Pharmacological and Stimulation Approaches to Sleep and Memory Consolidation in Schizophrenia

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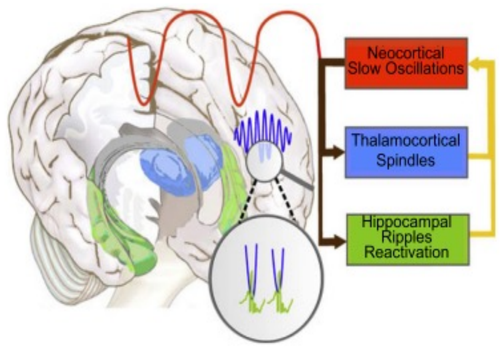
Introduction

- Cognitive deficits are a core feature of schizophrenia
- Current treatments focus on psychotic symptoms and do not adequately address cognitive deficits
- Previous literature has documented a thalamocortical spindle deficit in schizophrenia which correlates with sleep-dependent memory consolidation
- Sleep-dependent memory consolidation involves the coordination of sleep spindles, slow oscillations (SOs), and hippocampal ripples



Aim

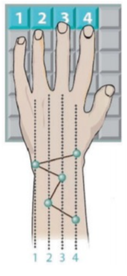
The objective of this research is to approach the problem of unresolved cognitive deficits both pharmaceutically and through non-invasive stimulation, with a focus on increasing coupled spindle activity

Pharmacological Approach

Eszopiclone using EEG
- Nonbenzodiazepine sedative hypnotic
- Increases spindles

Zolpidem using EEG/MEG
- Nonbenzodiazepine sedative hypnotic
- Increased ripples in rodents and spindles and slow oscillations in humans

Finger Tapping Motor Sequence Task (MST): Eszopiclone Trial



Sequence
4-1-3-2-4

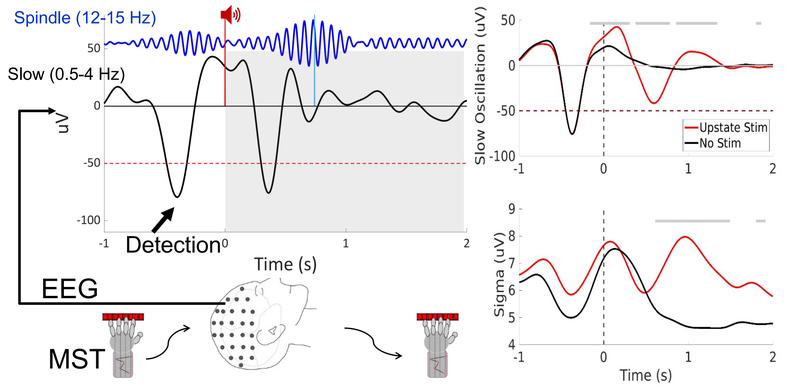
- 30sec typing – 30sec rest
- 12 trials

Word Pair Task: Zolpidem Trial

- Word Pair Example:
  - Screen Display:
    Crow
    +
    Knight
  - Prompt: Crow → ?
  - Say: "Knight"

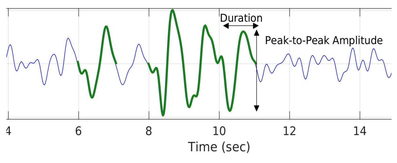
Stimulation Approach

Noninvasive closed-loop auditory stimulation where a quiet sound is played during the SO upstate to evoke SOs and spindles, and improves memory

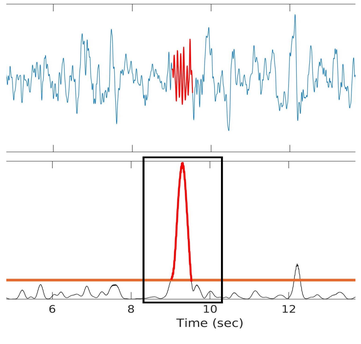


Methods

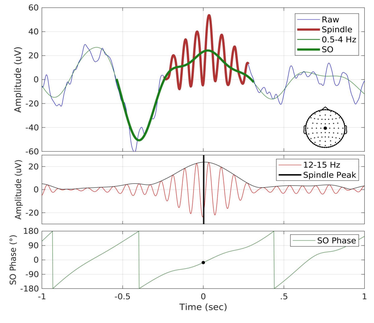
Slow Oscillation (SO) Detection (0.4-5 Hz)



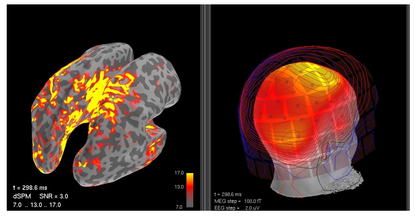
Spindle Detection (12 – 15 Hz)



Spindle-SO Coordination



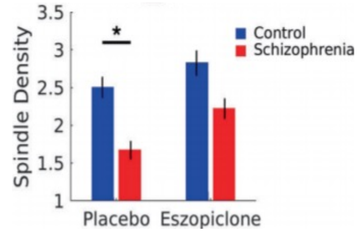
EEG/MEG Source Imaging

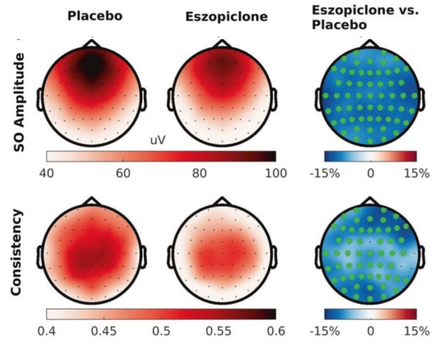


- Polysomnography (PSG) 58 EEG electrodes : All trials
- Magnetoencephalography (MEG) 306 channels : Zolpidem trial

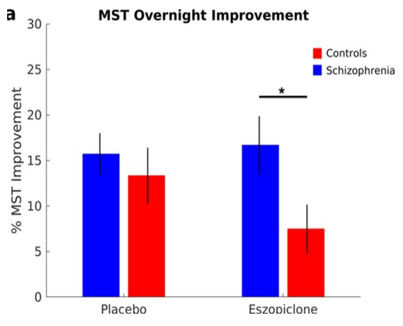
Results

Eszopiclone increased spindle density but disrupted spindle-SO coordination

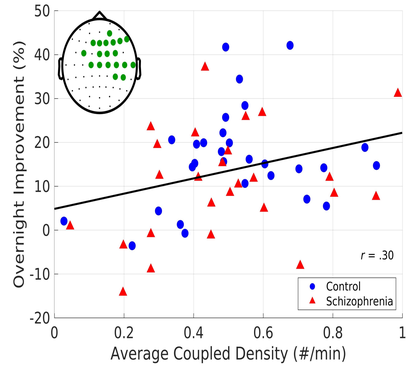




Eszopiclone did not improve overnight MST performance



Spindle-SOs Density Predicts Overnight MST Improvement



Conclusions + Ongoing Work

- The eszopiclone trial reveals the importance of preserving coordination between sleep spindles, slow oscillations, and hippocampal ripples to enhance sleep-dependent memory consolidation
- We are currently running a trial to investigate if zolpidem increases coordinated spindles and improves sleep-dependent memory consolidation in schizophrenia
- Non-invasive auditory stimulation may be an alternative or used in conjunction with pharmaceuticals to increase coupled spindles and ameliorate cognitive deficits in schizophrenia

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