# TREATING SLEEP AND MEMORY DEFICITS IN SCHIZOPHRENIA

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**Cognitive deficits in schizophrenia** are the strongest predictor of functional outcome but their causes are poorly understood and effective treatments are lacking.

Sleep plays a critical role in cognitive function, particularly in consolidating new memories.

Sleep spindles, a defining characteristic of NREM2 sleep, index human intelligence and mediate memory consolidation.

Our findings in schizophrenia demonstrate ***dramatically reduced sleep spindles*** that correlate with marked impairments of sleep-dependent memory consolidation.

This sleep spindle deficit may be treatable: Eszopiclone (Lunesta), a non-benzodiazepine hypnotic that preferentially acts on γ-aminobutyric acid (GABA)ergic neurons in the thalamic reticular nucleus where spindles are generated increases spindle activity in schizophrenia (Wamsley et al., Sleep, 2013).

Spindles coordinate with other brain oscillations, particularly slow waves (SW), to facilitate memory processing during sleep (Fig.1). This temporal coordination is disrupted in a rat neurodevelopmental model of schizophrenia (Phillips et al., Neuron, 2012).

We investigated the SW-spindle orchestration in relation to memory consolidation in schizophrenia, and its modulation by eszopiclone, both as a potential biomarker for schizophrenia and as a novel target for treatment.

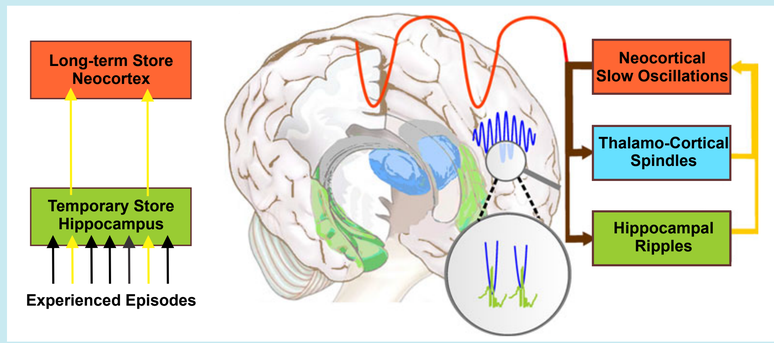


**Figure 1: Active system consolidation during sleep. Adapted from Born & Wilhelm, 2012**

## methods

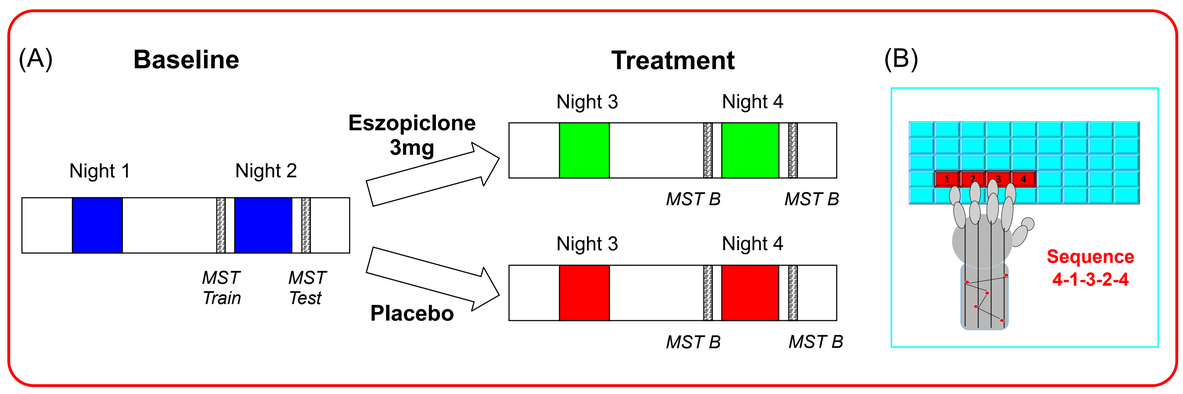


**Figure 2: Experimental Design. (A) Time course of study: Controls had Baseline visit, Schizophrenia patients had both Baseline and Treatment visits; (B) Finger tapping motor sequence task (MST)**

### I. Experimental Design

- Participants: 21 chronic, medicated schizophrenia outpatients (age: 34 ± 9 years) and 17 matched healthy controls (age: 36 ± 7 years)
- Double-blind study: schizophrenia patients randomly assigned to receive either placebo (N=11) or 3mg of eszopiclone (N=10) on 2 consecutive nights of polysomnography (PSG; Fig. 2A)
- On 2nd night, they were trained on the MST (Fig. 2B) at bedtime and tested the following morning
- PSG data acquired at 100 Hz, 5-8 EEG electrodes ( F3, F4, C3, Cz, C4, Pz, O1, O2) referenced to linked mastoids
- Main outcome measure: overnight MST improvement = % increase in the number of correct sequences from the last 3 training trials to the first 3 test trials

### II. Slow Waves and Sleep Spindles Analysis

- PSG was preprocessed and visually scored into stages according to standard criteria
- NREM2 sleep spindles (sigma band: 12-15 Hz) and slow waves (0.5-1.5 Hz) were detected using methods described in Phillips et al., Neuron, 2012
- Sleep spindles occurring on the upstate of SWs were classified as SW-modulated
- SW-triggered spectrograms were used to quantify the coordination of SWs with spindles (as in Fig. 3A)
- Coordination of the SW-modulated spindles across the cortex was measured by coherence

## slow wave modulation of sleep spindles

### I. Baseline Results

- Maximal spindle power occurred on the upstate of the SWs. Patients showed reduced SW-modulated spindle power during Stage 2 sleep in comparison to controls (Fig. 3A)
- In both groups, only SW-modulated spindle coherence correlated with overnight MST improvement (Fig. 3B): ***functionally privileged SW-modulated spindles contribute to memory consolidation***

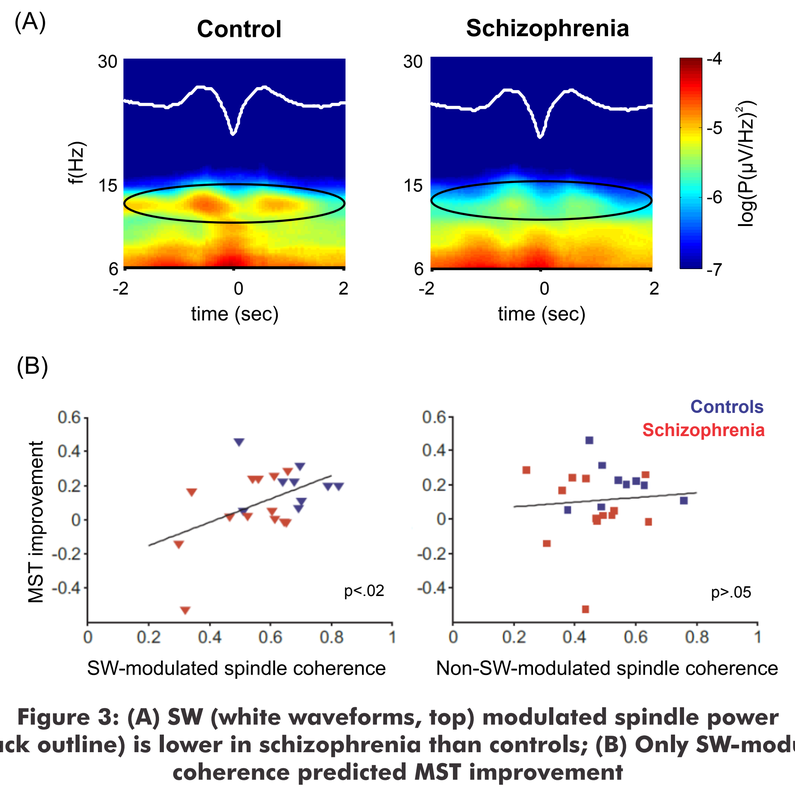


**Figure 3: (A) SW (white waveforms, top) modulated spindle power (12-15 Hz; black outline) is lower in schizophrenia than controls; (B) Only SW-modulated spindle coherence predicted MST improvement**

### II. Treatment Results

- Compared to placebo, patients on eszopiclone showed significantly increased non-SW-modulated sigma power and sigma power that was time-locked to the upstate of SWs ($F_{1,19}$=27.02, p<0.001; Fig. 4A)
- SW-modulated spindles were more coherent across EEG-channels in the eszopiclone group than the placebo group ($F_{1,19}$=42.44, p<.0001; Fig. 4B)
- In the eszopiclone group, coherence in the sigma-band was greater during the sleep that followed MST learning than during the preceding night ($F_{1,19}$=12.08, p<.0005; Fig. 4B)

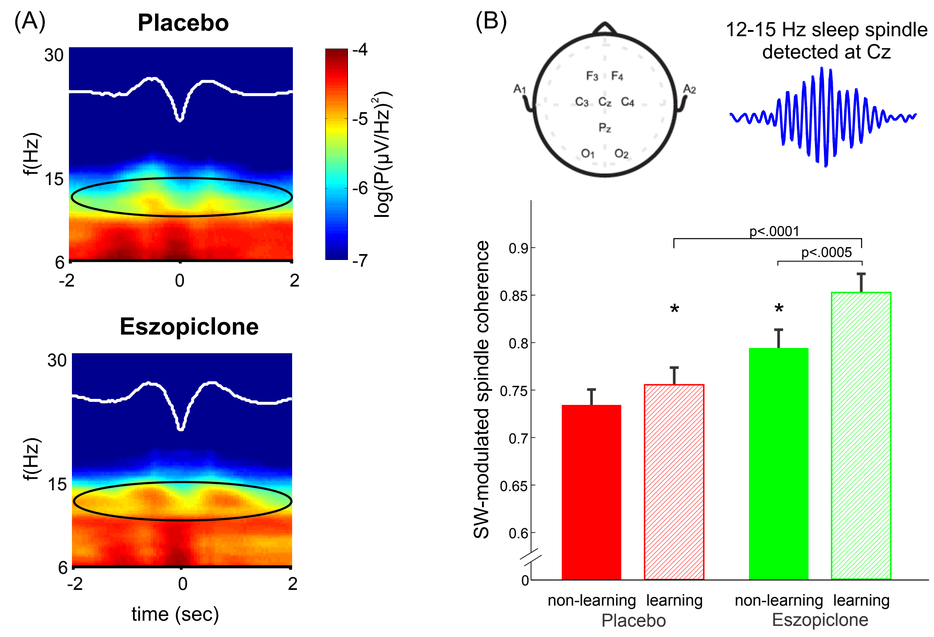


**Figure 4: In schizophrenia eszopiclone increased (A) SW-modulated spindle power; (B) Coherence across the cortex in the spindle frequency band (sigma) following learning**

## conclusions and future directions

- Our findings suggest that the modulation of thalamocortical spindles by neocortical slow waves is important for sleep-dependent memory consolidation.
- We show a deficit of this modulation in schizophrenia.
- Eszopiclone, which increases spindle activity in schizophrenia, also significantly increased both the power and coordination across the cortex (coherence) of SW-modulated sigma activity in schizophrenia.
- In the context of eszopiclone, spindle coherence is enhanced by learning.
- This work links a specific cognitive deficit of schizophrenia (in sleep dependent memory consolidation) to a particular mechanism (disrupted SW modulation of spindles) and paves the way to an effective treatment.

- **Future work:** develop a ***signal processing methodology*** to fully characterize the interaction between SWs and spindles, its relation to memory consolidation, and how this goes awry in schizophrenia.
- Apply these tools to a larger high-density EEG eszopiclone study, and to simultaneous EEG and magnetoencephalography (MEG) study in schizophrenia, since
- EEG and MEG are differentially sensitive to spindle types: MEG sees 50% more spindles than EEG, MEG detects spindles with a focal onset, EEG detects spindles covering extended cortical areas.
- Compute current source estimates of SW and spindle waveforms, anatomically constrained by structural MRI, to identify ***brain circuits*** involved in sleep-dependent memory consolidation.

## references

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