Thalamic stimulation reverses GABAergic but not anti-glutamatergic general anesthesia in monkeys

Jacob A. Donoghue[1], Jorge Yanar[1], Marek M. Kowalski[2], Simon Kornblith[1], Meredith K. Mahnke[1], Mikael Lundqvist[1], Jefferson E. Roy[1], Andre Bastos[1], Nancy J. Kopell[2], Emery N. Brown[1]+, Earl K. Miller[2]+

1. Picower Institute for Learning and Memory, MIT, Cambridge MA

2. Department of Mathematics and Statistics, Boston University, Boston MA

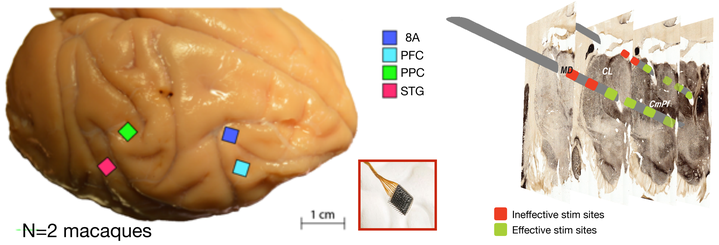
+ Co-senior authors

We need a systems-level description of anesthesia

- While the molecular targets and effects of various anesthetics are fairly well understood, a systems-level description is lacking.
- Non-human primates offer a particularly good model for studying anesthesia, due to their physiological similarities to humans and our ability to perform invasive recordings with high temporal and spatial resolution.
- Here we investigate two commonly-used anesthetics: propofol, a GABAa agonist, and ketamine, a dissociative anesthetic which acts primarily as an NMDA receptor antagonist.

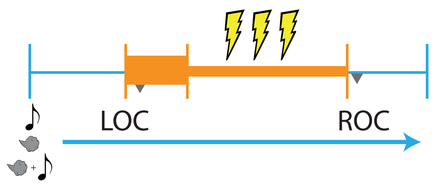
Experimental paradigm

- We recorded spiking and LFP activity from chronically implanted Utah arrays across frontoparietal cortex.
- We stimulated and recorded LFP from bilaterally-implanted chronic thalamic electrodes, targeting the mediodorsal (MD) and intralaminar (ILN) thalamic nuclei.

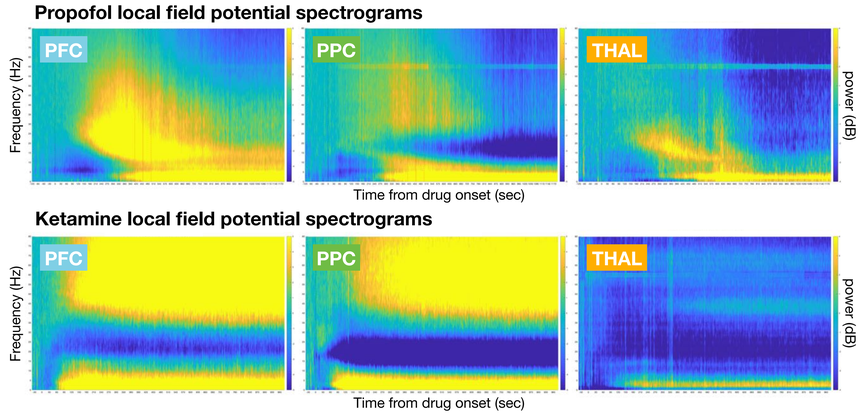


N=2 macaques

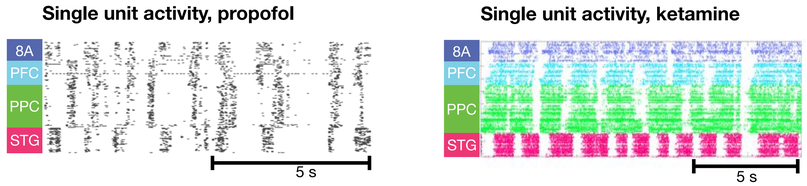
- For the propofol experiments, an induction dose of 0.28-0.58 mg/kg/min was intravascularly delivered for 15 minutes, followed by a holding dose of 0.14-0.23 mg/kg/min for 45 minutes.
- For ketamine experiments, a single 20mg/kg bolus was delivered intramuscularly.
- Air puffs and auditory stimuli were played throughout the session. Facial EMG, SpO2, pupil diameter, and heart rate were measured throughout.



Propofol and ketamine produce distinct neural dynamics

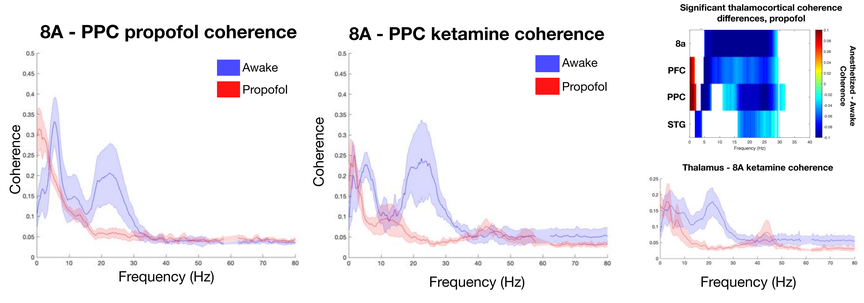


- During propofol infusion, gamma (>35 Hz) and high-beta power (peak frequency ~25-28 Hz) temporarily increased in frontal cortex and thalamus. High beta (not seen in PPC, STG) then slowly ramped down to 15 Hz around LOC (~10 minutes post drug-administration). Just before LOC, lower frequency (<4 Hz) power increased in all areas, and peaked after LOC.
- Ketamine infusion caused increases in slow-frequency and wide-band gamma (40-80 Hz) power across all recording sites.

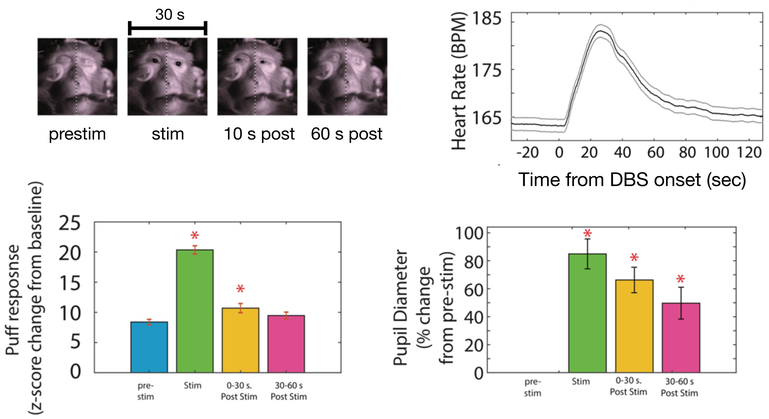


- Propofol induced prolonged Down-states with little to no spiking, punctuated by short Up-states with high amounts of spiking.
- Ketamine induced a near opposite effect: prolonged Up-states with short Down-states.

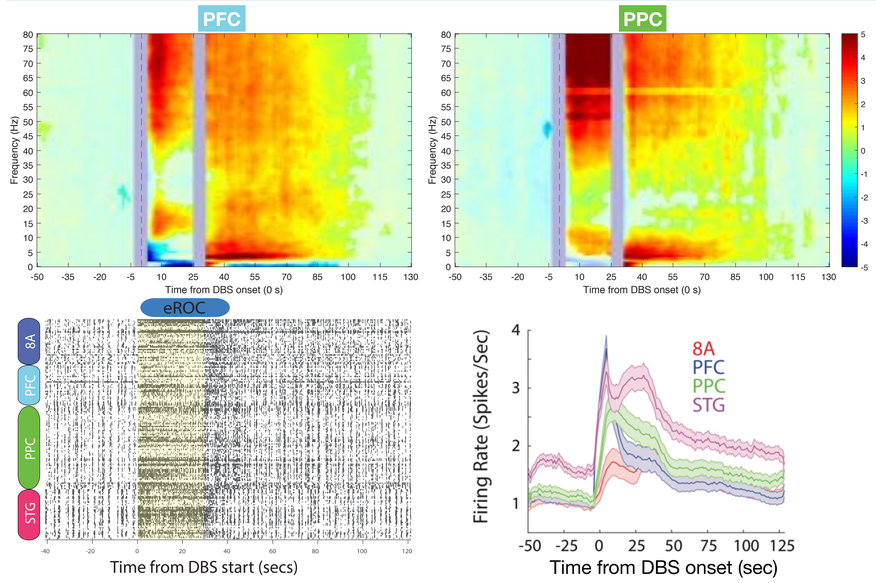
Both anesthetics abolished higher-frequency frontoparietal and thalamocortical coherence



180Hz biphasic electrical stimulation of the ILN during propofol anesthesia restores markers of wakefulness



ILN stimulation excites the cortex and partially restores beta and gamma power



Conclusions

- Both propofol and ketamine disrupt conscious processing and intracortical communication, but likely through massive inhibition and excitation, respectively.
- High-frequency electrical stimulation of the ILN, which provides diffuse excitatory input to the cortex, is sufficient to partially overcome the blanket of inhibition provided by propofol.

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Check out our recent preprint describing some of this work, out now on bioRxiv! **https://bit.ly/2Bywk69**