

Supplementary material

Here we document behavioral and imaging findings associated with sleep deprivation across the two tasks. We also describe the interindividual differences in response to donepezil as they relate to an individual's tolerance of sleep deprivation.

Behavioral findings

If sleep deprivation (SD) were to affect visual short-term memory (VSTM) without affecting attention, the effects of state would be expected to be more prominent at higher set sizes. Instead, the effect of SD was significant at all set sizes, but particularly at set sizes 1 and 2 where memory load is minimal (Chee and Chuah, 2007; Supplementary Table 1). In the ensuing analyses, accuracy was assessed by including all trials. See Supplementary Table 2 for accuracy computed after omitting non-responses.

The findings related to the event-related version used here replicate those of a previous experiment that used a block design. VSTM accuracy declined with sleep deprivation $F(1,27) = 36.95$, $p < 0.001$, and with increasing set size, $F(5,135) = 139.84$, $p < 0.001$. Across the entire cohort, there was no significant effect of drug, $F(1,27) = 1.12$, $p = 0.30$. Very similar effects were present in the visual perceptual control (VPC) task. There were significant effects of state, $F(1,27) = 63.65$, $p < 0.001$, and set size, $F(5,135) = 6.81$, $p < 0.001$. The effect of drug was not significant, $F(1,27) = .04$, $p = 0.95$.

The interaction of state and set size was significant for both the VSTM, $F(5,135) = 3.16$, $p = 0.01$ and the VPC tasks, $F(5,135) = 2.71$, $p = 0.02$. There were no other significant interactions in either task.

Separate state by set size and drug by set size ANOVA were conducted. For the VSTM task, state by set size ANOVA conducted separately for placebo and donepezil indicated significant effects of state and set size (largest $p < 0.001$), but the interaction did not reach significance for either condition (placebo: $F(5,135) = 1.83$, $p = 0.11$; donepezil: $F(5,135) = 1.93$, $p = 0.09$). Drug by set size ANOVA indicated

significant effects of set size for both RW and SD (largest $p < 0.001$). Both the effect of drug and the drug by set size interaction were not significant (all $p > 0.05$).

For the VPC task, the state by set size ANOVA for placebo returned significant effects of state, $F(1,27) = 31.15$, $p < 0.001$, set size, $F(5,135) = 5.24$, $p < 0.001$ and an interaction of state by set size, $F(5,135) = 2.94$, $p = 0.02$. Separate paired sample t tests indicated smaller effects of state for set size 8 ($p = 0.01$) relative to the other remaining set sizes (largest $p = 0.001$). For donepezil, there were significant effects of state, $F(1,27) = 42.21$, $p < 0.001$, and set size, $F(5,135) = 2.94$, $p = 0.02$, but these two factors did not interact, $F(5,135) = 0.63$, $p = 0.68$. The drug by set size ANOVA for both states returned only significant effects of set size (largest $p = 0.001$, p for all other effects > 0.05).

To test the hypothesis that donepezil would selectively benefit SD-vulnerable individuals when sleep deprived, we divided the entire cohort into three roughly-equal groups based on a composite indicator of vulnerability. This was defined as the difference in the collective number of non-responses for *both* in-scanner tasks between the SDP and RWP conditions i.e. (total non-responses at SDP – total non-responses at RWP; Supplementary Table 3). Supporting the notion that this measure is behaviorally meaningful, we found it to be highly correlated with PVT lapses (defined as response time > 500 ms; Supplementary Table 4). The three groups were defined as high-vulnerable (HV, $N=9$), moderate-vulnerable (MV, $N=10$) and low-vulnerable (LV, $N=9$). A three-way repeated-measures ANOVA taking these three groups into consideration showed a significant drug by state by group interaction in the VSTM condition, $F(2,25) = 9.14$, $p = 0.001$ (Fig. 4A) and the VPC condition $F(2,25) = 3.33$, $p = 0.05$ (Fig. 4B).

To clarify that the benefit of donepezil was manifest only following sleep deprivation, and in vulnerable volunteers, separate ANOVA were computed for each state. Following sleep deprivation, for the VSTM task, the 2 (drug) by 6 (set size) by 3 (group) ANOVA showed a drug by group interaction $F(2,25) = 6.47$, $p = 0.005$. Additional ANOVA for each group indicated a marginal benefit of drug in the VSTM task in the MV, $F(1,9) = 5.79$, $p = 0.04$, and HV groups, $F(1,8) = 4.94$, $p = 0.05$, while

the LV group **appeared** to have been adversely affected, $F(1,8) = 4.03$, $p = 0.08$. No group showed a drug by set size interaction (all $p > 0.05$). In contrast, following a normal night of sleep, a parallel analysis revealed a significant effect only for set size 1 ($p < 0.001$, p for all other effects > 0.05). Separate drug by set size ANOVA for each group revealed no effects of drug or any interaction between drug and set size (Fig. 4A).

Similarly for the VPC task, following sleep deprivation, there was a marginal drug by group interaction, $F(2,25) = 3.12$, $p = 0.06$ (Fig. 4B). Low-vulnerable subjects showed a trend towards being adversely affected by donepezil, $F(1,8) = 2.49$, $p = 0.15$, while high-vulnerable individuals showed a marginal benefit, $F(1,8) = 4.50$, $p = 0.06$. No effect of drug was present for the moderate-vulnerable group at SD, $F(1,9) = 0.09$, $p = 0.77$.

Neuroimaging findings

Intraparietal sulcus (IPS) activation

Short-term memory *capacity* can be indexed using K , defined as $((\text{Hit Rate} + \text{Correct Rejection Rate}) - 1) \times \text{Array size}$ (Cowan, 2000). Short-term memory capacity averaged approximately 3 colors after a normal's night sleep and decreased to around 2 following a night of sleep deprivation (Chee and Chuah, 2007; Supplementary Table 1, Supplementary Fig. 1). The manner in which K and intraparietal sulcus (IPS) activation saturated in the VSTM condition (Supplementary Table 6, Supplementary Fig. 1) suggests that part of the activation in this region relates to the short-term storage of visual items (Todd and Marois, 2004). These effects were bilateral but, for brevity, we limit our report to ROI in the right hemisphere.

IPS activity was markedly attenuated during sleep deprivation, $F(1,27) = 15.99$, $p < 0.001$ (Supplementary Fig. 1, Fig. 5). Although this state effect fluctuated across set

sizes, $F(5,135) = 4.38$, $p = 0.001$, it was significant at every level of memory load (smallest $p < 0.05$ at set size 1) suggesting impaired recruitment of attention.

Corresponding to the behavioral findings, there was no effect of drug, $F(1,27) = 0.21$, $p = 0.65$, for the group as a whole. There was no interaction between drug and state or drug and set size (all $p > 0.05$).

In accordance with our prediction that IPS is sensitive to memory load but not perceptual load, IPS activity did not vary as a function of set size in the visual perceptual control condition, $F(5,135) = 1.02$, $p = 0.41$ (Supplementary Table 7, Supplementary Fig. 1). A strong effect of state, $F(1,27) = 12.71$, $p = 0.001$ was invariant across set size as indicated by the insignificant interaction between state and set size, $F(5,135) = 0.67$, $p = 0.64$. The main effect of drug was insignificant, $F(1,27) = 0.05$, $p = 0.83$, as were the remaining interactions.

Extrastriate activation

Activation in the ventral occipital cortex increased monotonically with set size for both tasks (Supplementary Tables 6 and 7, Fig. 5). For the VSTM task, there was a strong effect of state, $F(1,27) = 28.01$, $p < 0.001$ and no interaction between state and set size, $F(5,135) = 1.66$, $p = 0.15$. There was no effect of drug or any significant interactions involving drug (all $p > 0.05$; Fig. 5).

Similarly, in the visual perceptual control condition, ventral occipital (VO) activity increased monotonically as a function of set size, $F(5,135) = 14.24$, $p < 0.001$ (Fig. 5), and was markedly attenuated following sleep deprivation, $F(1,27) = 26.31$, $p < 0.001$. This effect of state did not vary across set size, $F(5,135) = 1.40$, $p = 0.23$. There were no significant effects of drug or any interactions involving drug ($p > 0.05$).

Left Inferior Frontal Gyrus Activation

Neural activity in the left inferior frontal gyrus (LIFG) was modulated as a function of set size only for the VSTM task (Supplementary Fig. 2), in an *incremental* monotonic pattern similar to the IPS, $F(5,135) = 9.91$, $p < 0.001$. Activity in the LIFG

also decreased following sleep deprivation, $F(1,27) = 38.58$, $p < 0.001$ and was not modulated by drug, $F(1,27) = 0.06$, $p = 0.80$. There was a marginal interaction of state by set size, $F(5,135) = 2.33$, $p = 0.05$. However, further state by set size analyses did not reveal significant interactions for either drug condition.

The LIFG showed behavior-activation relationships (Supplementary Fig. 2) similar to those reported for the IPS and extrastriate cortex (see Fig. 6). Activity in this region positively tracked behavioral decline following sleep deprivation in the placebo condition as well as donepezil-induced improvement for the VSTM task. There was also an association between donepezil-induced increment in activation and sleep-deprivation-related decline in activity in this region (Supplementary Fig. 2).

REFERENCES

Chee MW, Chuah YM (2007) Functional neuroimaging and behavioral correlates of capacity decline in visual short-term memory after sleep deprivation. *Proc Natl Acad Sci U S A* 104:9487-9492.

Cowan N (2000) The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *Behav Brain Sci* 24:87-114; discussion 114-185.

Todd JJ, Marois R (2004) Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature* 428:751-754.