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Cortical UP/DOWN state synchrony drives propofol phase-amplitude coupling in slow waves

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Introduction

• The anesthetic propofol induces beta (12-20 Hz), alpha (8-12 Hz), and Slow Wave Oscillations (SWO, 0.1-1.5 Hz) on the EEG of human patients [1]

• At low propofol, near Loss of Consciousness, alpha **amplitude** is maximal during the **trough** of the SWO **phase**, called "**Trough-max**" phase-amplitude coupling (PAC) [1]

• At high propofol, in deep anesthesia, alpha **amplitude** is maximal during the **peak** of the SWO **phase**, called "**Peak-max**" PAC [1]

• SWOs in natural sleep often begin in the cortex [2], while simulations suggest propofol alpha is generated by the thalamus [3]

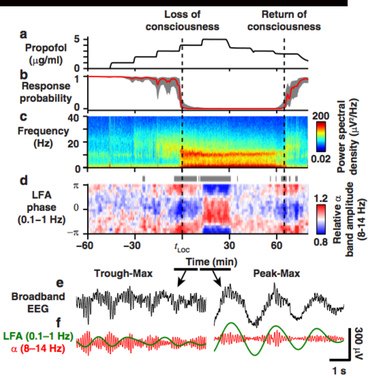

Figure 1: Example EEG data and spectral analysis of human patient undergoing propofol anesthesia, from [1]

• Propofol **"directly"** affects properties of thalamic and cortical cells and synapses such as GABA-A conductance, GABA-A decay time, and H-current conductance [1,3]

• Propofol **"indirectly"** affects thalamic and cortical cells via decreasing cortical acetylcholine (ACh) [4], which affects K(Na)-current conductance, corticocortical, and thalamocortical synaptic strengths [5]

• We hypothesized that the direct effects of propofol would produce and control both trough-max and peak-max PAC in a full, thalamocortical model, primarily by modulating thalamic behavior. However, we found that indirect effects from propofol on ACh and changes to the thalamocortical feedback loop could control trough-max vs peak-max changes.

Methods

•Our simulations modeled 100 cortical dendrite compartments (PYdr), 100 cortical axo-somatic compartments (PYso), 20 cortical interneurons (IN), 20 thalamic reticular neurons (TRN), and 20 thalamocortical neurons (TC) using the biophysical Hodgkin-Huxley formalism [3,5]. Synapses are connected via a nearest-neighbor radius.

•Our artificial EEG signal was modeled from the combination of AMPAergic corticocortical (PY→PY) and thalamocortical (TC→PY) synaptic currents onto cortical dendrites

•Our PAC analysis was based on the standard Modulation Index coupling measure [6]

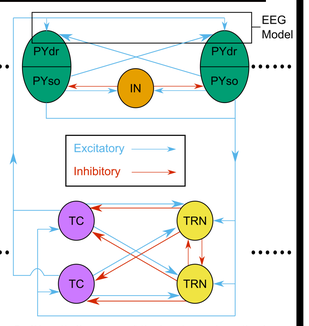

Figure 2: Circuit diagram of thalamic and cortical networks in model; synapses used for EEG model are indicated on top

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Funding / Conflicts of Interest Disclosure

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Conflicts of Interest: Massachusetts General Hospital has licensed intellectual property for EEG monitoring developed by EB and PP to Masimo. EB and PP hold interests in PASACALL, a start-up company developing EEG-based anesthetic state control systems for anesthesiology, of which PP is a Co-Founder.

EEG Trough-max Involves Synaptic Competition

• We found that while **direct** effects were necessary for thalamic propofol alpha, **indirect** effects were also necessary for SWO expression

• EEG signal had two components: thalamocortical and corticocortical synapses onto cortical dendrites

• In the thalamocortical synapse case:
  • Thalamic cells exhibit a **persistent** alpha oscillation, while target cortical cells exhibit a SWO rhythm
  • The TC→PY synaptic current produces a **Trough-max** PAC signal since the alpha amplitude is larger during cortical DOWN states, exhibiting a Slow Wave envelope
  • This coupling is maximal near a 1.0 Hz SWO frequency and a 12 Hz alpha frequency

• In the corticocortical synapse case:
  • The cortex is has low synchronization, so their SWO phases are somewhat out of alignment
  • Cortical alpha is only present during the UP states
  • Because the only alpha component of their synaptic currents are during UP states, these synapses produce a **Peak-max** PAC signal

• The thalamocortical synapses showing **Trough-max** PAC compete with the corticocortical synapses showing **Peak-max** PAC

• The thalamocortical **Trough-max** synapses have a much stronger synaptic current and therefore **dominate** the EEG signal

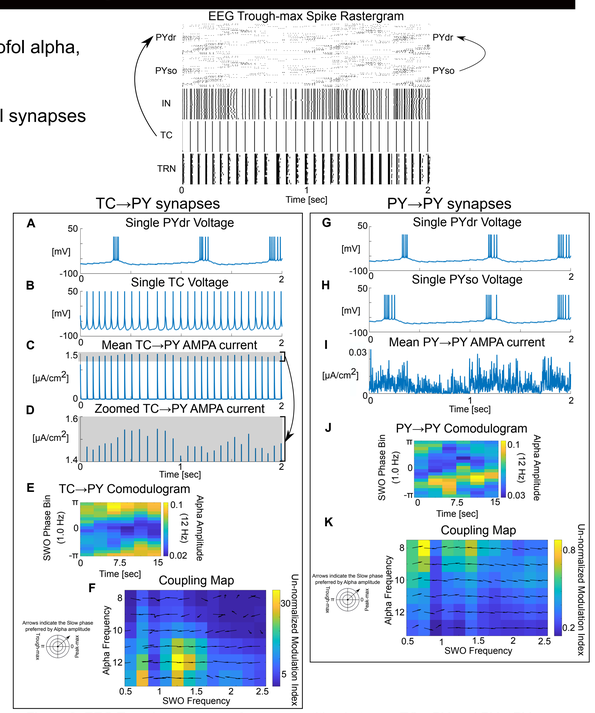

Figure 3: EEG Trough-max occurs from competition between TC→PY and PY→PY synapses

EEG Peak-max Involves Synaptic Cooperation

• Higher-dose propofol may cause a further decrease in ACh, leading to an increase in TC→PY synaptic strength, enabling Trough-max to switch to **Peak-max** PAC as shown here

• In the thalamocortical synapse case:
  • Spontaneous thalamic alpha elicits a stronger cortical response, feeding back enough depolarization to silence thalamic bursting
  • Thalamic alpha only occurs near cortical UP states, therefore producing **Peak-max** PAC in the synaptic current
  • This coupling prefers a slower SWO frequency near 0.5 Hz and a slower alpha frequency near 10 Hz

• In the corticocortical synapse case:
  • The cortex is has high synchronization, so UP state transmission across the cortex is more organized
  • Thalamic alpha is again only present during the UP states
  • Similar to the Trough-max case, these synapses produce a **Peak-max** PAC signal

• SWO power is larger than during EEG Trough-max, similar to experiment [1]

• The thalamocortical and corticocortical synapses both exhibit a **Peak-max** PAC in this higher propofol dose example

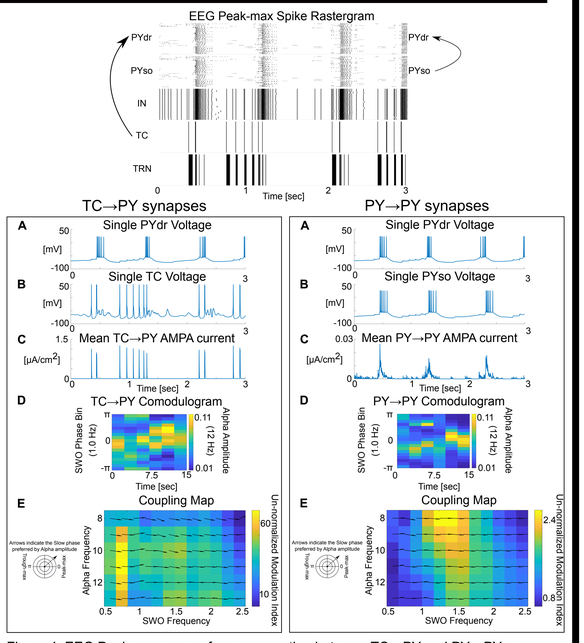

Figure 4: EEG Peak-max occurs from cooperation between TC→PY and PY→PY synapses

Cortical synchronization controls EEG Trough-max vs EEG Peak-max

• Cortical synchronization controls the network via limiting thalamic alpha oscillations and produce depolarized thalamic DOWN states

• Propofol gradually decreases ACh, strengthening thalamocortical synapses, therefore leading to cortical synchronization

• During EEG **Trough-max:**
  • Thalamocortical synaptic strength is not strong enough for alpha bursting to synchronize cortical UP states
  • At any given point in time, weakly synchronized cortical UPs lead to lower maximal activity in corticothalamic synapses
  • Weak corticothalamic activity fails to depolarize and halt thalamic bursting

• During EEG **Peak-max:**
  • Thalamocortical synaptic strength is strong enough to initiate and synchronize cortical UP states
  • Synchronized cortical UPs produce strong, synchronous corticothalamic AMPA firing
  • These strong corticothalamic volleys depolarize the thalamus above its bursting range, interrupting thalamic alpha bursting and resetting the SWO cycle

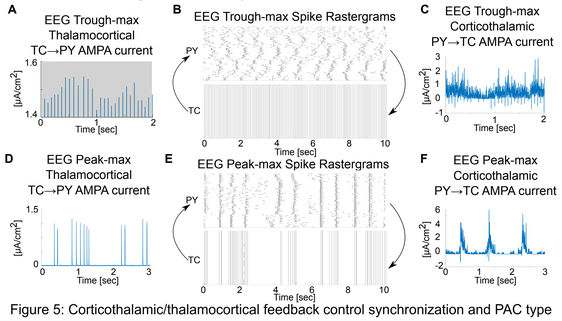

Figure 5: Corticothalamic/thalamocortical feedback control synchronization and PAC type

Conclusions

• While **direct** propofol effects are sufficient for generation of thalamic propofol alpha oscillations, **indirect** effects such as decreased ACh may be necessary for the generation of propofol SWOs

• When the cortex is locally weakly synchronized, strong thalamocortical alpha inputs dominate the **competition** with corticocortical synapses, producing EEG **Trough-max** PAC

• The network can transition from Trough-max to Peak-max PAC via increasing thalamocortical strength, or thalamocortical **feedback**

• When the cortex is highly synchronized, both synapse types **cooperate** to produce EEG **Peak-max** PAC

• The thalamus does **not** have to undergo **intrinsic** changes to switch the system between Trough-max and Peak-max - changing its feedback to the cortex is sufficient

• Propofol-induced reduction in cortical **ACh** levels alter both activation of cortical SWO mechanisms and strength of thalamocortical synapses

• Other neuromodulators may also contribute to cortical synchronization in the context of propofol [7]