

Neurobiology of sleep/wake transitions

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Disclosures

- Boehringer Ingelheim - Research Grant
- Jazz Pharmaceuticals - Research Grant
- Attune Neuroscience- Founder and shareholder
- Consulting for Aditum, Septerna, Idorsia, Pepsico

Identifying markers to define circuits

DPPX

G-protein gamma 7

Cortistatin

Hypocretins/orexins

KCNN4

Neuropeptide S

GPR139

Neuronal circuitry of sleep/wake regulation

Implementing methods for circuit interrogation

Cholera toxin B transgenics

Viral-mediated tracing

Optogenetics

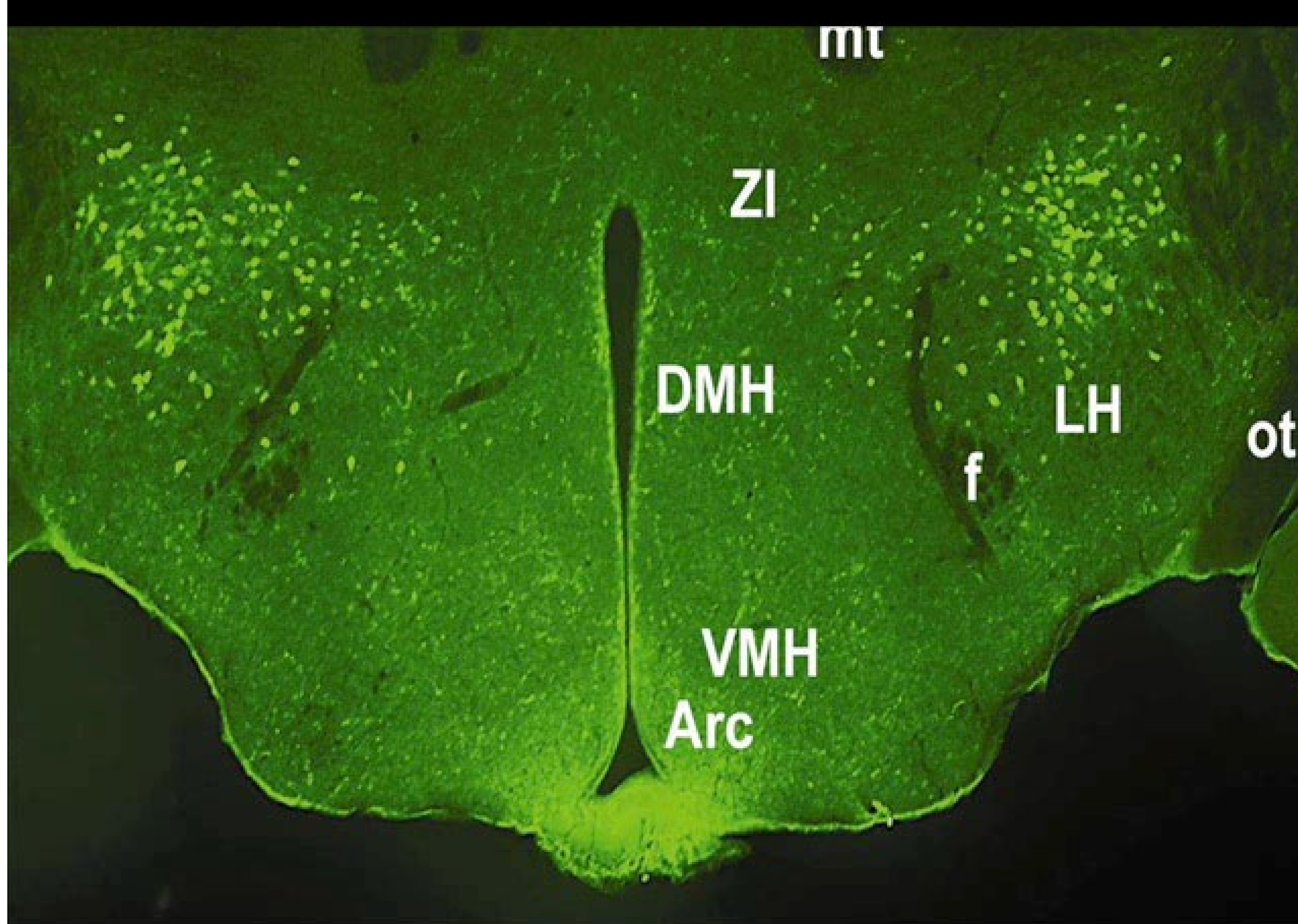
Chemogenetics

Photopharmacology

Calcium imaging

CRISPR knockdowns

Ultrasound



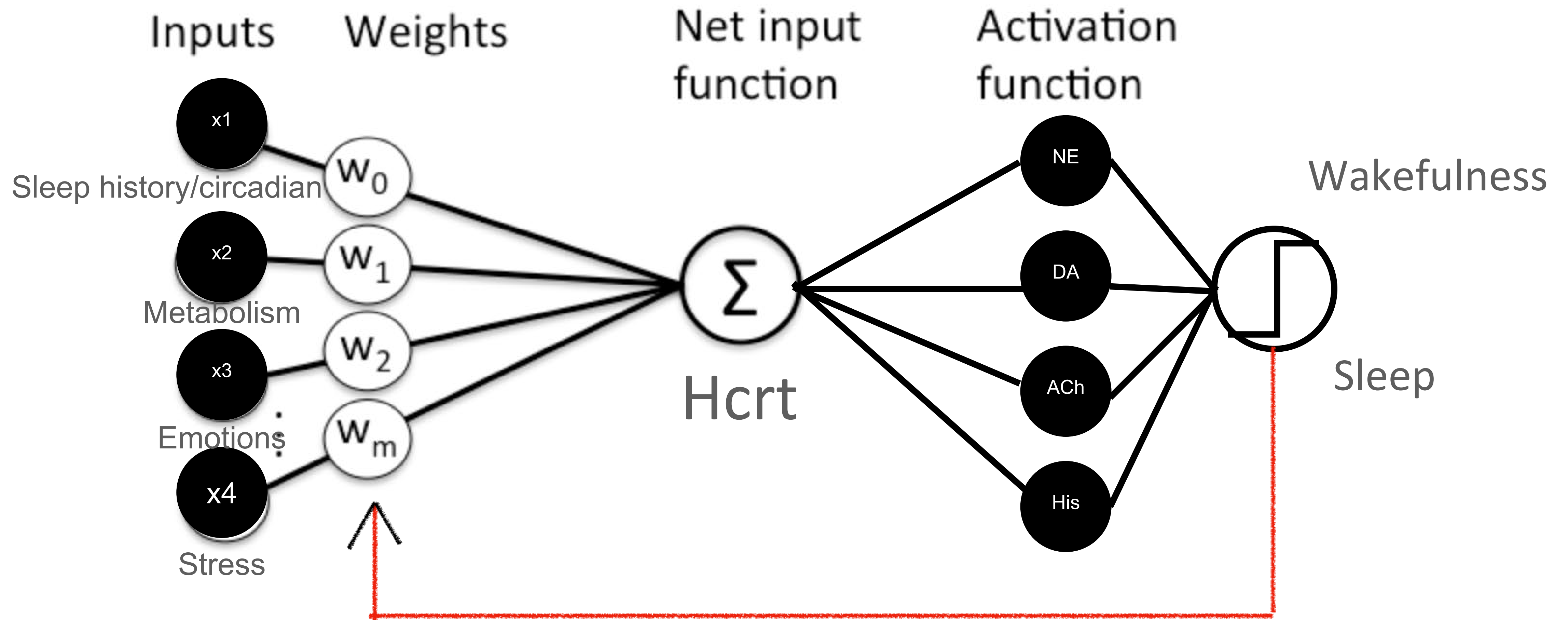
Hcrt neuronal activity

- Hcrt ac

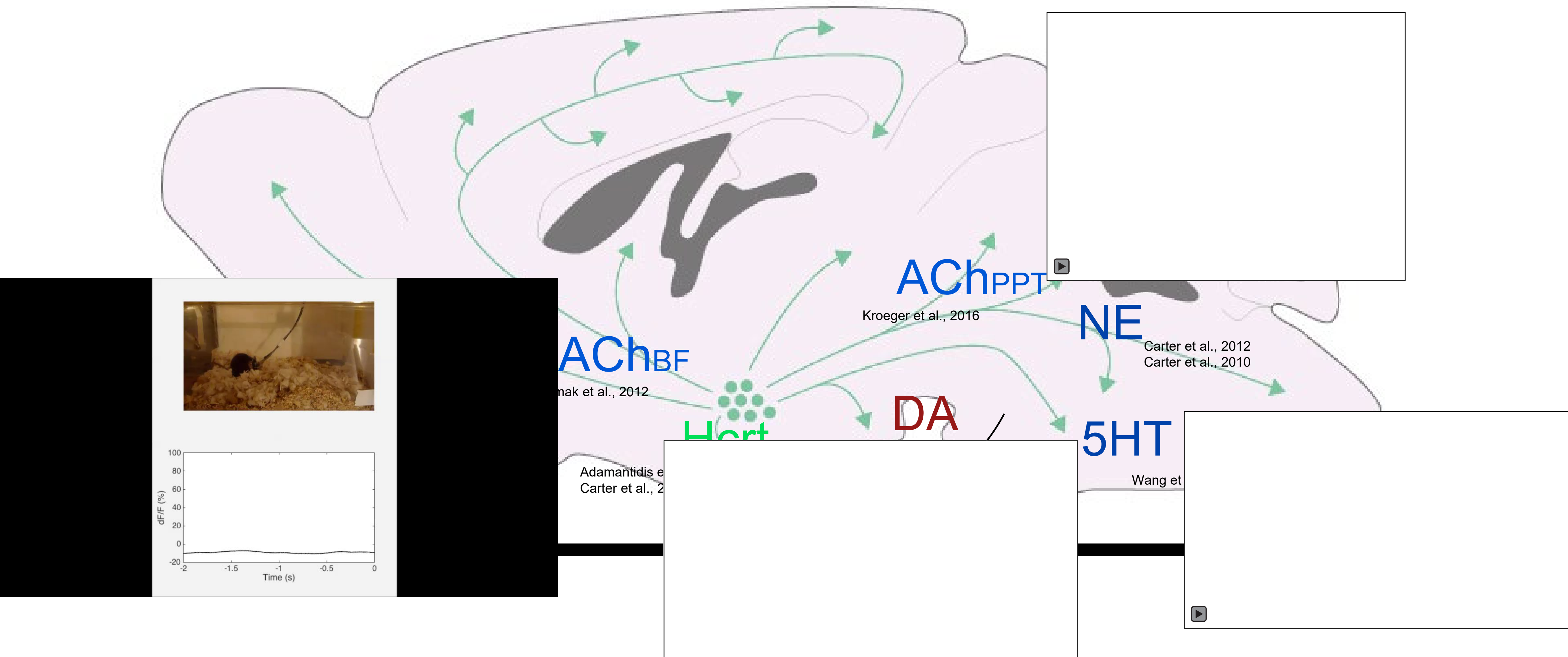


Hcrt neurons integrate information to regulate transitions

- Perceptron model



Functional interrogation of Hcrt targets



Hcrts: Ultimate translational neuropeptides

Orexin receptor antagonism for treatment of insomnia

A randomized clinical trial of suvorexant



Suvorexant Clinical Trials

Herring et al., Neurology

Crystal structure of Hcrts receptors

(Li et al., Nature)

2012

2015

Hcrts: Ultimate translational neuropeptides

Nonpeptide orexin type-2 receptor agonist ameliorates narcolepsy-cataplexy symptoms in mouse models

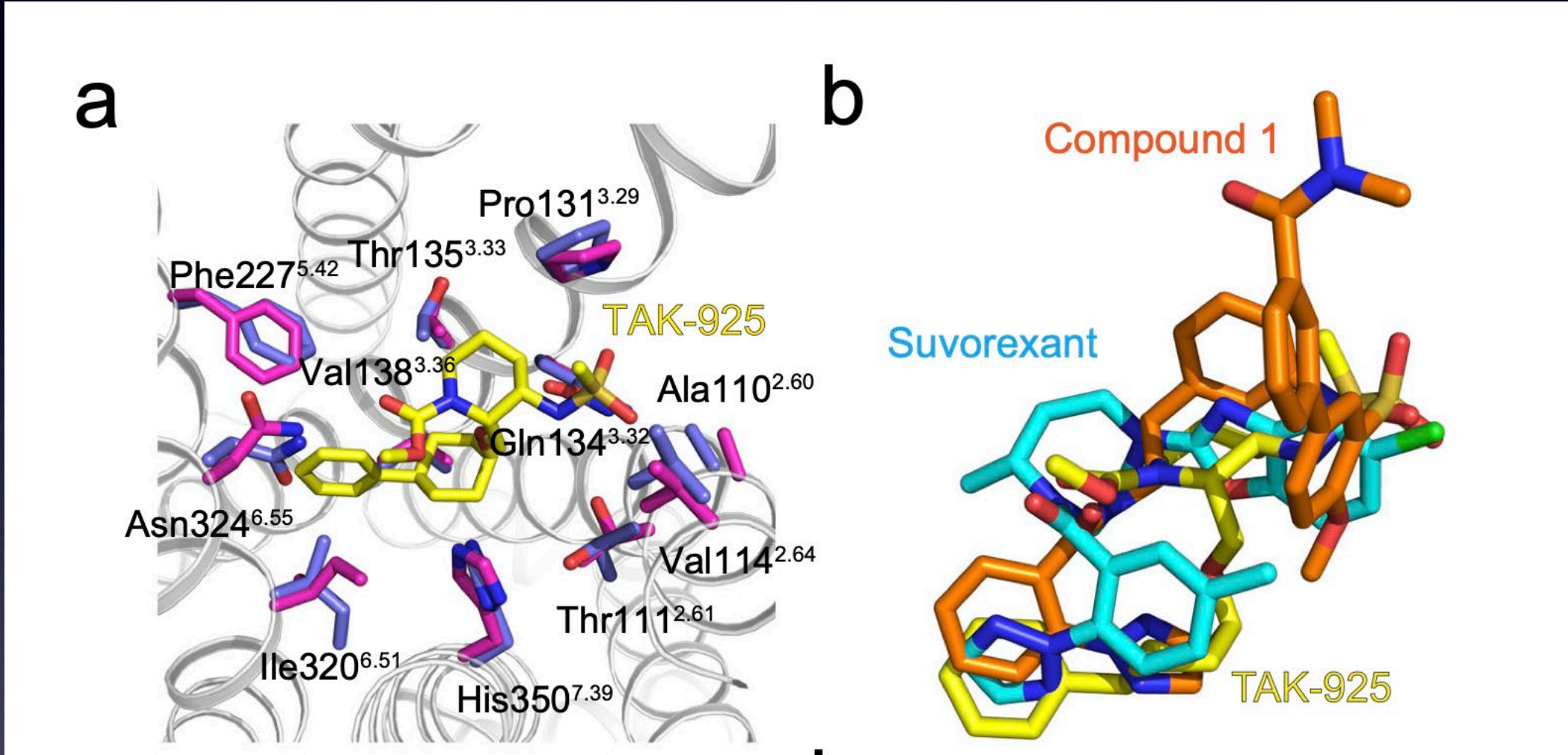
Yoko Irukayama-Tomobe^{a,1}, Yasuhiro Ogawa^{a,1}, Hiromu Tominaga^{a,1}, Yukiko Ishikawa^a, Naoto Hosokawa^a, Shinobu Ambai^a, Yuki Kawabe^a, Shuntaro Uchida^a, Ryo Nakajima^a, Tsuyoshi Saitoh^a, Takeshi Kanda^a, Kaspar Vogt^a, Takeshi Sakurai^a, Hiroshi Nagase^a, and Masashi Yanagisawa^{a,2}

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Small molecule agonists
(Irukayama et al)

2017

Mechanism of action of TAK-925

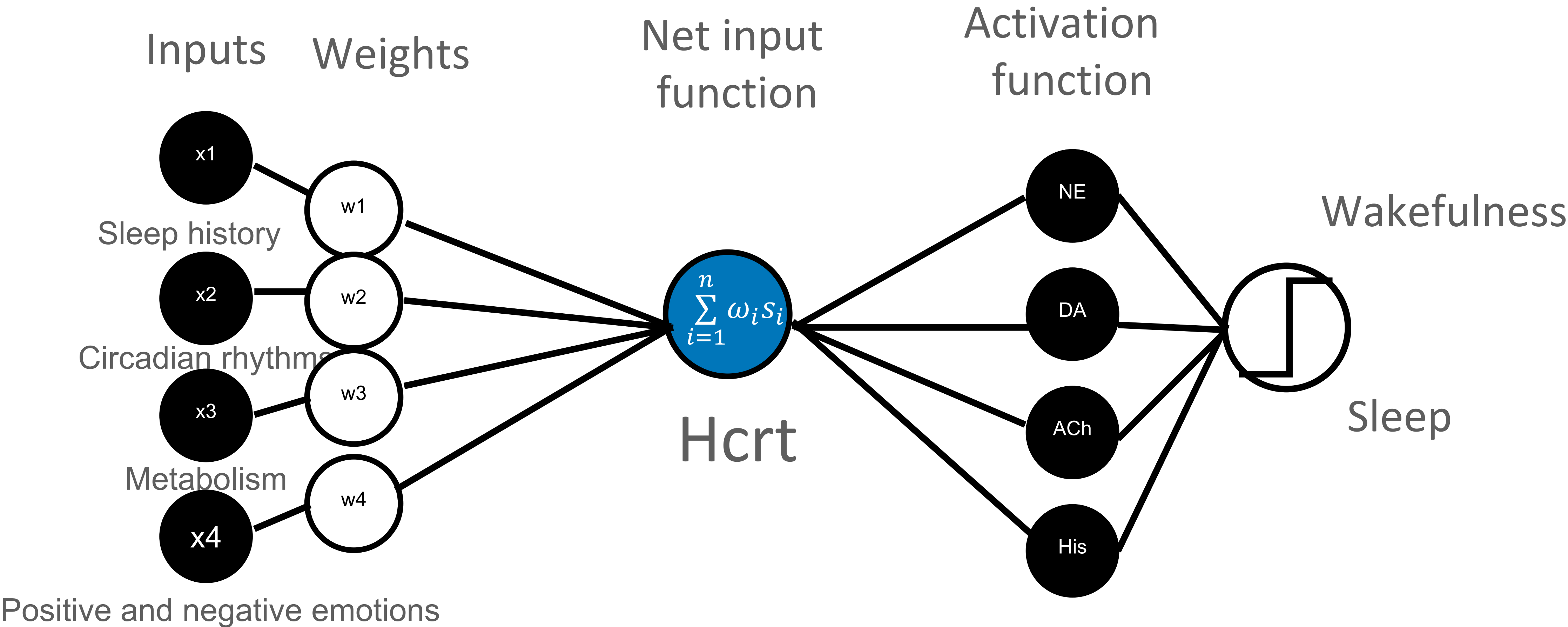


Daridorexant FDA approval

2022

What is the cause of sleep instability during aging?

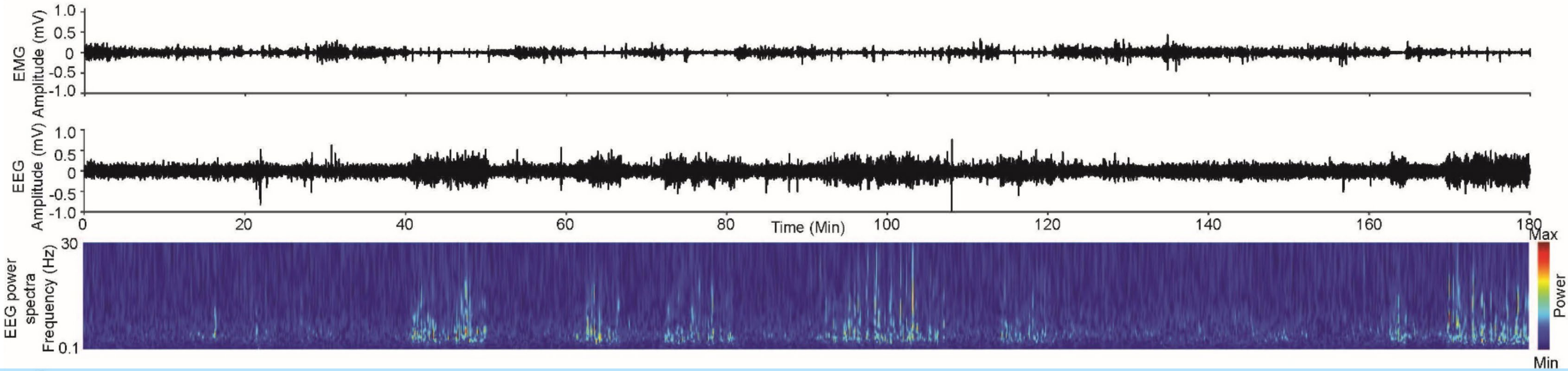
Hypothesis: Arousal circuits are dysfunctional



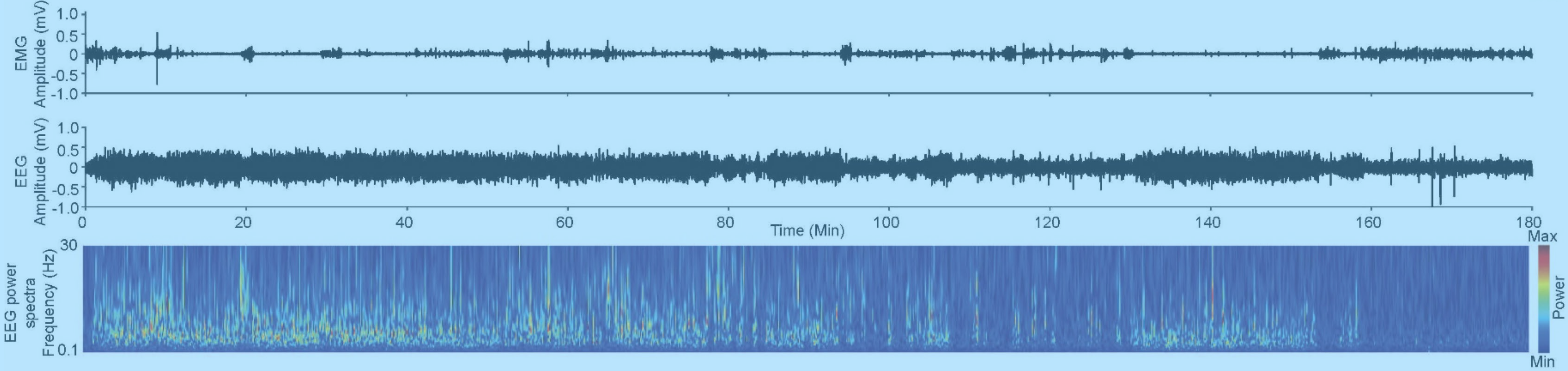
KCNQ openers: A new pharmacological target for sleep fragmentation

Aged

+ Vehicle

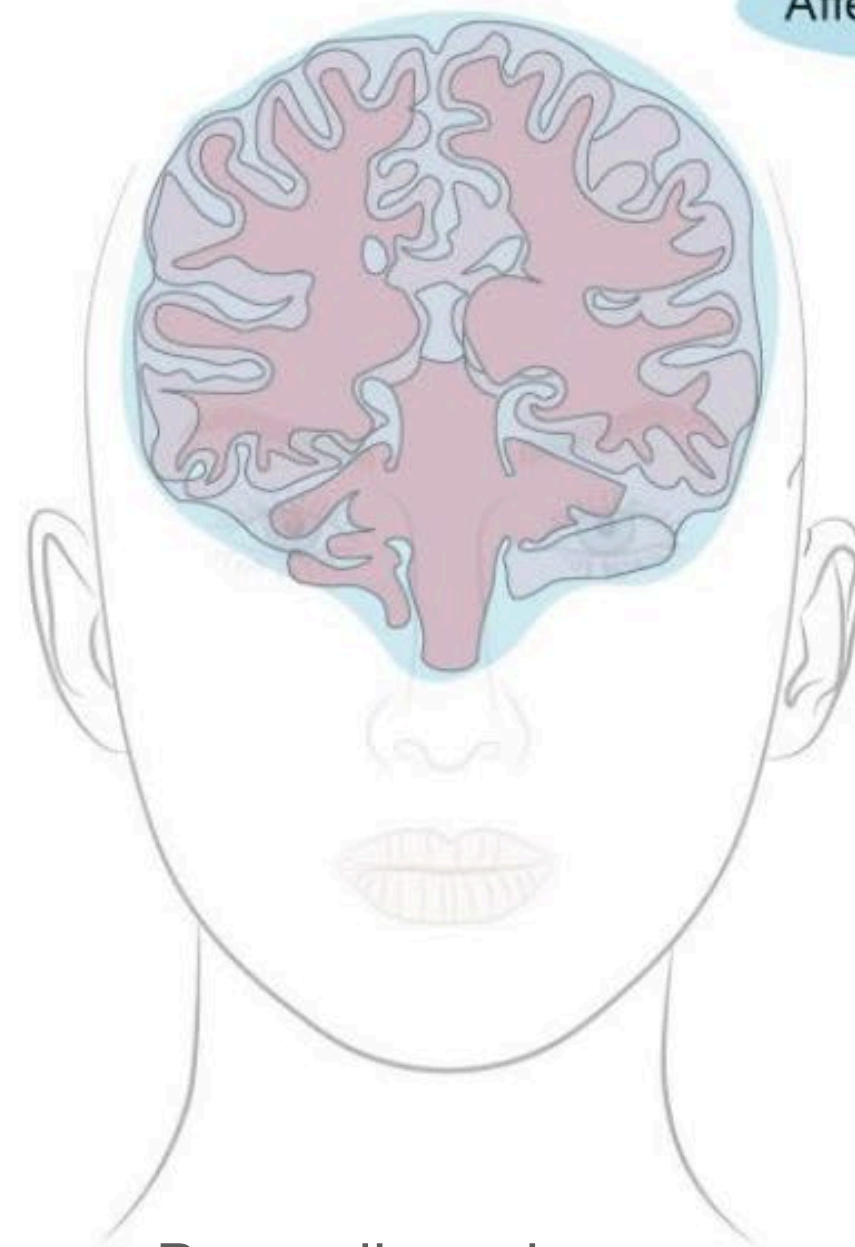


+ Flupirtine



Sleep intervention strategies

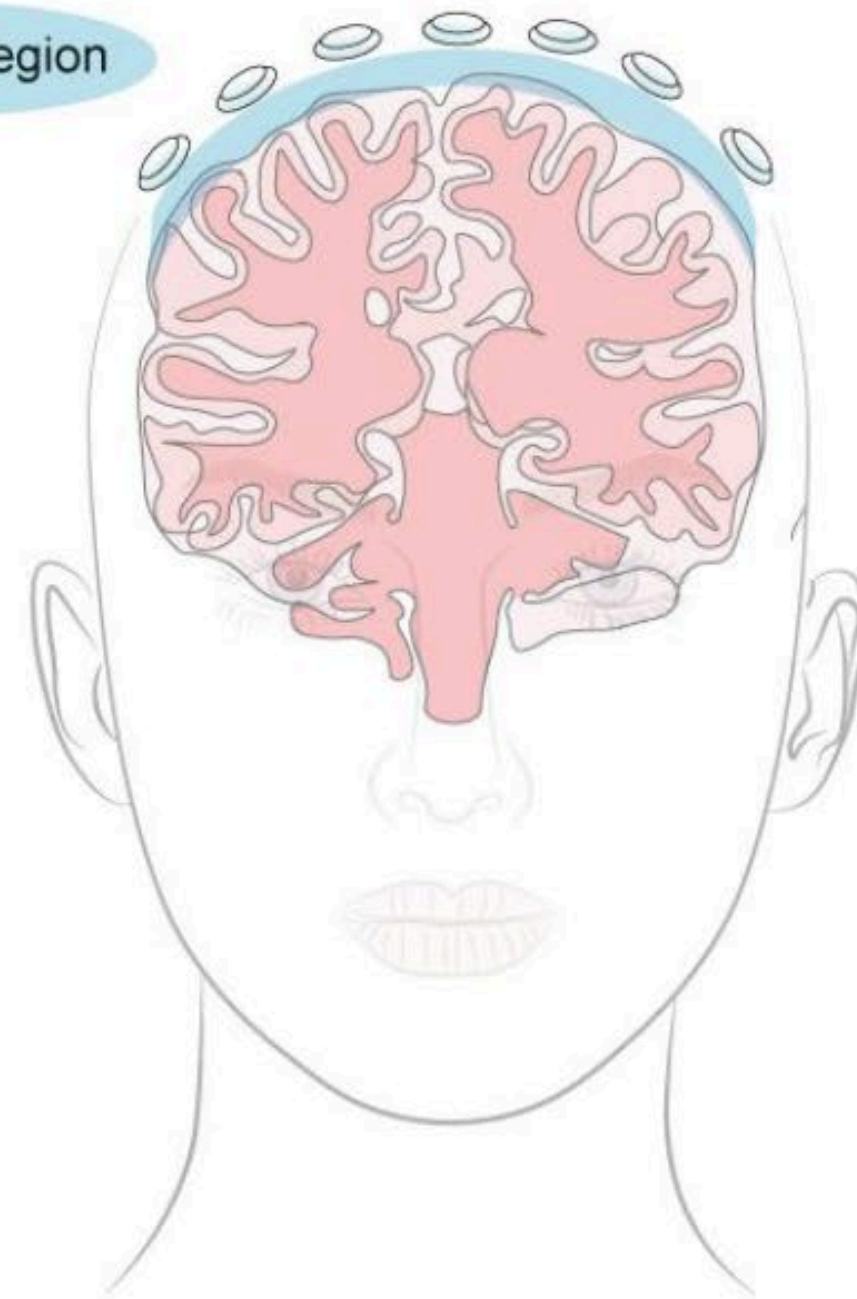
Pharmacology



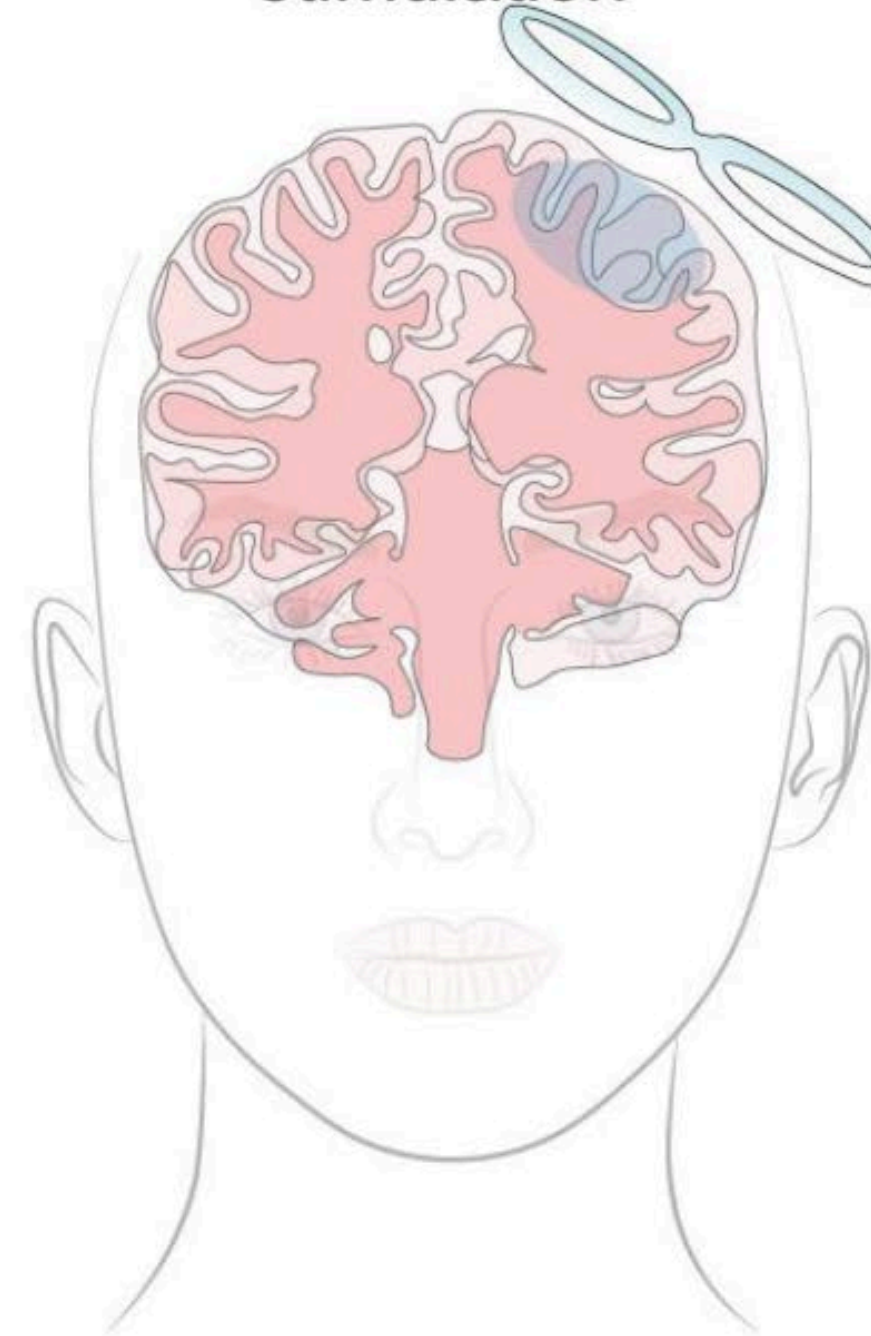
Benzodiazepines
Z-drugs
Ramelteon
Suvorexant
Retigabine

Transcranial direct current stimulation

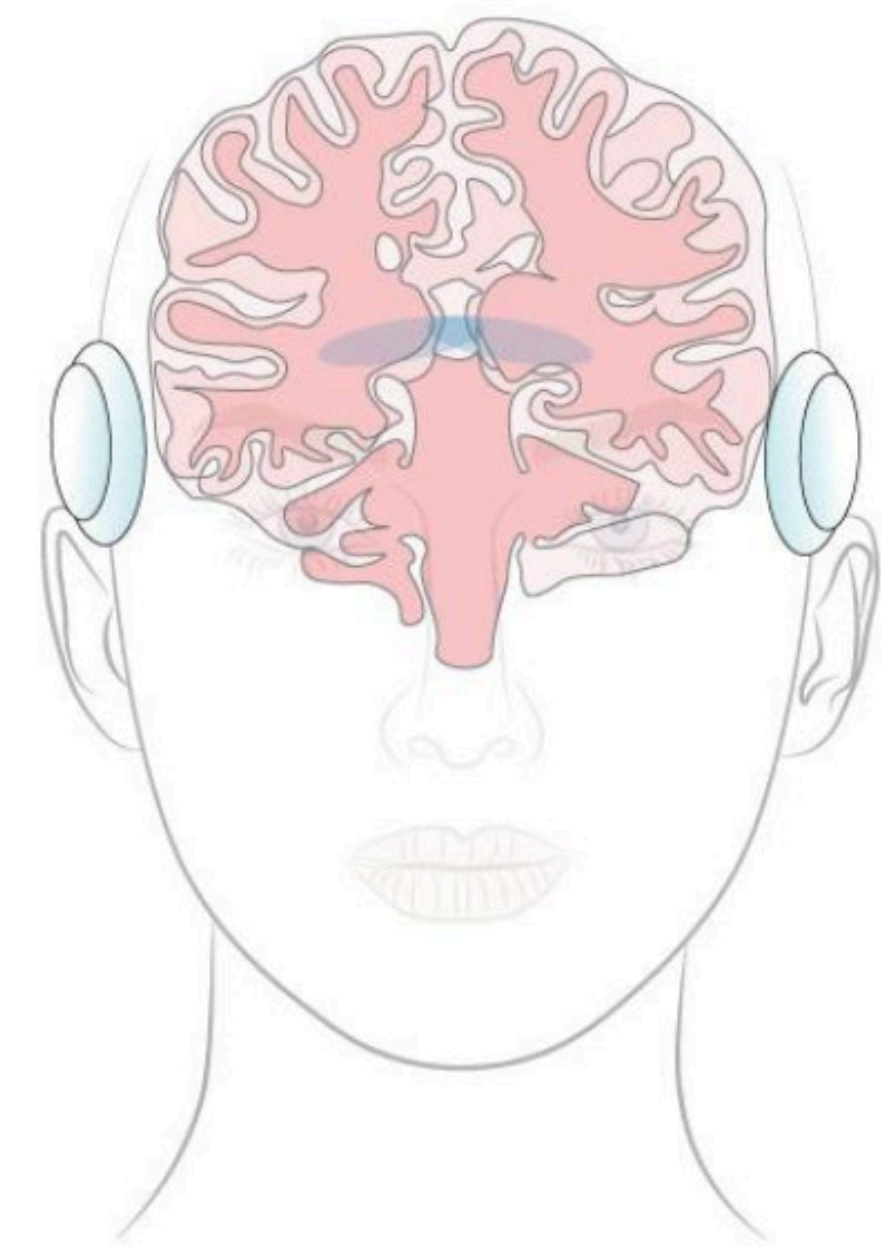
Affected region



Transcranial magnetic stimulation

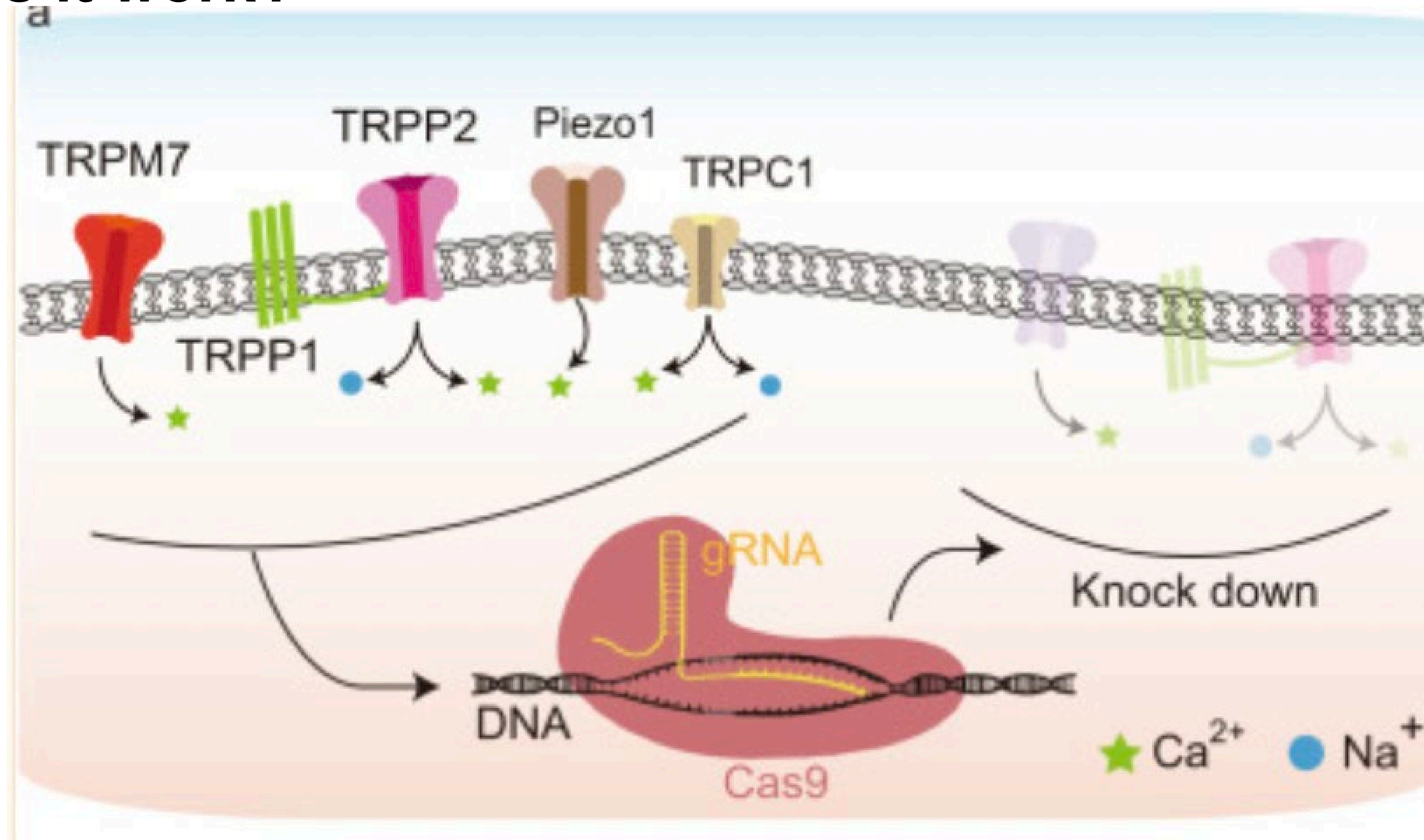


Focused ultrasound



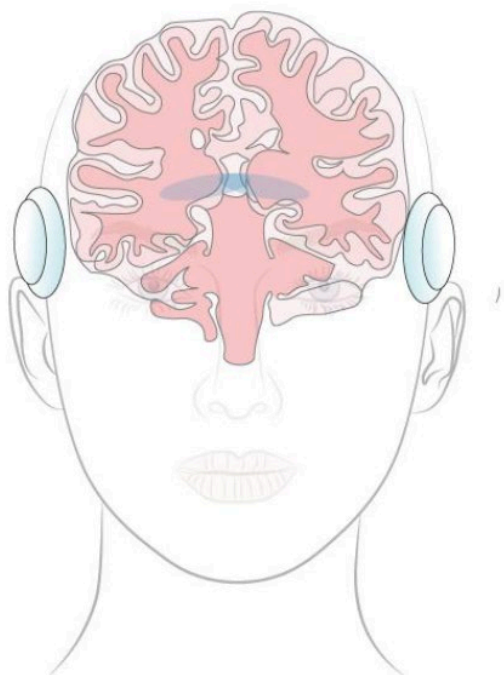
Focused ultrasound

How does it work?



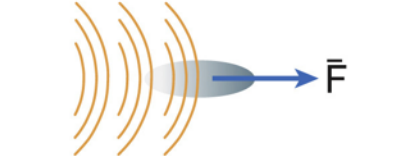
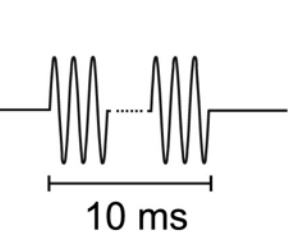
Sleep intervention strategies

Focused ultrasound



ed Ultrasour

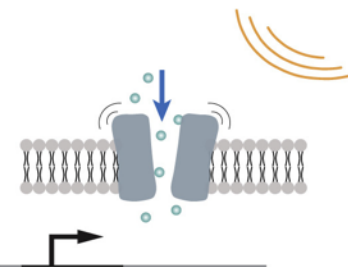
Push



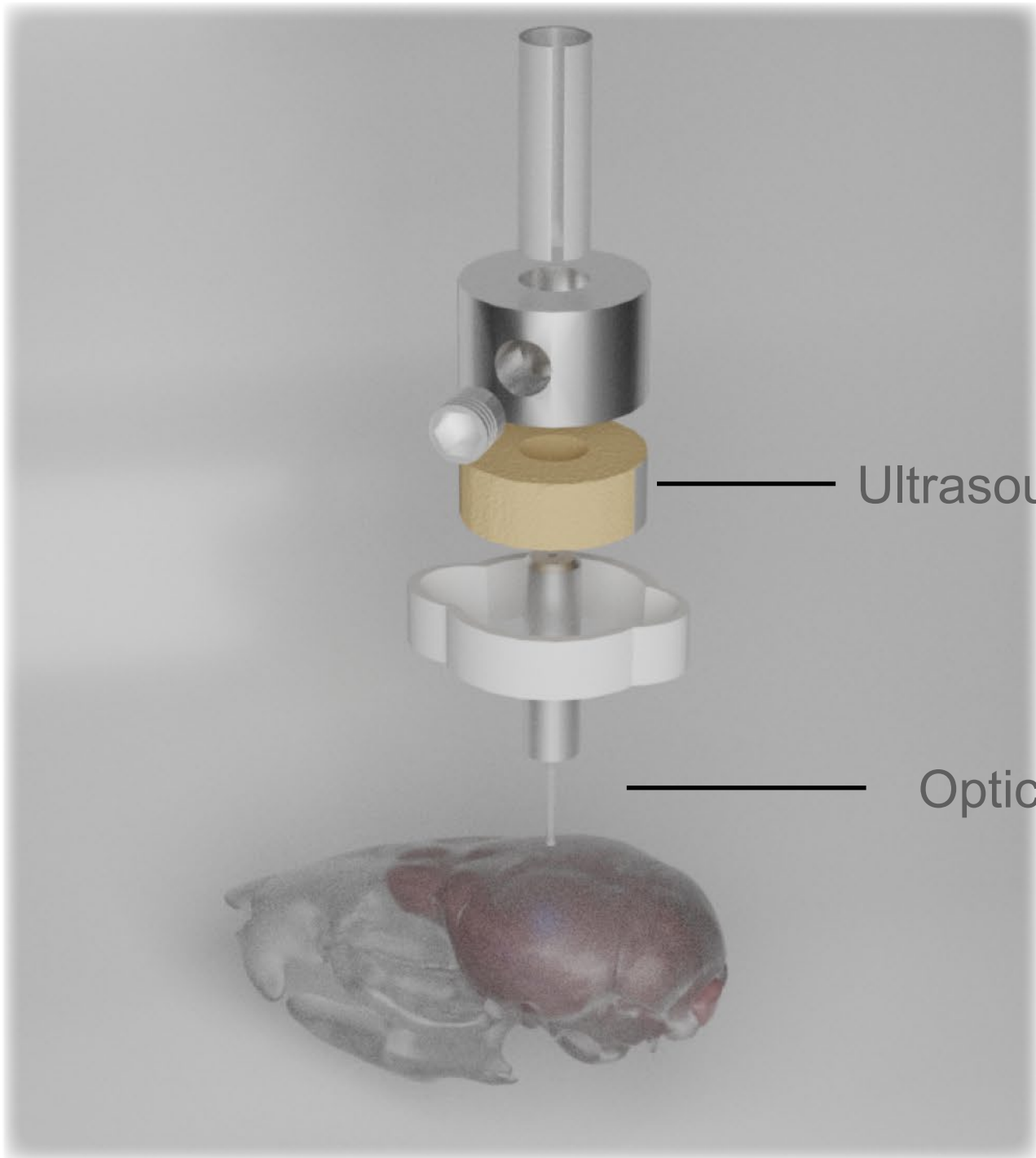
Acoustic radiation force



Neuromodulation

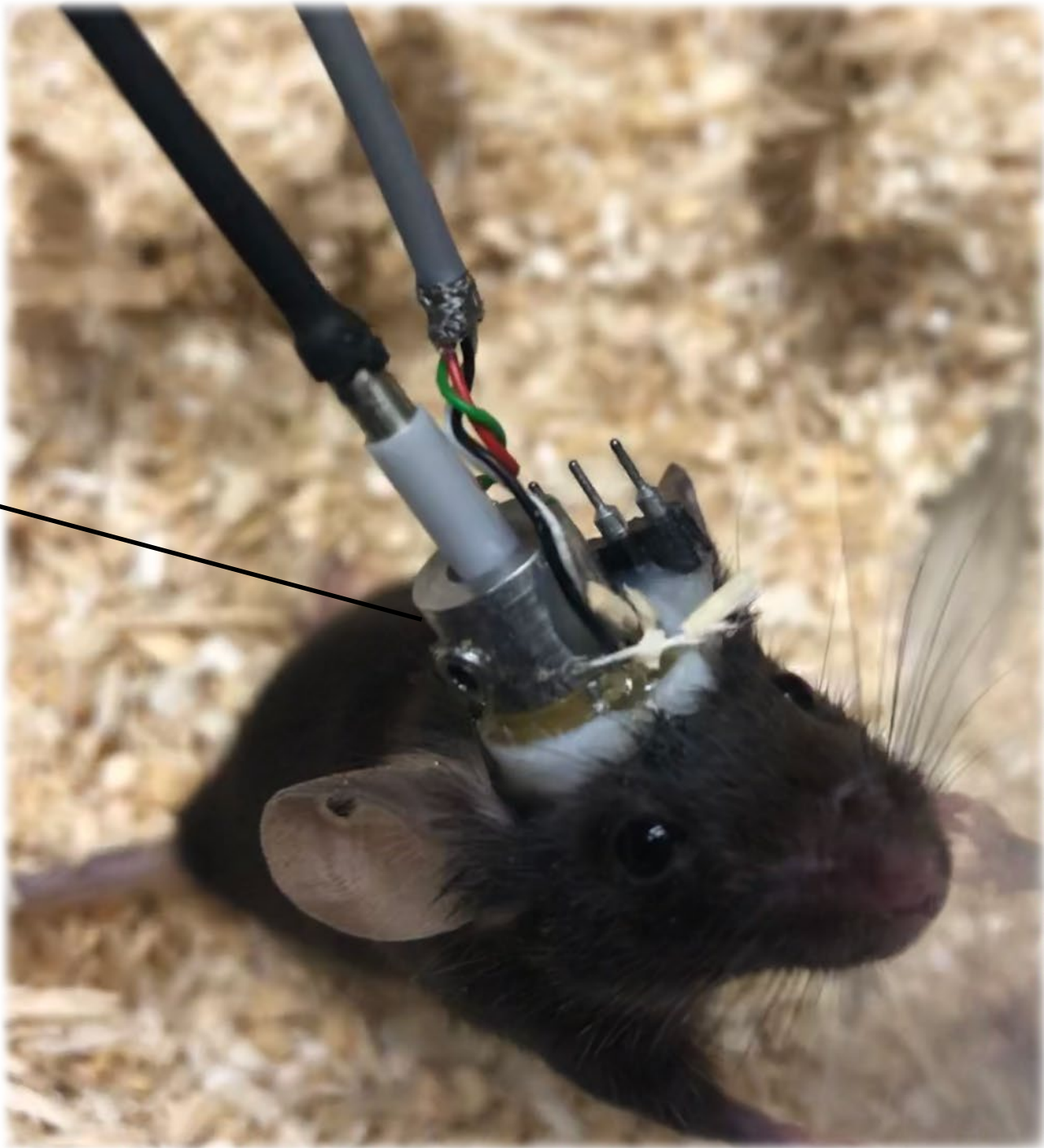


Mechano-Sonogenetics



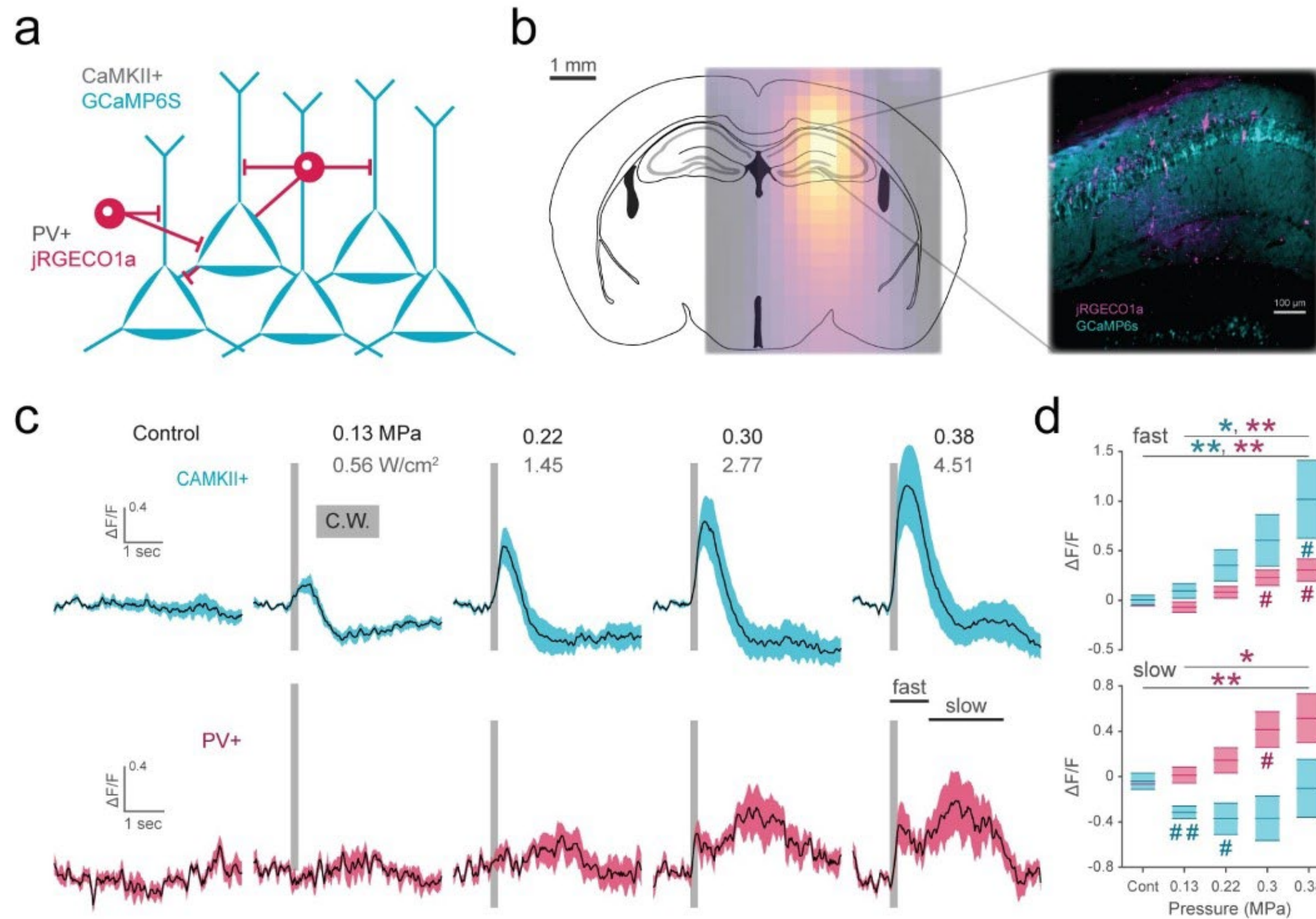
Ultrasound transducer

Optical fiber



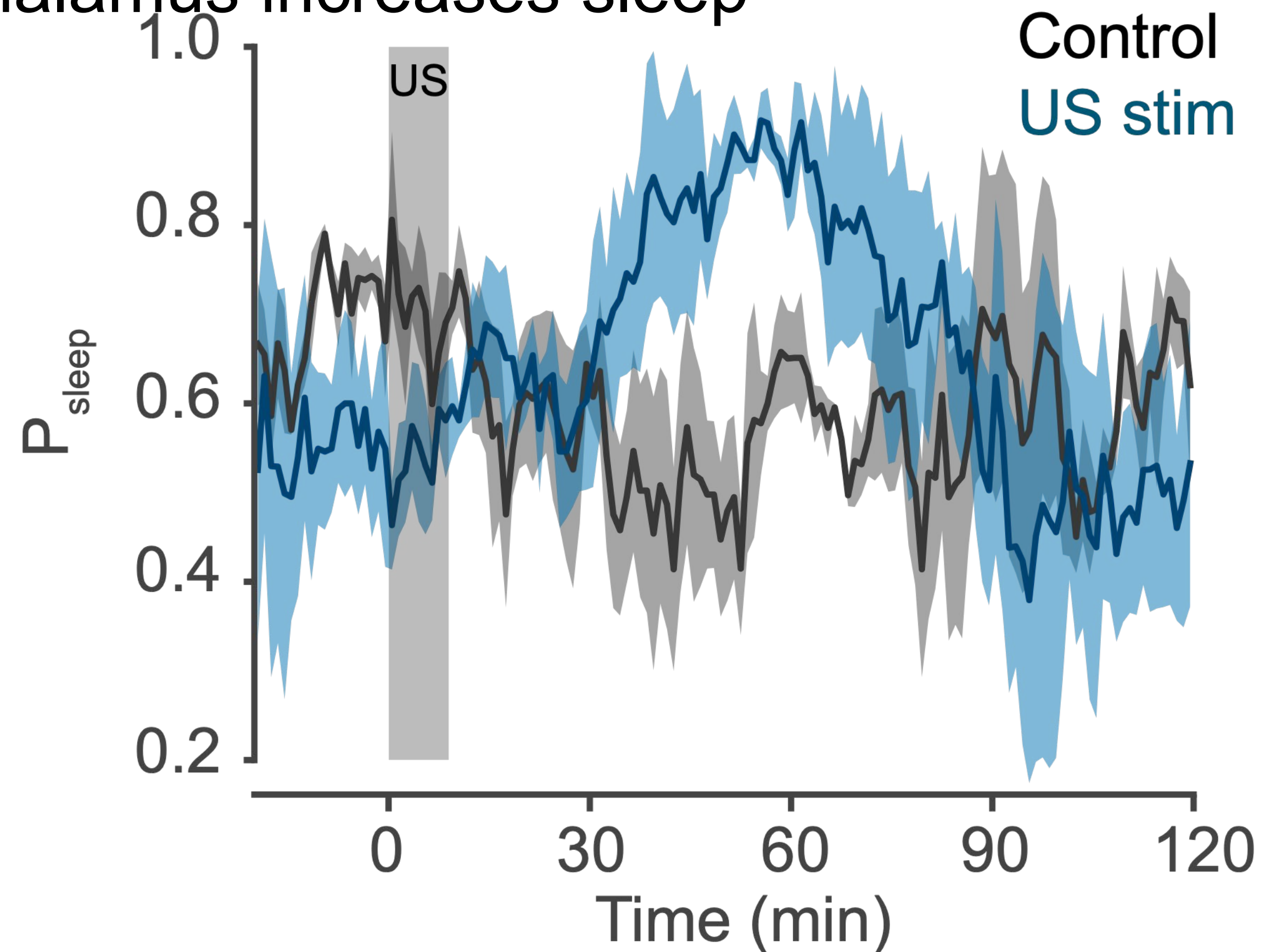
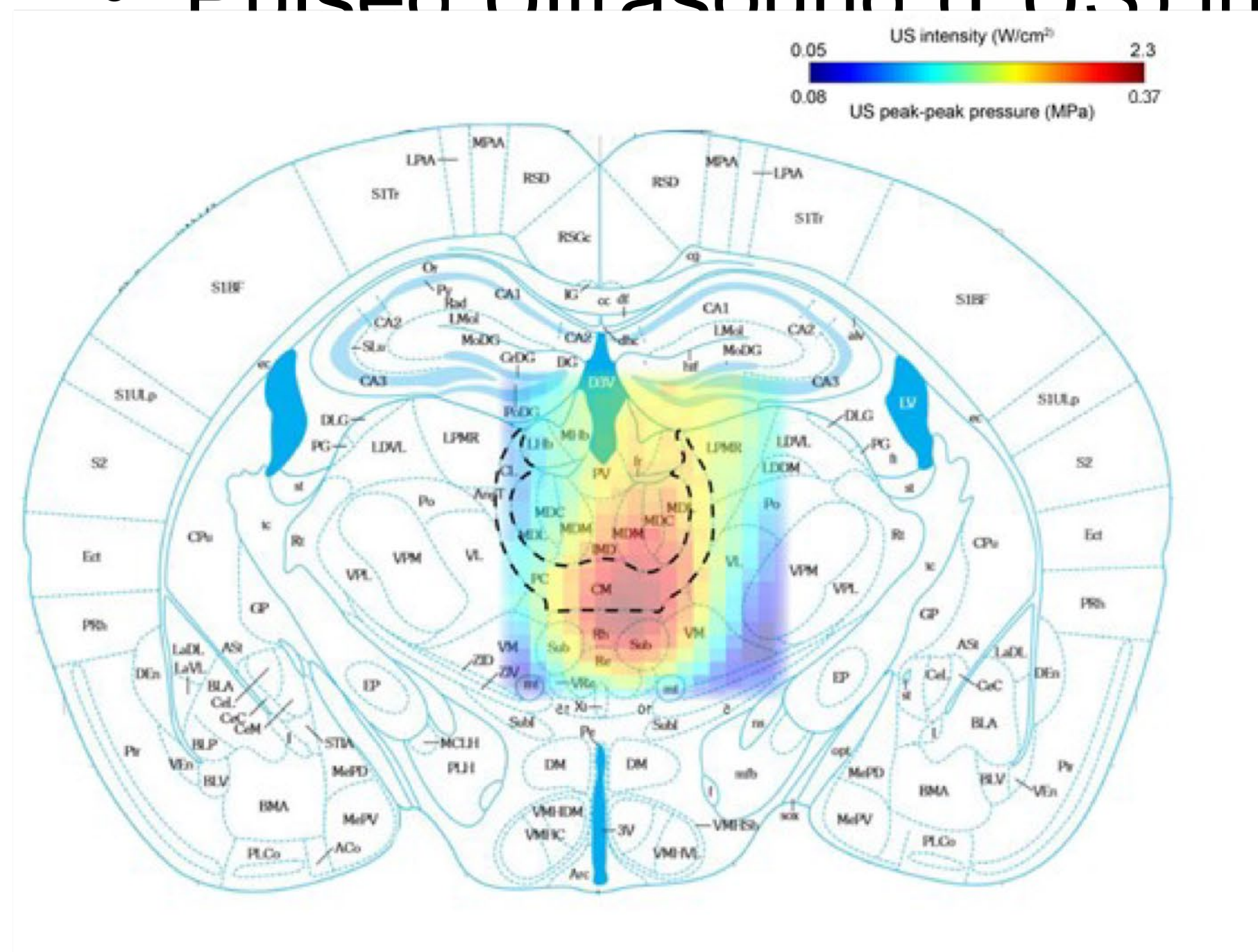
Focused ultrasound

Cell-type specific responses in hippocampus



Sleep intervention strategies

- Pulsed Ultrasound (FUS) in thalamus increases sleep



- **Characterization of Hypocretins/orexins** as a Rosetta Stone that allows us to decipher the circuitry regulating sleep states
- **Mechanism of sleep fragmentation** during aging and neurodegeneration
- **New translational tools** for non-invasive neuromodulation of sleep/wake circuits