The intracranial mechanisms and outcomes of phase-targeted auditory stimulation in children with epilepsy

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At-a-glance

Auditory stimulation during NREM sleep recruits salience and low-level sensory processing networks and triggers a sensory-evoked k-complex. Auditory stimulation targeted to the up-phase potentiates endogenous sleep slow oscillations, laying the foundation for PTAS in children with epilepsy.

Introduction

Children with epilepsy are a population in need for sleep-targeted interventions:

- Adequate sleep is essential for seizure control[1,2]
- Sleep quality significantly impacts cognitive function[3,4]—a critical aspect of quality of life for individuals with epilepsy
- Sleep during childhood is critical for cortical maturation, learning, and development[5,6]

Closed-loop phase-targeted auditory stimulation (PTAS) is a promising new strategy for directly modulating slow wave sleep[7]:

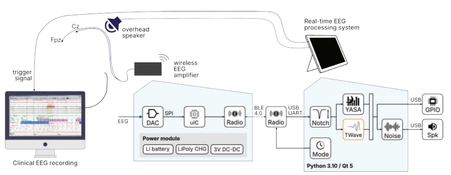
- Detect slow-wave oscillations in real-time
- Deliver auditory stimuli at precise phases
- Amplifies slow-wave activity
- Improves cognition and metabolic health in healthy adults

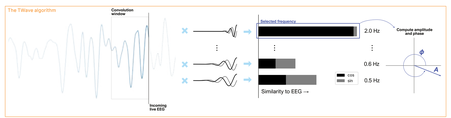
Can PTAS help children with epilepsy?
Which EEG and phase targets work best in children with epilepsy?

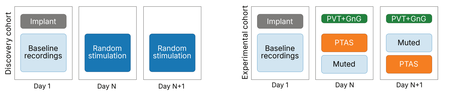
PTAS delivers auditory stimuli at a precise phase based on live EEG recordings

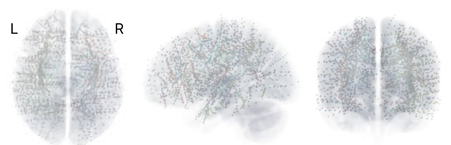
Methods

Our custom-built system for PTAS with epileptic EEG in the neuro ICU









A system for PTAS with epileptic EEG

We developed and built a system for delivering closed-loop PTAS. (A) A wireless EEG amplifier streams a real-time signal from the Fpz - Cz bipolar montage to a bedside table. The signal is processed with the novel TWave algorithm and YASA sleep staging to adaptively predict upcoming stimulation opportunities that align with the targeted phase. (B) We developed the TWave algorithm to robustly estimate and parameterize slow wave sleep phase, amplitude, and frequency.

Experimental design

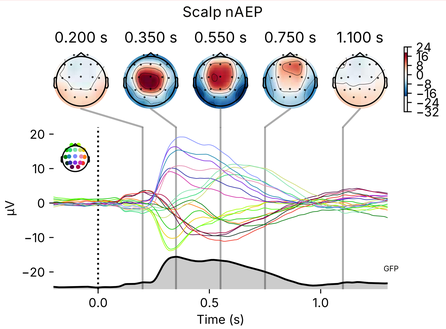
First, to identify optimal phase of PTAS, we recruited 15 patients undergoing SEEG from the Hospital for Sick Children into the discovery cohort, who received random stimulation throughout the night. (C) We then recruited 15 patients into the experimental cohorts who received phase-targeted stimulation with a counterbalanced stimulation withheld condition. The SEEG electrode placements aggregated in template MNI space from our cohort of participants show extensive bilateral coverage.

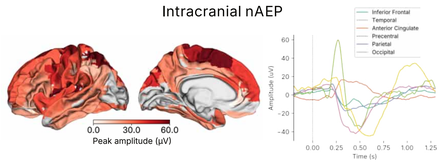
Data analyses

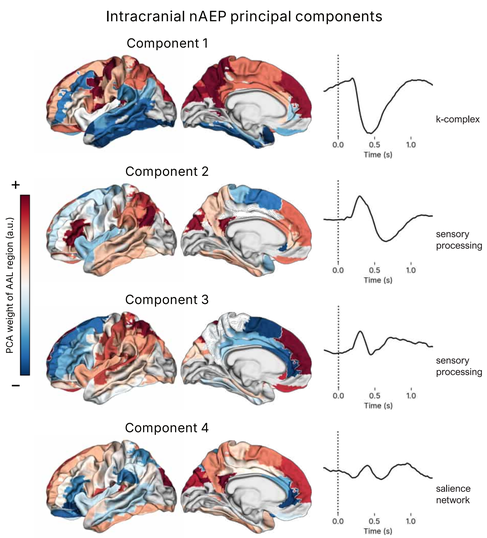
Simultaneous scalp and intracranial EEG were collected with the Natus Quantum system, exported in EDF format, and analyzed in MNE-Python.

Results

1. The nocturnal auditory evoked potential (nAEP)

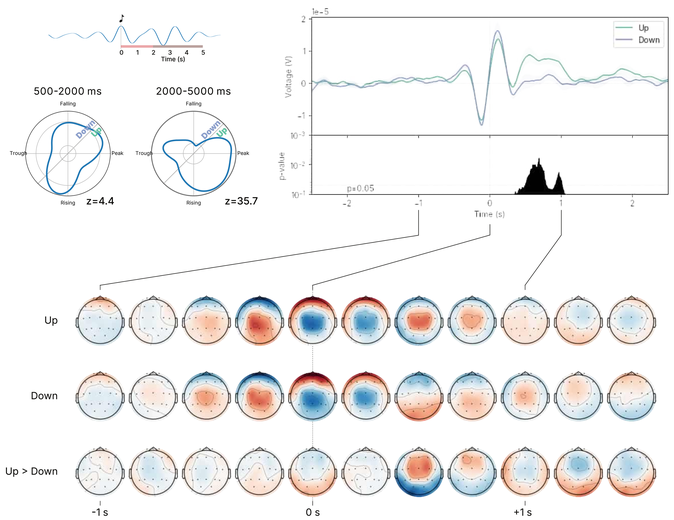


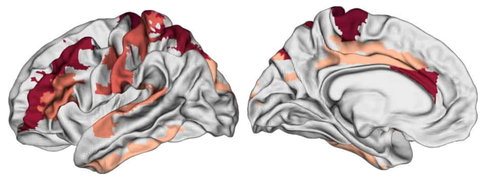




- We present the first direct measurement of the intracranial generators of the nAEP and the intracranial effects of auditory stimulation
- The nAEP is comprised of dissociable contributions from attention and salience regions, sensory processing cortices, and a widespread k-complex-like waveform

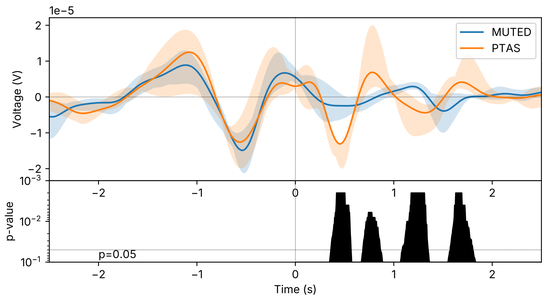
2. Stimulation at positive-going phases preferentially boosts slow oscillations

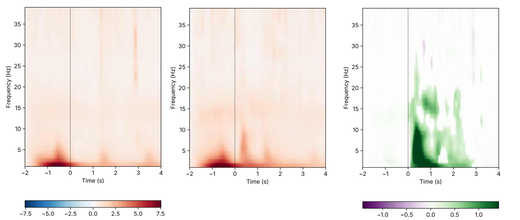


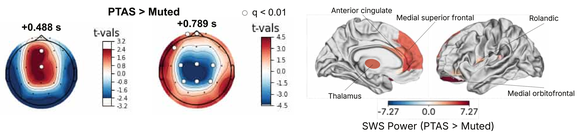


- Up-phase stimulation uniquely boosts slow oscillation power
- Down-phase stimulation disrupts normative slow oscillation topology
- The regions exhibiting significant power increases during up-phase stimulation mirrored regions involved in the nAEP

3. Up-phase targeted auditory stimulation (up-PTAS) boosts sleep slow oscillations







Up-PTAS increases slow wave amplitude

In the experimental cohort, we delivered closed-loop PTAS targeted to the upwards going phase ("up-PTAS") with a phase target of Φ = 0 in the Fpz – Cz bipolar channel. Compared to the sham condition, up-PTAS resulted in significant increase in slow wave amplitude in the Fpz – Cz bipolar derivation up to 1.8 s post-stimulation.

Conclusion

In this work, we've shown that **auditory stimulation during sleep evokes a k-complex**. The k-complex shares similar thalamocortical pathways as endogenous sleep slow waves[8].

Auditory stimulation delivered at the appropriate phase can either potentiate or disrupt sleep slow oscillations in children with epilepsy. Auditory stimulation during the **up-phase from the Fpz – Cz montage, is most effective at potentiating sleep slow oscillations.**

This approach represents a significant advancement in our understanding of PTAS in children with epilepsy, and forms the foundation for future work on the effects of PTAS on seizures, interictal epileptiform activity, neurocognition, and quality of life in children with epilepsy. This enhanced understanding of PTAS mechanisms could lead to novel non-invasive treatments aimed at reducing seizure frequency and improving cognitive functions in affected children.

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