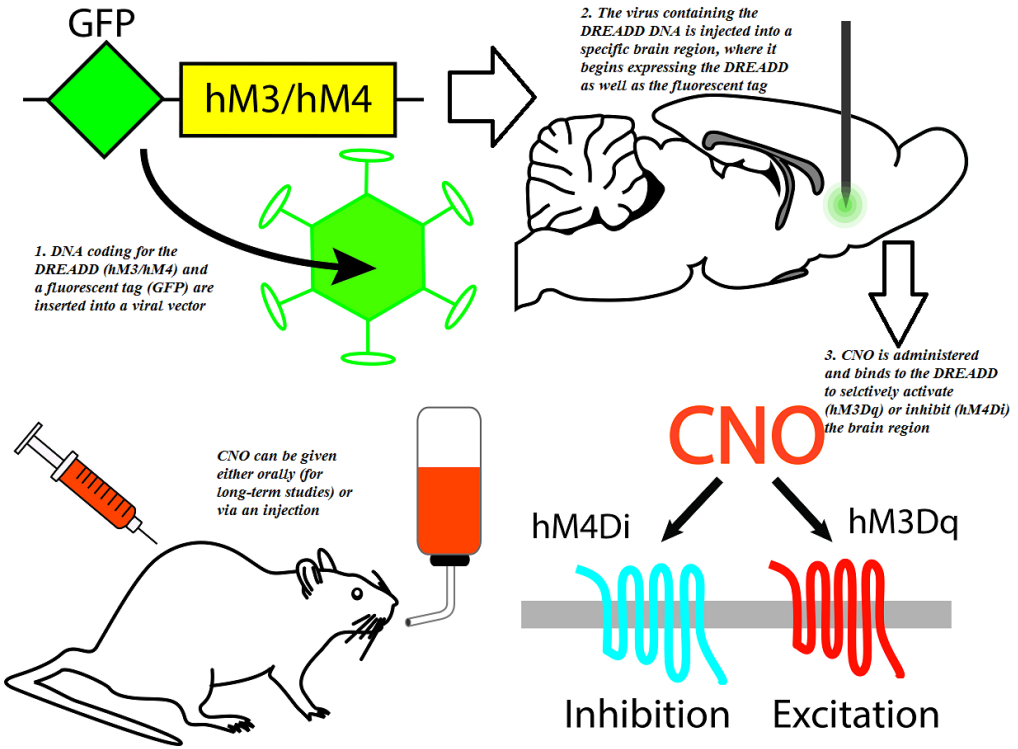


Neuronal inhibition

CHEMOGENETICS

DREADDs

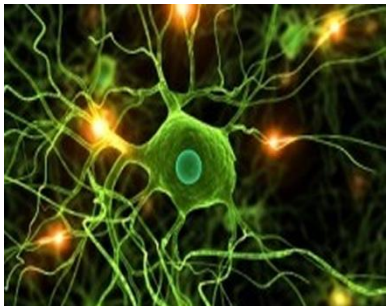
Designer
Receptors
Exclusively
Activated by
Designer
Drugs



CHEMOGENETICS or OPTOGENETICS?

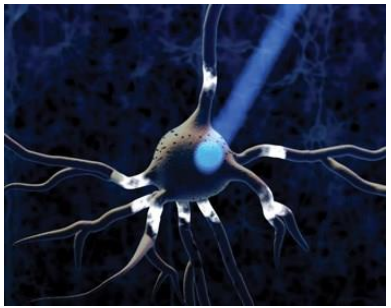
Chemogenetic: DREADDs

- AAV delivery
- Neuron-specific
- Activated systemically by drug
- Reversible
- No external implant
- Effect lasts 30min-2h



Optogenetics

- AAV delivery
- Neuron-specific
- Activated locally by light
- Reversible
- Requires external implant
- Millisecond control



SONOGENETICS

Replacing light with soundwaves?

ELSEVIER

Brain Stimulation

Volume 15, Issue 5, September–October 2022, Pages 1308-1317

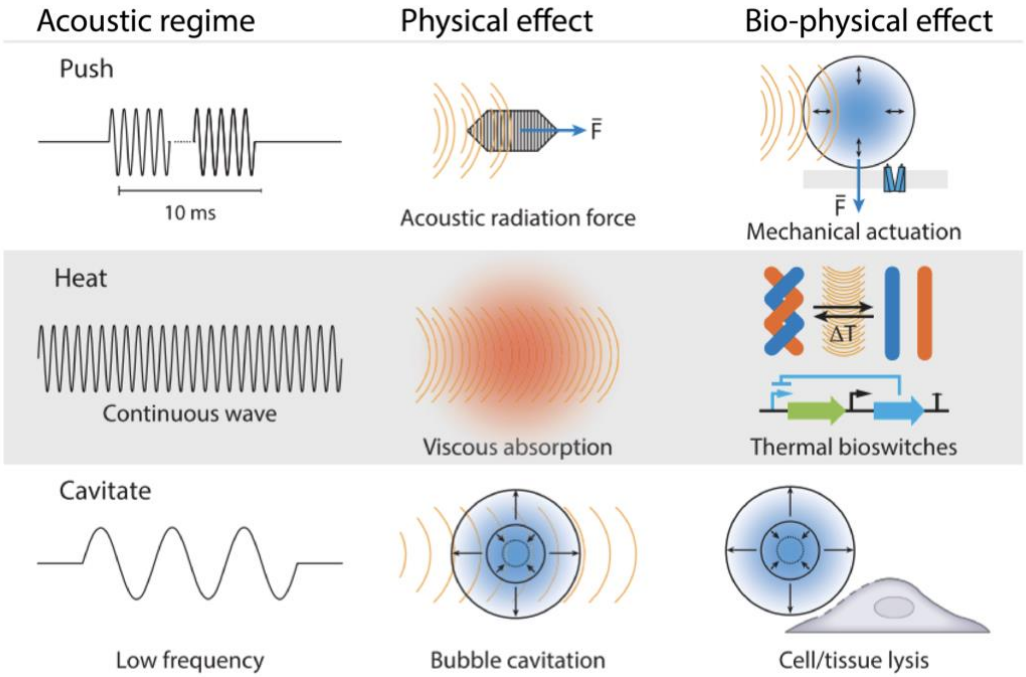
Sonogenetics: Recent advances and future directions

Tianyi Liu [a], Mi Hyun Choi [b], Jiejun Zhu [a], Tingting Zhu [a], Jin Yang [a], Na Li [a e], Zihao Chen [a e], Quanxiang Xian [c], Xuandi Hou [c], Dongmin He [a], Jinghui Guo [c d], Chunlong Fei [e], Lei Sun [c], Zhihai Qiu [a]

SONOGENETICS

How Does it Work?

US can produce **thermal or mechanical** effects on the tissue



SONOGENETICS

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Replacing light with soundwaves?

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Table 1
Mediators for Sonogenetics *in vivo*.

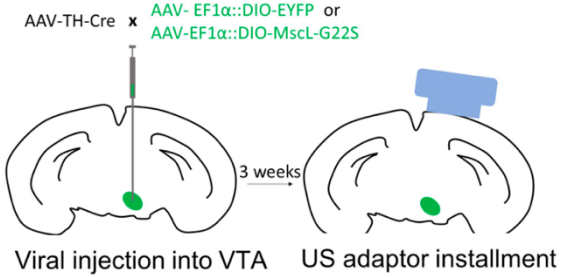
Mediator	Nature of the mediator	Frequency (MHz)	Acoustic pressure (MPa)	Promoter	Validation method
MscL-G22s	Mechanosensitive ion channel	0.5, 2.25, 15	>0.3	hSyn, CaMKII, SNCG,	Cellular calcium imaging, EMG, fiber photometry, MEA, EcoCG, Behaviors
TRPV1	Thermal sensitive ion channel	1.5, 1.7	>0.9	CaMKII	In vitro calcium imaging, *in vivo* two photon calcium imaging, Place preference behaviors
*m*Prestin	Membrane protein for electromobility in hair cell in ear	0.5	>0.5	hSyn	Cellular calcium imaging *in vitro*, c fos staining
*hs*TRPA1	Ion channel	7	>1.05	hSyn DIO, hSyn. Cre	EMG, c-fos staining, Behaviors
Gas vesicles	Nano-sized protein structure	1	0.2	N.A.	fiber photometry, EMG, c fos staining

SONOGENETICS

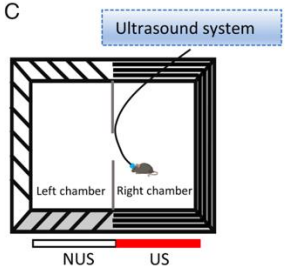
Valerio Zerbi

Sonogenetics of dopaminergic neurons in VTA & behavior

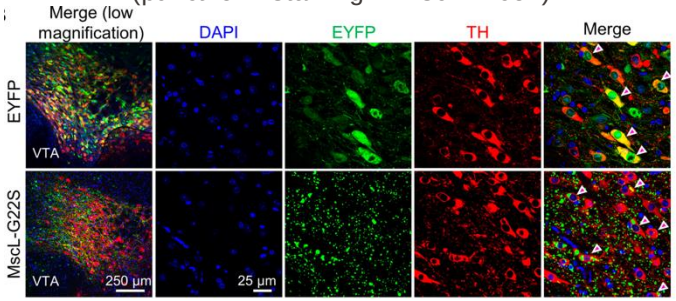
Mix of AAVs to target the TH+ neurons (Cre strategy)



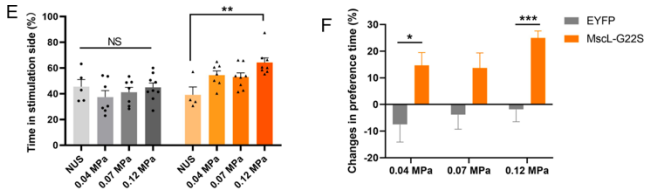
Appetitive conditioning
(real-time place preference essay)



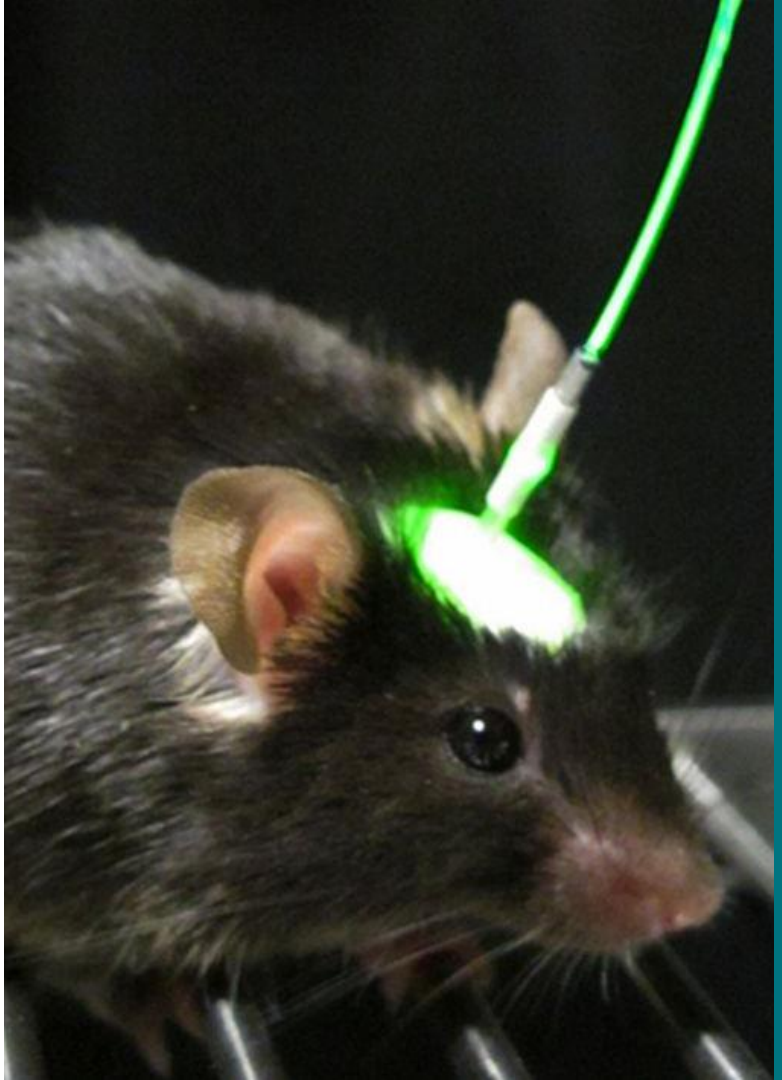
Co-expression of EYFP and TH
(punctiform staining in MscL mice?)



MscL mice spend more time in the stimulated side



NB: worked only with smooth waveform, rectangular had an aversive effect in control mice
-> unspecific auditory effects?



OUTLINE

1. Neural activity and action potentials
   - Generation
   - Transmission
   - Propagation
   - The synapsis

2. Engineering neural activity
   - Optogenetics
   - Chemogenetics
   - Sonogenetics

3. Some cool examples

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OPTOGENETICS – EXAMPLES (1)

Can memories be controlled via optogenetics?

nature > letters > article

Published: 01 June 2014

Engineering a memory with LTD and LTP

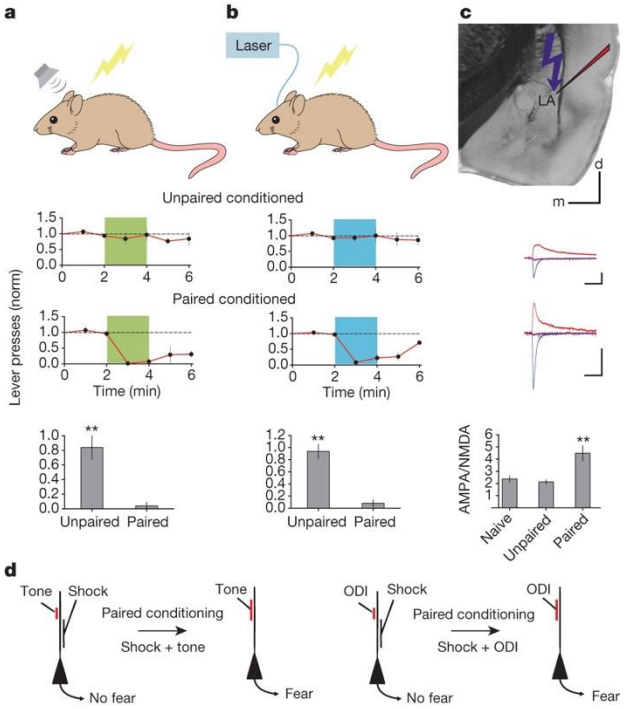
Sadegh Nabavi, Rocky Fox, Christophe D. Proulx, John Y. Lin, Roger Y. Tsien & Roberto Malinow

Nature **511**, 348–352 (2014) | Cite this article

78k Accesses | **633** Citations | **504** Altmetric | Metrics

Abstract

It has been proposed that memories are encoded by modification of synaptic strengths through cellular mechanisms such as long-term potentiation (LTP) and long-term depression (LTD)[1]. However, the causal link between these synaptic processes and memory has been difficult to demonstrate[2]. Here we show that fear conditioning[3,4,5,6,7,8], a type of associative memory, can be inactivated and reactivated by LTD and LTP, respectively. We began by conditioning an animal to associate a foot shock with optogenetic stimulation of auditory inputs targeting the amygdala, a brain region known to be essential for fear conditioning[3,4,5,6,7,8]. Subsequent optogenetic delivery of LTD conditioning to the auditory input inactivates memory of the shock. Then subsequent optogenetic delivery of LTP conditioning to the auditory input reactivates memory of the shock. Thus, we have engineered inactivation and reactivation of a memory using LTD and LTP, supporting a causal link between these synaptic processes and memory.



OPTOGENETICS – EXAMPLES (1)

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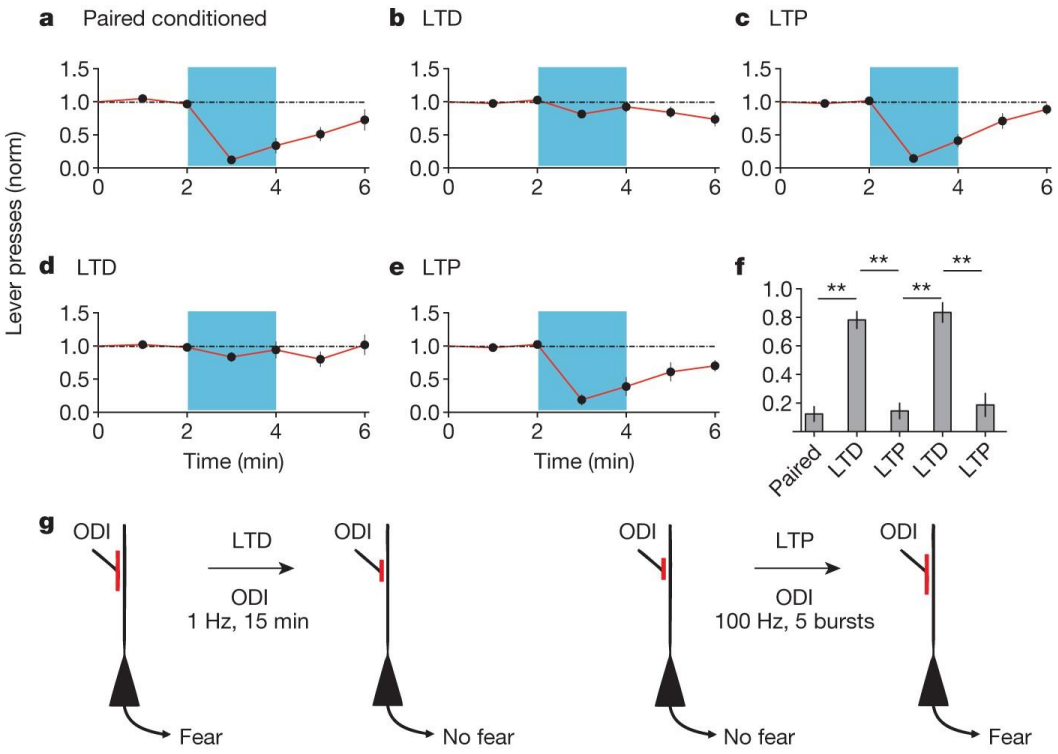
Can memories be controlled via optogenetics?

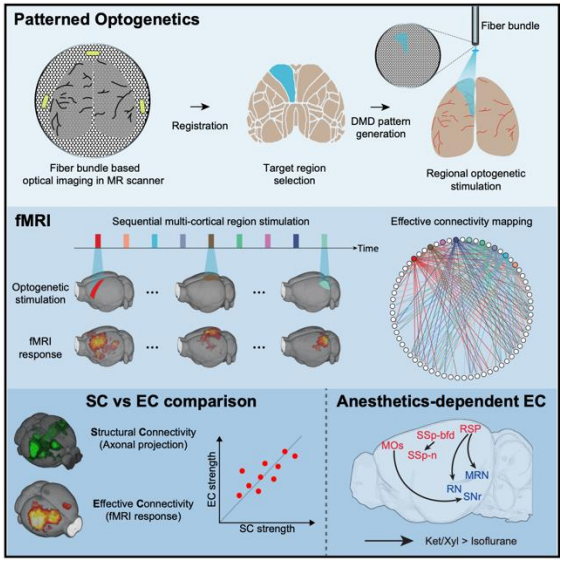


LTD Optogenetics protocol abolishes CS responses (erase fear memory)

LTP Optogenetics protocol re-establishes CS responses

OPTOGENETICS – EXAMPLES (2)

Opto-fMRI to perform whole-brain mapping of effective connectivity?



Neuron

CellPress

Volume 111, Issue 11, 7 June 2023, Pages 1732-1747.e6

NeuroResource

Whole-brain mapping of effective connectivity by fMRI with cortex-wide patterned optogenetics

Seonghoon Kim [1 2 6], Hyun Seok Moon [1 3 4 6], Thanh Tan Vo [1 3 4], Chang-Ho Kim [2 5], Geun Ho Im [1], Sungho Lee [2], Myunghwan Choi [1 2 5], Seong-Gi Kim [1 3 4 7]

OPTOGENETICS – EXAMPLES (2)

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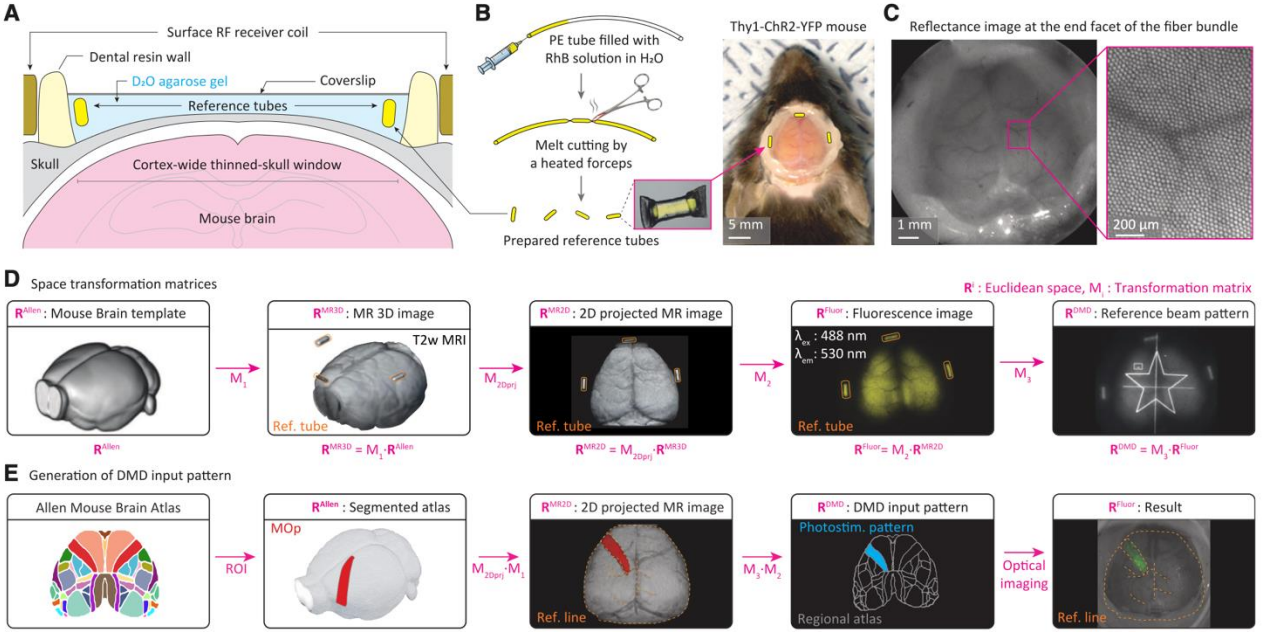
Opto-fMRI to perform whole-brain mapping of effective connectivity?

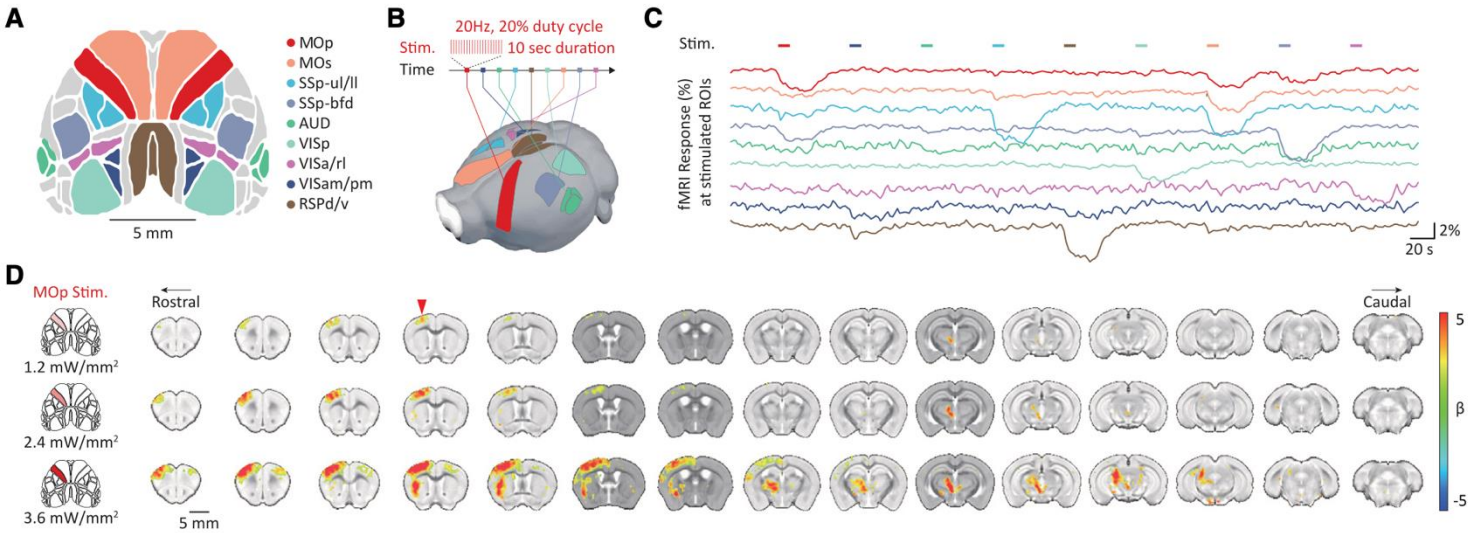


Kim et al., 2023

Valerio Zerbi

OPTOGENETICS – EXAMPLES (2)

Opto-fMRI to perform whole-brain mapping of effective connectivity?



Kim et al., 2023

OPTOGENETICS – EXAMPLES (2)

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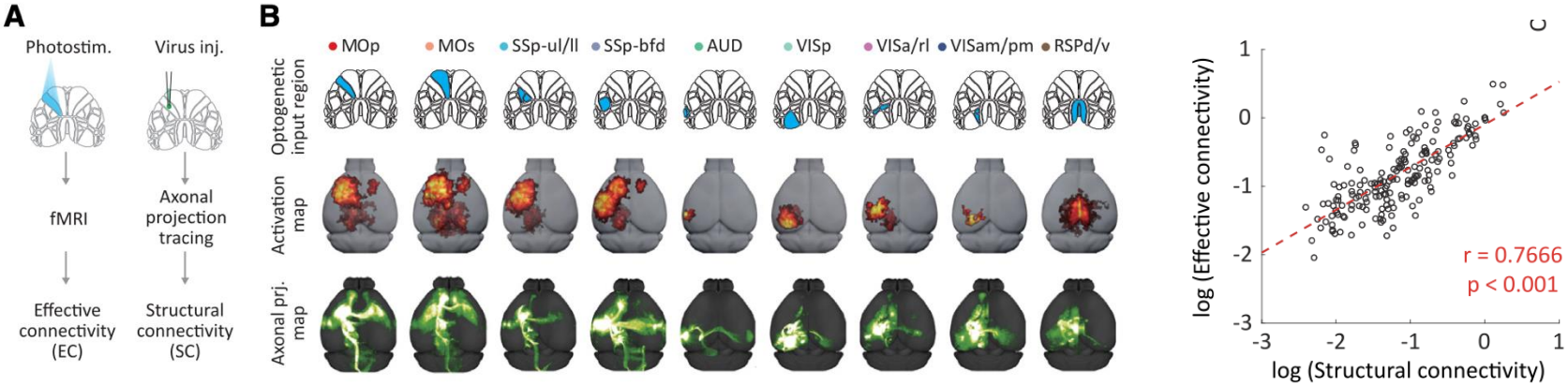
Opto-fMRI to perform whole-brain mapping of effective connectivity?

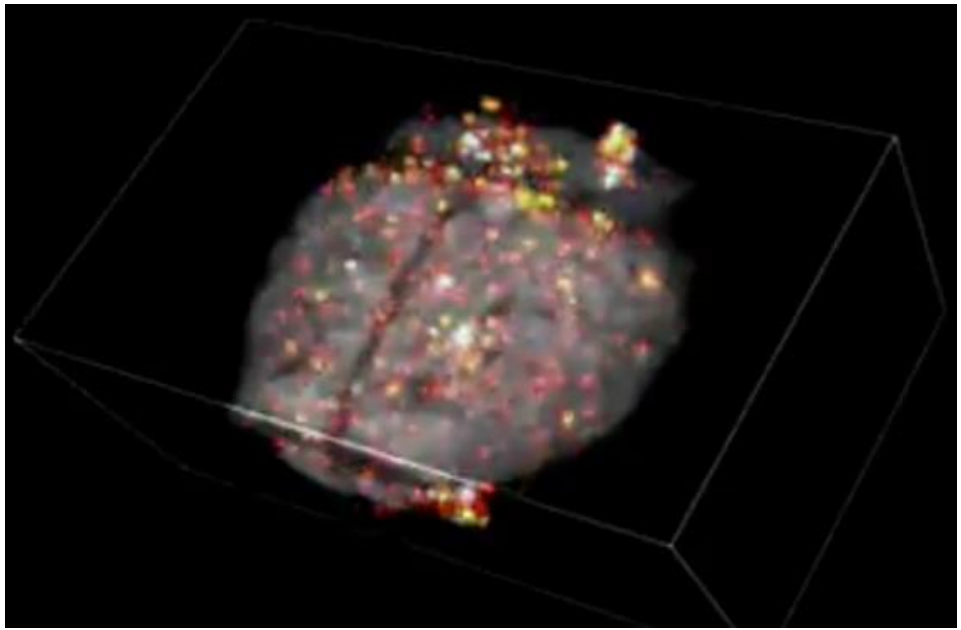


Excellent agreement between effective FC and structural axonal connectivity (from the cortex)

Kim et al., 2023

OPTOGENETICS – EXAMPLES (2)

Opto-fMRI to perform whole-brain mapping of effective connectivity?



Kim et al., 2023

OPTOGENETICS – EXAMPLES (3)

Optogenetics & addiction

nature

Explore content | About the journal | Publish with us

nature > letters > article

Published: 03 April 2013

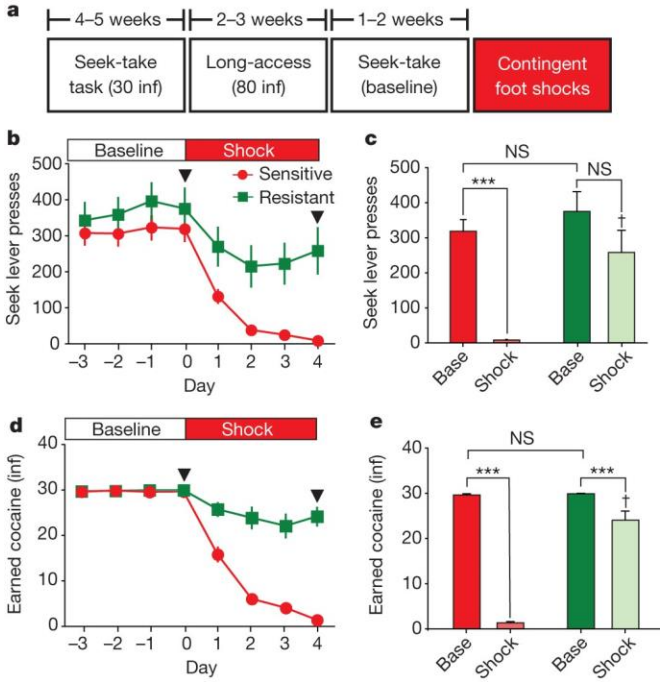
Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking

Billy T. Chen, Hau-Jie Yau, Christina Hatch, Ikue Kusumoto-Yoshida, Saemi L. Cho, F. Woodward Hopf & Antonello Bonci

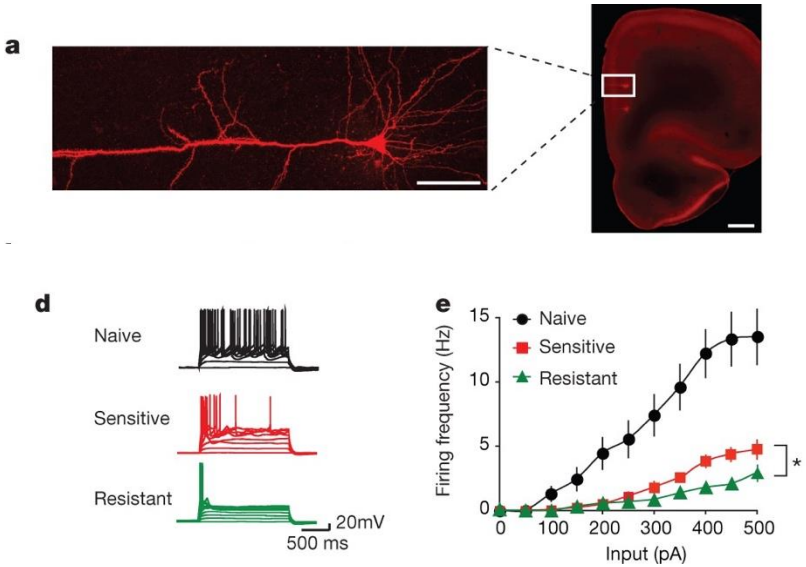
Nature **496**, 359–362 (2013) | Cite this article

32k Accesses | **348** Citations | **289** Altmetric | Metrics

OPTOGENETICS – EXAMPLES (3)

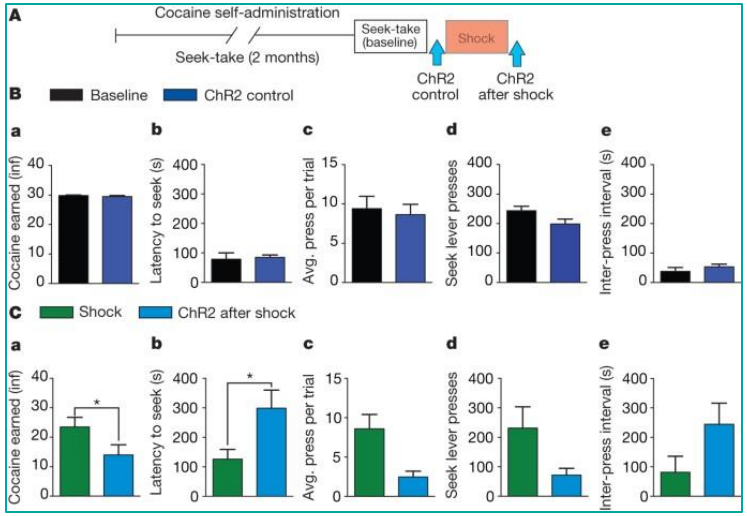


Some rats keep seeking cocaine despite foot shock

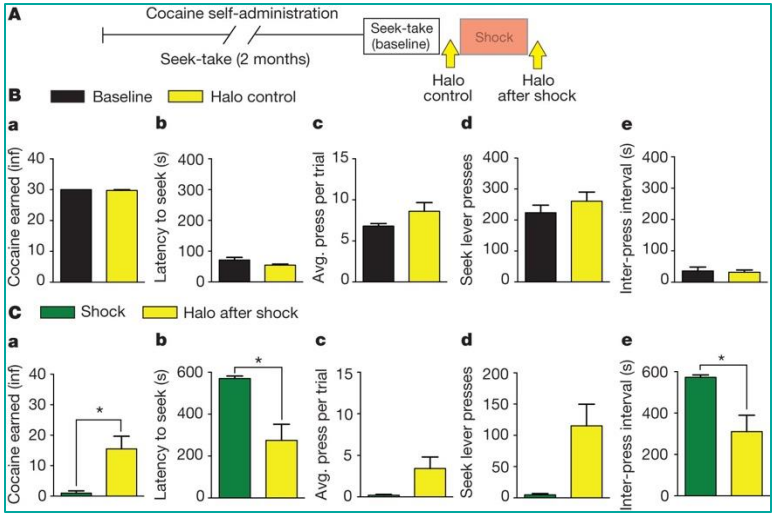


These rats have lower activity in inflarimbic cortical neurons

OPTOGENETICS – EXAMPLES (3)



In vivo optogenetic stimulation of prelimbic cortex suppresses compulsive cocaine seeking



In vivo optogenetic inhibition of prelimbic cortex enhances compulsive cocaine seeking

OPTOGENETICS – EXAMPLES (3)

Clinical impact of optogenetics

Randomized Controlled Trial > Eur Neuropsychopharmacol. 2016 Jan;26(1):37-44.
doi: 10.1016/j.euroneuro.2015.11.011. Epub 2015 Dec 4.

Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study

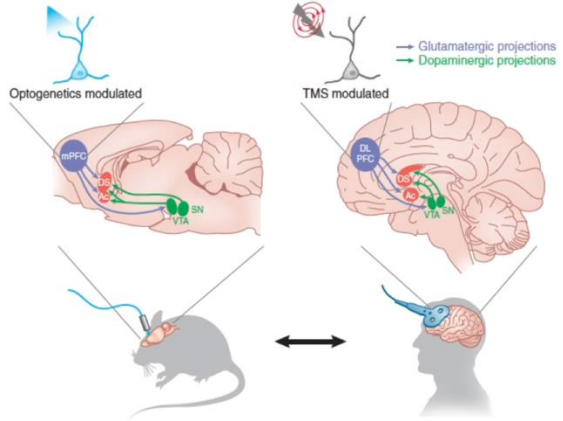
Alberto Terraneo [1], Lorenzo Leggio [2], Marina Saladini [3], Mario Ermani [3], Antonello Bonci [4], Luigi Gallimberti [1]

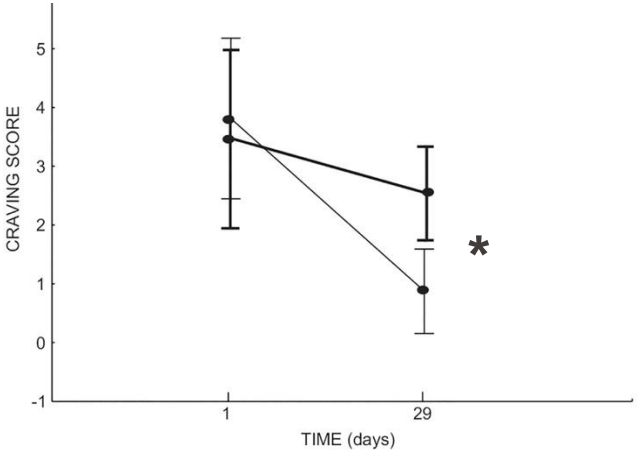
Affiliations + expand

PMID: 26655188 PMCID: PMC9379076 DOI: 10.1016/j.euroneuro.2015.11.011
Free PMC article

Abstract

Recent animal studies demonstrate that compulsive cocaine seeking strongly reduces prelimbic frontal cortex activity, while optogenetic stimulation of this brain area significantly inhibits compulsive cocaine seeking, providing a strong rationale for applying brain stimulation to reduce cocaine consumption. Thus, we employed repetitive transcranial magnetic stimulation (rTMS), to test if dorsolateral prefrontal cortex (DLPFC) stimulation might prevent cocaine use in humans. Thirty-two cocaine-addicted patients were randomly assigned to either the experimental group (rTMS) on the left DLPFC, or to a control group (pharmacological agents) during a 29-day study (Stage 1). This was followed by a 63-day follow-up (Stage 2), during which all participants were offered rTMS treatment. Amongst the patients who completed Stage 1, 16 were in the rTMS group (100%) and 13 in the control group (81%). No significant adverse events were noted. During Stage 1, there were a significantly higher number of cocaine-free urine drug tests in the rTMS group compared to control (p=0.004). Craving for cocaine was also significantly lower in the rTMS group compared to the controls (p=0.038). Out of 13 patients who completed Stage 1 in the control





Thank you

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