Not all unconscious states are equal: differences in response to electrical stimulation during sleep and under general anesthesia in humans

Rina Zelmann[1], A. C. Paulk[1], P. Kahali[2], F. Tian[2], G. Balanza Villegas[2], B. Crocker[1], G. R. Cosgrove[4], Z. Williams[3], M. Richardson[3], P. L. Purdon[2], and S. S. Cash[1]

Departments of [1]Neurology, [2]Anesthesia and [3]Neurosurgery, Massachusetts General Hospital/Harvard Medical School; [4]Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA, USA

Introduction

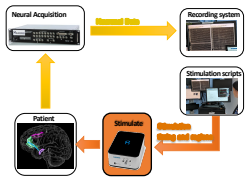
- Even though being asleep or under general anesthesia are considered states of unconsciousness, they are separable physiological conditions.
- Under the assumption that the brain's response to perturbations is different during sleep or general anesthesia in contrast to a conscious state, we used multi-region single-pulse direct electrical stimulation (SPES) to probe the human brain in each of these states.

Aim

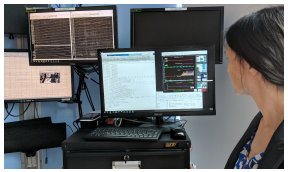
- To investigate the local, network, and global difference in the response to single-pulse direct electrical stimulation (SPES) in the intracranial EEG (iEEG) while participants are awake, asleep, or under general anesthesia.

System Overview

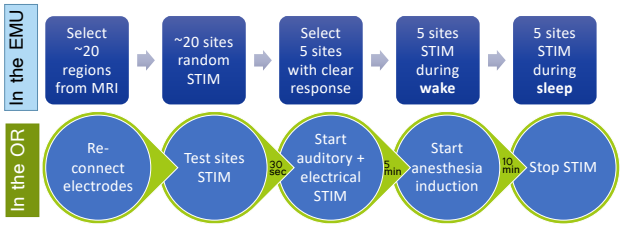
Multi-focal electrical intracranial stimulation and simultaneous iEEG recording



Schematic of experimental setup.



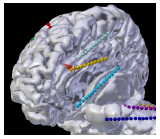
System in the epileptic monitoring unit (EMU) during wake and sleep experiment working in parallel to clinical system.



Materials

Twenty-one patients with semi-chronic depth electrodes implanted to localize the origin of their seizures participated after fully informed consent.

We delivered a small SPES to 4-10 regions per patient in pseudo-random order during **wake**, **sleep ,** and **anesthesia.**



Depth electrodes location in one patient.

Methods

We compared **WakeEMU vs. SleepEMU** (N=15; nSTIM=166 ch; mREC=2605 ch), **WakeOR vs. Anesthesia** (N=15; nSTIM=73; mREC= 1264) and **WakeEMU vs. WakeOR** (N=11; nSTIM=57; mREC=1104 ch).

State Comparisons

1. **WakeEMU**: awake in the EMU.
2. **SleepEMU**: sleeping in the EMU.
3. **WakeOR**: awake in the operating room before electrode explantation.
4. **Anesthesia**: loss of consciousness as indicated by lack of response to auditory task (Propofol).

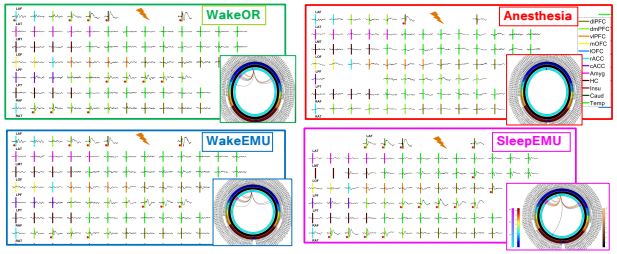
Regional Comparison

- **Anterior** regions: frontal + anterior cingulate cortices.
- **Posterior** regions: parietal + posterior cingulate + occipital cortices.

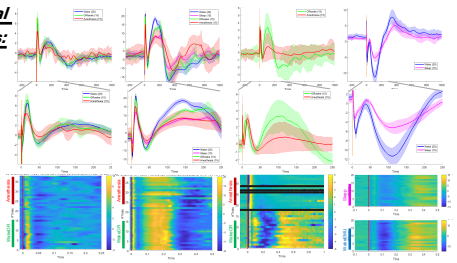
Analysis

- Cortico-cortical evoke potentials (CCEP) in response to SPES, in intracranial EEG.
- **% Resp Channels**: Percentage of channels with CCEP to SPES.
  - iEEG was low-passed filter below 45Hz, after removal of stimulation artifact, and normalized per trial.
- **Complexity**: perturbational complexity index (PCI^{st}) in first 600ms in the raw iEEG. Relative PCI = (PCI_{s1}- PCI_{s2}) / (PCI_{s1}+ PCI_{s2})
- **Variability**: standard deviation (STD) of the absolute response amplitude.
- Wilcoxon test (paired) between states.
- Within region analysis: stimulation AND recordings occur in that region.

Results I - Examples

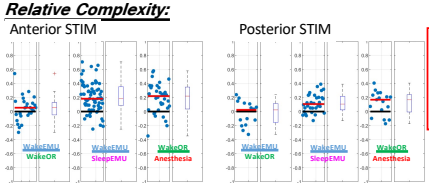


Examples individual recording channels:



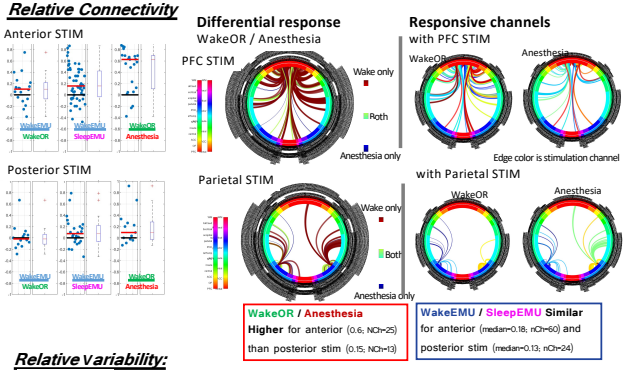
Results II – Relative

Relative Complexity:



Complexity:
Similar for different loss of consciousnesses sates across stimulation regions (median ~0.2)

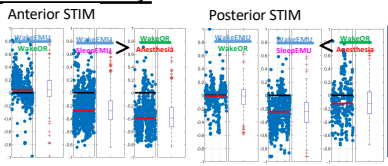
Relative Connectivity



WakeOR / Anesthesia
Higher for anterior (0.6; NCh=25) than posterior stim (0.15; NCh=13)

WakeEMU / SleepEMU Similar
for anterior (median=0.18; nCh=60) and posterior stim (median=0.13; nCh=24)

Relative variability:



Variability
WakeEMU / SleepEMU Similar for anterior (median=0.25; mREC=931 ch) and posterior (median=0.22; mREC=223 ch)
WakeOR / Anesthesia
Higher for anterior (0.4; NCh=411) than posterior (0.15; NCh=182)

Conclusions

- Our results suggest that in anterior regions, during sleep complexity is reduced but connections are preserved while during anesthesia complexity and connectivity are impaired. Increased variability might help explain this difference.
- Our work could help towards the use of stimulation-evoked neuronal signatures for assessing the state of consciousness in clinical scenarios.

Acknowledgements

This work was supported by the Tiny Blue Dots foundation, NIH grant K24-1K24NS088568, NIH grant R01-2R01NS062092, and the Defense Advanced Research Projects Agency (DARPA) under Cooperative Agreement Number W911NF-14-2-0045, issued by the Army Research Office contracting office in support of DARPA'S SUBNETS program. The views, opinions, and/or findings expressed are those of the authors and should not be interpreted as representing the official views or policies of the Department of Defense or the U.S. Government.

contact: **rzelmann@mgh.harvard.edu**