The Effect of Zolpidem on Memory Consolidation and Sleep Features Over a Night of sleep

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Background

- Thalamo-cortical spindles (12-15Hz) are associated with hippocampus-dependent memory consolidation.
- Interventional studies that directly increase spindles are scarce.
- As a GABA-A agonist, zolpidem boosts sigma frequency (12-15Hz) and sleep spindles.
- Here, we used a double-blind, placebo-controlled within-subjects design to test the hypothesis zolpidem will boost spindle density and spindle-SO coupling, which would lead to increased memory performance after the night of sleep.

Method

- 28 healthy (13 females), well-rested subjects, age 18-24, were recruited.
- Subjects arrived at the Sleep and Cognition lab in the morning (8AM) and were trained on 60 un-related word pairs. Their memory for the word pairs was tested twice, at 9AM and at 9PM.
- Subjects were hooked-up to high-density electroencephalography (EEG) and were then given either zolpidem (5mg) or placebo before lights out. The order of the drugs was counterbalanced with a 1-week washout period in between.
- In the morning (10:30AM), subjects' memory was tested for a third time.
- Due to the short half-life of zolpidem (1.5-4.5hr), we divided the night of sleep into four quartiles and calculated power spectra in SO (0.5-1.0 Hz), delta (1-4Hz), theta (4-7Hz), sigma (12-15Hz), spindle density, and spindle/SO complexes.
- The difference in power spectra between zolpidem and placebo conditions was calculated at each electrode to examine drug effects on *a priori* sleep features.
- Pearson's r between performance change and power spectra change at each electrode was calculated to examine the correlation between performance and spectra power.

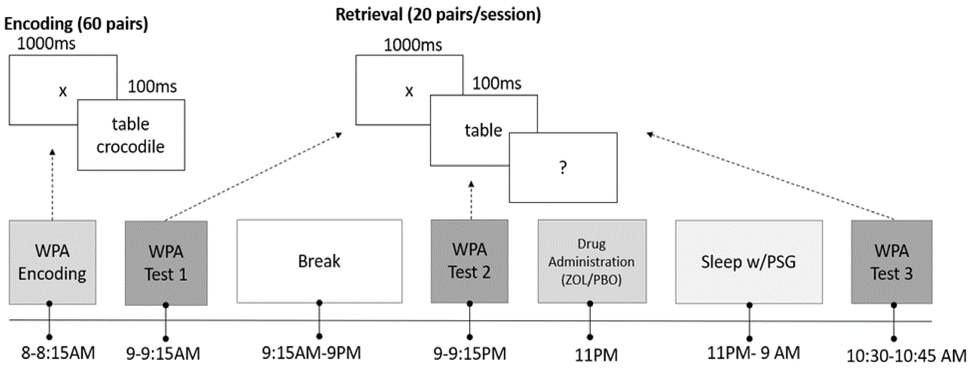

Figure 1. Experimental Timeline

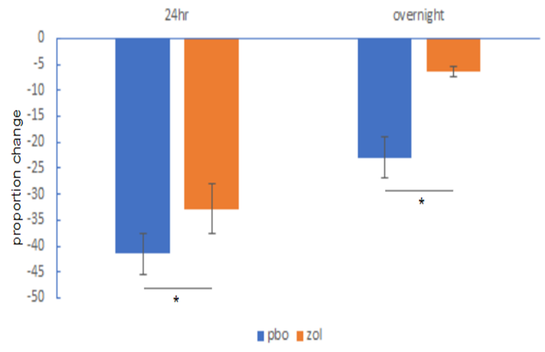

Figure 2, Behavioral Result

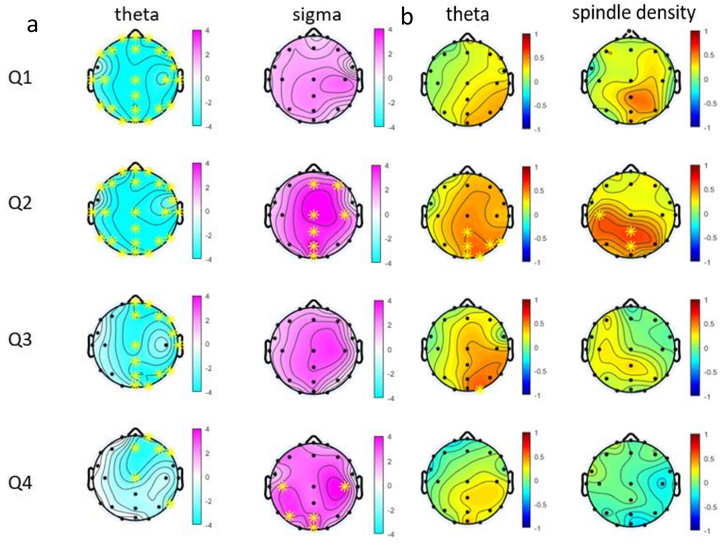

Figure 3, (a) Power spectra change from zolpidem to placebo
(b) Pearson's r in spectral power change (zol-pbo) and performance change (zol-pbo) for overnight retention

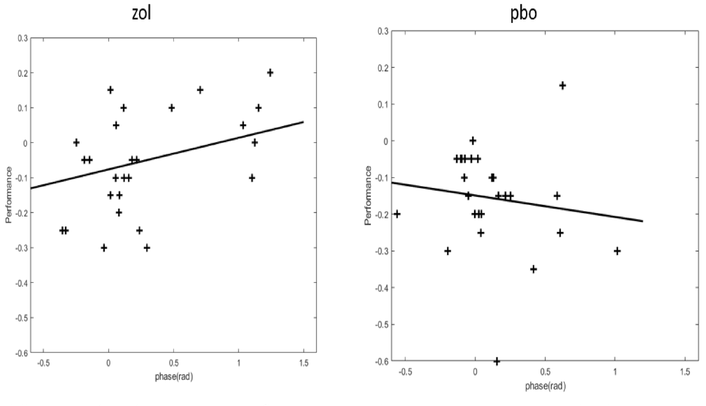

Figure 4, Memory performance improvement and phase-amplitude timing

Results

Zolpidem led to better memory, partly due to increased spindle density and spindle-SO coupling. Less reduction in theta is also good for memory.

- Zolpidem condition had better verbal memory retention for 24-hr retention (t_{27}=2.23, p<0.05) as well as overnight retention (t_{27}=2.78, p<0.01) compared to placebo (figure 2).
- Zolpidem led to an increase in sigma power and a decrease in theta power compared to placebo (figure 3a).
- Better memory performance was associated with more increase in spindle density and less reduction in theta power (figure 3b).
- The phase of the SO-spindle complex was associated with overnight retention in zolpidem (r=0.48, p<0.01) but not placebo (r=-0.1329, p=0.5) (figure 4).

Implications

This study provides new information about the effect of zolpidem on memory over night sleep.

- Consistent with our hypothesis, zolpidem-induced spindle density and spindle-SO coupling facilitate memory consolidation.
- Even though zolpidem leads to a decrease in theta power globally, participants who had the least reduction in theta tend to have a better memory performance.
- Reversing the EEG reduction effect of zolpidem not only leads to EEG characteristics that closely resemble natural sleep, but also produces optimal memory consolidation.