TREATING SLEEP AND MEMORY DEFICITS IN SCHIZOPHRENIA

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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.

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.

Spindle activity, a defining characteristic of NREM2 sleep, index human intelligence and mediate memory consolidation.

Our findings in schizophrenia demonstrate dramatically reduced spindle activity and slow waves (Fig.1). This temporal coordination is disrupted in a rat neurodevelopmental model of 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).

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).

Eszopiclone, which increases spindle activity in schizophrenia, also significantly increased both the power and coordination of the SW-modulated spindle activity (Fig. 2).

In both groups, only SW-modulated spindle coherence correlated with overnight MST improvement (Fig. 3B): 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 =27.02, p<0.001; Fig. 4A).

In the eszopiclone group, coherence in the sigma-band was greater during the sleep that followed MST learning than during the preceding night (F =12.08, p<.0005; Fig. 4B).

Our findings suggest that the modulation of thalamic-cortical spindles by neocortical slow waves is important for memory consolidation in schizophrenia.

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.

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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).

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 =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 =42.44, p<.0001; Fig. 4B).

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

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)

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

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.

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