Study 2
One driving test, of a 72-year-old female subject, was terminated prematurely by the driving instructor, because he judged the subject too drowsy to continue safely. The test was stopped after 45 minutes on day 2 of placebo treatment. None of the tests were stopped after suvorexant and zopiclone treatment.

Mean changes from placebo in SDLP for study 2 are shown in the right panel of figure 1. Mean changes from placebo in SDLP scores in after suvorexant 15 and 30 mg were very small on both test days: they ranged from -0.43 to +0.60. None of these changes were statistically significant, or clinically meaningful, as determined by the lower limits of the 90% CI of these changes which all fell below 0 cm, and the upper limits of the 90%CI which all fell below the criterion of 2.4 cm, respectively. After use of zopiclone 7.5 mg mean SDLP was increased by 1.89 cm on day 2, and by 1.17 cm on day 9. These results show that effects of zopiclone on driving were statistically significant on both days (demonstrating assay sensitivity), and clinically relevant on day 2, but not on day 9.

DISCUSSION
Results showed that measurable impairment occurred in non-elderly drivers after suvorexant 20 and 40 mg as compared to placebo, but the mean effects on SDLP were less severe than previously found for alcohol in blood concentrations of 0.5 g/L, which is the legal limit for driving in most countries. The effects were therefore not considered to be clinically meaningful. Nonetheless, four non-elderly subjects requested that a total of 5 driving tests be stopped before scheduled completion, because they felt too drowsy to continue safely. Results of study 2 showed that driving performance of elderly, as measured by SDLP, was not impaired following suvorexant 15 and 30 mg. Mean drug-placebo differences in SDLP following suvorexant 15 and 30 mg on Day 2 and 9 were small, and not clinically meaningful or statistically significant.

It can be concluded that the residual effects of suvorexant 15 to 40 mg are on average not clinically meaningful, but there may be some individuals who experience next-day effects. Use of the recommended dose of 10 mg is likely to be safe for patients who have to drive to work after bedtime administration.

REFERENCES

IMPACT OF SLEEP DEPRIVATION AND CAFFEINE ON WORKING MEMORY MANAGEMENT


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INTRODUCTION
Sleep deprivation adversely affects cognition and task performance in a wide range of contexts. However, the ability to maintain information in the focus of attention, i.e., in working memory (WM), is largely preserved during sleep deprivation, even as the flow of information into WM is compromised. Less clear is how processes involved in the management of WM are affected by sleep deprivation or how these processes are affected by caffeine, a commonly used sleep deprivation countermeasure. Here we explored the effects of sleep deprivation on the ability to manage the contents of WM by deactivating and reactivating information in response to changing response requirements and to what extent caffeine could decrease the detrimental effects of sleep deprivation on task performance.

METHODS
Data were available for 11 healthy subjects (ages 19–39, 5 females) who participated in an 18-day (17-night) study inside a strictly controlled laboratory setting. After 3 baseline days with 10 h sleep opportunities (21:00–07:00), subjects were kept awake for 48 h. The 48 h total sleep deprivation (TSD) period was followed by a 5 h nap (07:00–12:00) and 3 recovery days with 10 h sleep opportunities (21:00–07:00). The pattern of 48 h TSD followed by a nap and 3 recovery days was repeated two more times – that is, subjects were exposed to TSD three times in total. The last TSD period was followed by 2 instead of 3 recovery days. During each of the TSD periods, caffeine or placebo was administered after 6, 18, 30 and 42 h of scheduled wakefulness (at 13:00, 01:00, 13:00 and 01:00, respectively). At each time point, subjects were provided with 3 pieces of chewing gum that each could contain either 100 mg caffeine or placebo. During one TSD period, the total dose of caffeine at each time point was 0 mg; during another TSD period, the total dose at each time point was 200 mg; and during the remaining TSD period, the total dose at each time point was 300 mg. The three caffeine dose conditions occurred in double-blind, randomized order. During each TSD period, subjects performed a computerized WM task 30 min post gum administration, after 6.5 h of scheduled wakefulness (baseline) and again 24 h later after 30.5 h of scheduled wakefulness (sleep-deprived). In the WM task, subjects were presented two memory sets, labeled 1 and 2, with each set containing three random letters. A cue was presented indicating which set was the active set to use as the basis for responding. Subjects were then presented with a probe letter (probe 1) and asked to identify whether the probe was in the cued memory set with a speeded "yes" or "no" response on a computer keyboard. Then, another cue was presented indicating the active set to use in responding to...
a second probe. On half of the trials the active set was the same for both probes, and on the other half the active set switched. Subjects were then presented with the second probe letter (probe 2) and asked to identify whether the probe was in the cued memory set with a speeded "yes" or "no" response. Half of the probe stimuli were in the active set, requiring a "yes" response, and half the stimuli were not in the active set, requiring a "no" response. On the "no" trials half of the stimuli were from the non-cued memory set and half the stimuli were in neither memory set. Each test session contained 128 trials.

Overall response time and accuracy were measured for each test session, in the baseline and sleep deprivation conditions and across all three caffeine doses. Furthermore, the amount of interference produced by having to respond "no" to a probe from the non-cued memory set was assessed relative to when the probe was in neither memory set. This interference effect represents the ability to "deactivate" the non-cued set in favor of the cued set. Finally, the cost to performance of switching between memory sets in preparation for probe 2 was assessed relative to not switching. The switch cost provides an index of the ability to manage WM by returning the non-cued set to the active focus of attention. 5 Response time and accuracy data were analyzed with mixed-effects analysis of variance (ANOVA) with fixed effects for condition (baseline or sleep-deprived), caffeine dose (0 mg, 200 mg, or 300 mg), probe context (probe in cued, non-cued or neither memory set), and switch trial type (switching or no switching), and a random effect over subjects on the intercept.

RESULTS AND DISCUSSION

Overall performance was impaired in the sleep deprivation condition compared to the baseline condition as measured by probe 1 accuracy ($F_{1,8458}=46.93, P<0.001$) and response time ($F_{1,8458}=19.95, P<0.001$) and probe 2 accuracy ($F_{1,8396}=35.33, P<0.001$) and response time ($F_{1,8389}=4.85, P=0.028$), as shown in figure 1.

Figure 1. Responses as a function of condition. The left panel shows accuracy (mean ± standard error) and the right panel shows response time (mean ± standard error) for probe 1 (black) and probe 2 (grey). BL: baseline; SD: sleep-deprived.

When subjects received caffeine, there was a significant improvement in probe 1 accuracy ($F_{1,8458}=19.96, P<0.001$) and response time ($F_{1,8458}=16.83, P<0.001$) regardless of condition (baseline or sleep-deprived), as shown in figure 2. This pattern held true across baseline and sleep deprivation conditions for probe 2 accuracy ($F_{1,8396}=8.32, P<0.001$) but did not reach significance for probe 2 response time ($F_{1,8389}=2.24, P=0.106$).

We obtained the expected effects by probe type, as shown in figure 3. Probes from the non-cued memory sets produced significant interference for probe 1 accuracy ($F_{1,8396}=75.82, P<0.001$) and response time ($F_{1,8389}=89.30, P<0.001$) as well as probe 2 accuracy ($F_{1,8396}=48.33, P<0.001$) and response time ($F_{1,8389}=83.43, P<0.001$). The effect of probe type did not interact significantly with condition (baseline or sleep-deprived).

Figure 2. Probe 1 responses as a function of caffeine dose. The left panel shows accuracy (mean ± standard error) and the right panel shows response time (mean ± standard error).

Figure 3. Responses as a function of probe context. The left panel shows accuracy (mean ± standard error) and the right panel shows response time (mean ± standard error) for probe 1 (black) and probe 2 (grey).

Figure 4. Probe 1 accuracy level (mean ± standard error) by probe context as a function of caffeine dose.

Probe 2 context did not have a statistically significant interaction with caffeine dose for accuracy ($F_{1,8396}=1.35, P=0.249$) or response time ($F_{1,8389}=0.19, P=0.946$). Likewise probe 1 context did not have a significant interaction with caffeine dose for response time.
a second probe. On half of the trials the active set was the same for both probes, and on the other half the active set switched. Subjects were then presented with the second probe letter (probe 2) and asked to identify whether the probe was in the cued memory set with a speeded "yes" or "no" response. Half of the probe stimuli were in the active set, requiring a "yes" response, and half the stimuli were not in the active set, requiring a "no" response. On the "no" trials half of the stimuli were from the non-cued memory set and half the stimuli were in neither memory set. Each test session contained 128 trials.

Overall response time and accuracy were measured for each test session, in the baseline and sleep deprivation conditions and across all three caffeine doses. Furthermore, the amount of interference produced by having to respond "no" to a probe from the non-cued memory set was assessed relative to when the probe was in neither memory set. This interference effect represents the ability to "deactivate" the non-cued set in favor of the cued set. Finally, the cost to performance of switching between memory sets in preparation for probe 2 was assessed relative to not switching. The switch cost provides an index of the ability to manage WM by returning the non-cued set to the active focus of attention. Response time and accuracy data were analyzed with mixed-effects analysis of variance (ANOVA) with fixed effects for condition (baseline or sleep-deprived), caffeine dose (0 mg, 200 mg, or 300 mg), probe context (cued, non-cued or neither memory set), and switch trial type (switching or no switching), and a random effect over subjects on the intercept.

RESULTS AND DISCUSSION

Overall performance was impaired in the sleep deprivation condition compared to the baseline condition as measured by probe 1 accuracy ($F_{(2,44)}=46.93, P<0.001$) and response time ($F_{(2,44)}=19.95, P<0.001$) and probe 2 accuracy ($F_{(2,89)}=35.33, P<0.001$) and response time ($F_{(2,89)}=4.85, P=0.028$), as shown in figure 1.

![Figure 1](image1.png)

**Figure 1.** Responses as a function of condition. The left panel shows accuracy (mean ± standard error) and the right panel shows response time (mean ± standard error) for probe 1 (black) and probe 2 (grey). BL: baseline; SD: sleep-deprived.

When subjects received caffeine, there was a significant improvement in probe 1 accuracy ($F_{(2,44)}=19.96, P<0.001$) and response time ($F_{(2,44)}=16.83, P<0.001$) regardless of condition (baseline or sleep-deprived), as shown in figure 2. This pattern held true across baseline and sleep deprivation conditions for probe 2 accuracy ($F_{(2,89)}=8.32, P<0.001$) but did not reach significance for probe 2 response time ($F_{(2,89)}=2.24, P=0.106$).

![Figure 2](image2.png)

**Figure 2.** Probe 1 responses as a function of caffeine dose. The left panel shows accuracy (mean ± standard error) and the right panel shows response time (mean ± standard error).

We obtained the expected effects by probe type, as shown in figure 3. Probes from the non-cued memory sets produced significant interference for probe 1 accuracy ($F_{(2,44)}=75.82, P<0.001$) and response time ($F_{(2,44)}=89.30, P<0.001$) as well as probe 2 accuracy ($F_{(2,89)}=48.33, P<0.001$) and response time ($F_{(2,89)}=83.43, P<0.001$). The effect of probe type did not interact significantly with condition (baseline or sleep-deprived).

![Figure 3](image3.png)

**Figure 3.** Responses as a function of probe context. The left panel shows accuracy (mean ± standard error) and the right panel shows response time (mean ± standard error) for probe 1 (black) and probe 2 (grey).

![Figure 4](image4.png)

**Figure 4.** Probe 1 accuracy level (mean ± standard error) by probe 1 context as a function of caffeine dose.

Probe 2 context did not have a statistically significant interaction with caffeine dose for accuracy ($F_{(2,89)}=1.35, P=0.249$) or response time ($F_{(2,89)}=0.19, P=0.946$). Likewise probe 1 context did not have a significant interaction with caffeine dose for response time.
However, probe 1 context did interact significantly with caffeine dosage for accuracy ($F_{(2,34)}=4.03, P=0.003$), as shown in figure 4. Overall switch effects were significant for accuracy ($F_{(2,34)}=10.19, P=0.001$), with subjects responding 3.4% less accurately after a switch versus no switch. Switch effects were not statistically significant for probe 2 response time ($F_{(2,34)}=1.51, P=0.220$). Furthermore, switch effects did not exhibit significant interaction with condition for accuracy ($F_{(2,34)}=0.02, P=0.894$) or response time ($F_{(2,34)}=0.53, P=0.465$) or with caffeine dose for accuracy ($F_{(2,34)}=0.09, P=0.916$) or response time ($F_{(2,34)}=0.43, P=0.653$). Finally, switch effects did not have a significant interaction with probe 2 context for accuracy ($F_{(2,34)}=1.79, P=0.167$) or response time ($F_{(2,34)}=1.12, P=0.327$).

These observations of impaired cognitive performance in sleep-deprived individuals are consistent with previous findings of a general decline in speed and accuracy of responding. Our result of improved overall performance on the task when subjects received caffeine is also consistent with previous studies. However, there was little evidence for effects of sleep deprivation or caffeine on specific components of the management of WM.

CONCLUSIONS

Our findings are consistent with previous examinations of WM performance under sleep deprivation showing that while non-executive task elements such as stimulus encoding and response execution may be impaired by sleep deprivation, WM processes of maintenance and updating remain intact. Our findings are also consistent with the observation that caffeine may not mitigate all aspects of performance impairment during sleep deprivation.

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8. SOMNAMBULISM AND MILITARY SERVICE

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INTRODUCTION

A medical and psychological screening is a standard procedure for everybody willing to join the army. This procedure is designed to select healthy recruits who have no medical or psychological conditions which can obstruct military service. Recruits are medically examined, followed by an interview protocol in which one of the issues assessed is the nature of their sleep. One of the items discussed is the occurrence of sleepwalking, since dangerous situations may arise when a soldier, having access to weapons, displays episodes of sleepwalking. In the last years, the item has become more relevant since it became clear that several cases of aggressive acts were carried out by apparently sleepwalking persons. The question is how to deal with recruits with somnambulism who would like to join the military forces.

SOMNAMBULISM

Sleepwalking, or somnambulism, is a sleep disturbance that belongs to the group of sleep disorders called ‘parasomnias’, referring to abnormal behaviours that can occur while asleep. Examples are nightmares, bedwetting, sleep talking and sleepwalking. The latter is a behavioural disorder that starts in arousal from sleep and results in sitting in bed, walking or in performing other complex behaviours. The brain condition of a sleepwalker is between sleeping and waking, in a sort of confusional arousal or twilight state. Somnambulism is often indicated as an ‘incomplete arousal’ response. Sleepwalking is much more common in children than in adults. The prevalence of sleepwalking in children is up to 15%. It is not regarded as an abnormal phenomenon in children; it is usually benign and rarely needs treatment. Typically, at the first onset of a sleepwalking episode, the child obeys to an internal trigger like a full bladder. The child stands up to go to the toilet, is confused and loses the way. Generally, sleepwalking decreases with the onset of puberty to a prevalence of approximately 2.5% in adulthood. Somnambulism has a genetic component, with 10 to 20% of the family members of the sleepwalker that also present with this parasomnia.

Symptoms of sleepwalking range from simply sitting up in bed and shortly looking around (the ‘abruptive form’ of sleepwalking) to an execution of series of complex behaviours (the ‘manifest’ form of sleepwalking). Episodes commonly last 5 to 10 minutes. The prevalence of abruptive sleepwalking is about 2%, while 0.5% for the manifest form. When we discuss sleepwalking, the manifest form is usually implied, as the abruptive form is oftentimes regarded as genuine sleepwalking.

The most obvious behavioural pattern of the manifest form is walking, mostly around the room or the house, but also routine behaviours such as eating, dressing and cleaning can occur. Walking behaviour ranges from quiet walking to agitated running, and may even involve complex behavioural patterns, looking like ‘escaping from a frightening situation’ or ‘walking without a purpose’. Sometimes the person leaves the house and even moves over a considerable distance.