Cover Letter
Title: Enhancing Memory Consolidation in Older Adults
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Aim 1 Expected Results: Determine the effect of pharmacological intervention during sleep on memory performance.

Studies 1-4 will address Aim 1.

Study 1: The effect of pharmacologically modulating sleep spindles on declarative associative verbal memory.

We hypothesize that declarative associative verbal memory performance will be increased with ZOL in a dose-dependent manner and decreased with SO, compared with placebo. In addition, we predict that sleep spindles will be correlated with verbal memory performance in all four drug conditions and placebo. Furthermore, the ZOL condition will show absolute increases in spindle density compared to placebo. These results would be consistent with our hypothesis that sleep spindles are associated with declarative memory.

Study 2: The effect of pharmacologically modulating sleep spindles on emotional memory and emotional arousal.

We hypothesize that ZOL will show dose-dependent increases in memory for negative and high arousal emotional memo- ries, compared with neutral, positive and low arousal memories, and compared with placebo. We also hypothesize that SO will decrease memory for negative valence and high arousal memories compared with placebo. In addition, we hypothesize that spindles will correlate with negative and high arousal emotional memories in all five drug conditions, whereas REM sleep will be correlated with emotional arousal, consistent with our hypothesis that spindles increase consolidation of emo- tional memories, and REM sleep increases processing of emotional arousal (Baran et al. 2012).

Study 3: The effect of pharmacologically modulating sleep spindles on motor memory.

We hypothesize that there will be no changes in motor learning with either ZOL (increased spindle density) or SO (decreased spindle density). How- ever, similar to previous results, we predict a positive correlation between spindle density and motor learning in all four drug conditions and placebo. This pattern of results would suggest that previous findings of correlations between spindles and motor learning are a marker of some as of yet unexplained factor, and would increase the specificity of our understand- ing of the role of spindles in declarative and non-declarative memory.

Study 4: The effect of pharmacologically modulating sleep spindles on perceptual learning. We hypothesize that ZOL will show dose-dependent decreases in perceptual learning compared with placebo and SO. We also predict a positive correlation between REM sleep and perceptual learning, and a negative correlation between spindle density and perceptual learning in all five conditions. The results will be a strong negative control for the role of sleep spindles in declarative and non-declarative memory.

Aim 2 Expected Results: Determine the effect of pharmacological intervention during sleep on memory in older adults.

Study 5: The effect of pharmacologically modulating sleep spindles on memory in older adults. We hypothesize that older adults will show a dose-dependent increase in declarative associative verbal memory compared with placebo. In addition, we hypothesize that spindle density will increase in a dose-dependent manner, compared with placebo, and that performance will be correlated with spindle density.

Aim 3 *Expected Results*: Characterize the physiological effects of pharmacological intervention on sleep spindles. We hypothesize that sleep will be modulated similarly across Studies 1-4. In the experimental nap, we will see a dose-dependent increase in sleep spindle density in ZOL, whereas SO will significantly decrease spindle density, compared with placebo. We predict that spindle density will be modulated equally for fast and slow frequency spindles, and no differences in spindle amplitude, frequency, or duration between drug conditions. However, we predict that declarative verbal and emotional memory and motor learning will be correlated with the density of fast frequency spindles, but not slow frequency spindles. That is, ZOL will increase the amount of normally occurring fast and slow spindles, not affect spindle morphology, and only fast spindles will correlate with performance. We will examine spindles in Stage Two and SWS separately, and NREM (Stage Two + SWS) sleep combined. We expect Stage Two spindles and sigma power to be topographically dominant over the central electrodes and that spindles and sigma power in deeper NREM sleep will be concentrated in frontal electrode sites. As a negative control for spindles, we will examine slow oscillations and expect no differences across drug conditions. For sleep stages, we expect that there will be increased SWS in the ZOL and SO drug conditions compared with placebo. Furthermore, we predict dose-dependent decreases in REM sleep with ZOL, compared with SO and placebo. Both drug conditions will increase sleep efficiency by decreasing wake after sleep onset and sleep latency, compared with placebo. No differences between conditions in Stage 1, Stage Two sleep, or Total Sleep Time (which will be held constant) are predicted.
In the experimental night (9-10 hours post-drug administration), we hypothesize that there will be no differences across drug conditions in spindle density, amplitude, or frequency, either in slow or fast frequency spindles. We also hypothesize that SWS will not differ across conditions due to a prior study that alternated nights of sleep with ZOL and placebo and reported no carry over effects of the drug on NREM sleep (Parrino et al. 2008). The study, however, did show increased total sleep time on the placebo night, which we also predict for our experimental drug nights, compared with placebo.
In Study 5, we hypothesize that older adults will show a dose-dependent increase in sleep spindle density with ZOL, and increased frequency of frontal spindles (i.e. faster spindles), compared with placebo. Furthermore, the density of fast spindles at frontal sites will correlate with memory improvement in ZOL conditions.