increase in slow wave activity. This major novel findings in defeated subordinate animals i.e. a remarkable flattening of the EEG power between 0-30 Hz was accompanied with a marked increase in body temperature and a decrease in locomotor activity; a dissociation that in view of the EEG changes may reflect increased brain activity and metabolism. However, such EEG alterations disappeared at the end of the stress conditions. Furthermore, psychosocial stress leads to an increase in serotonin and dopamine levels. This transient stimulation of the monoamine systems such as 5-HT and dopamine have been hypothesized to impair the permeability of the blood brain barrier and consequently can result in the flattening of EEG activity as it was described in long-term immobilisation stressed rats. Both correlational and differential changes as quantified simultaneously within subjects in this study emphasize the importance of assessing the processes underlying sleep and stress dynamics in a parallel systems neuroscience approach. These changes can further be evaluated as potentially useful (bio)markers in the aetiology and/or treatment of stress-related aspect of psychiatric disorders such as depression.

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TIME ON TASK EFFECT IN REACTION TIMES DURING A SIMULATED DRIVING TASK

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INTRODUCTION

The time-on-task effect entails a decrement in cognitive performance across the duration of a performance task. The Psychomotor Vigilance Test (PVT) is sensitive to the time-on-task effect, showing a lengthening of average response time (RT) and an increase in RT variability in as little as 10 min, especially under conditions of sleep deprivation. The PVT is a simple reaction time task in which subjects press a button when a stimulus appears on a computer screen. It is believed that high stimulus density and the associated continuous requirement for sustained attention are what make the PVT particularly sensitive to the time-on-task effect.

The time-on-task effect has also been observed during simulated driving tasks. In one driving simulator study, steering performance appeared to deteriorate during a 30 min driving task. In another driving simulator study, steering wheel movements increased across the duration of a 40 min driving task performed twice (once under monotonous conditions and once under more varied conditions), which suggested a time-on-task effect in steering performance.

Drews et al. used a driving task on a high-fidelity driving simulator to investigate the effect of distracted driving on driving performance. The task, which was approximately 30 min in duration, involved following a leading car, and braking when, from time to time, the leading car decelerated (as indicated by its brake lights). An overall slowing of braking RTs during distracted driving was observed relative to a non-distracted control condition.

Both the simulated driving task of Drews et al. and the PVT appear to require sustained attention to produce motor responses to visual stimuli across the duration of the task. The research reported here sought to adapt the simulated driving task to make it more closely resemble the PVT, so as to achieve high sensitivity to the time-on-task effect (in braking RTs) while maintaining the face validity associated with high-fidelity driving simulation.

METHODS

High-fidelity driving simulator. A high-fidelity PatrolSim IV driving simulator (MPR, Salt Lake City), which is widely used to train professional drivers, was employed. The simulator has three screens that form a 180° angle of view. These serve to project the road through simulated windshield and side windows around the driver. A rear-view mirror and two side-view mirrors are also projected on the screens, and the scenery in the windows and mirrors is updated in real time. The simulator has an open-seat driver cockpit with an automatic transmission design. It includes a car seat, steering wheel, brake and gas pedals, lever to select the operating mode, and full dashboard. The simulator imitates the dynamics of a real car, including interaction with the road. The steering wheel provides feedback from the simulated wheels by subtle movements; however, the rest of the cockpit does not move. We
installed hardware and software for capturing driving performance data (sampled at 60 Hz), in order to adapt the simulator for research use.

**Simulated driving task.** In the driving task, subjects drove a simulated sports sedan on a 2 to 3 lane freeway, set in a sunset environment for optimal visual contrast of the leading car’s brake lights. Subjects were asked to follow a leading car, which was programmed to cruise at 64 miles/h, for 30 min. At set times during the drive, the leading car decelerated, turning on its brake lights. There were 90 deceleration events, spread out over the drive at inter-stimulus intervals of 10-30 s (uniformly randomly distributed in 4 s increments). Subjects were required to press the brake pedal of the driving simulator as soon as they observed the brake lights of the leading car. The leading car then accelerated back to its cruising speed, and the subjects were to resume following the leading car. Subjects were instructed to maintain a safe driving distance behind the leading car. If they could read the leading car’s license plate, they were too close. They received a message on the center screen if they were more than 100 m behind the leading car, which was too far. There was no other (simulated) traffic.

RTs were calculated from the onset of the deceleration of the leading car until the moment the brake pedal was pressed by the subject. On a few occasions (4 times in total), subjects pressed the brake pedal before the start of a deceleration event. For the present study, these were treated as missing data.

**Other neurobehavioral measures.** A 20 min PVT was administered prior to the driving task, and a 10 min PVT was administered following the driving task. These PVTs were performed while in the car seat of the simulator, using software implemented on a Palm Centro smartphone. Visual stimuli were presented on the display at 2–10 s response-stimulus intervals (uniformly randomly distributed in 1 s increments). One outlier RT (greater than 10 times the mean), occurring during the first 10 min of the pre-driving PVT, was discarded.

Before the pre-driving PVT and after the post-driving PVT, subjects filled out the Karolinska Sleepiness Scale (KSS).

**Experimental procedures.** Subjects first completed a screening session in the laboratory, during which they performed a 5 min simulated practice drive to introduce them to the simulator and the basic aspects of the simulated driving task. Between 1 and 23 days after their screening session, subjects attended a laboratory experimental session of about 2 h duration in the morning (at either 09:00 or 11:00). At the beginning of the session, they again performed the 5 min practice drive, filled out the KSS, and took a 15 min break. They then performed the 20 min PVT, carried out the 30 min simulated driving task, performed the 10 min PVT, and filled out the KSS once more. During the 24 h prior to the experimental session, subjects were not allowed to drink caffeine or alcohol.

**Subjects.** Eleven subjects (7 men, 4 women) aged between 21 and 41 y (mean ± s.d.: 28.9 ± 7.4 y) completed the study. One additional subject experienced symptoms of simulator adaptation syndrome during the driving task, and withdrew from the study. All subjects were in possession of a valid driver’s license, had normal or corrected-to-normal vision. They were screened for absence of medical conditions, sleep disorders, psychological disorders, and current alcohol abuse, and they reported not having abused any drugs within the past year.

**Statistical analyses.** Simulated driving task braking RTs and PVT RTs were grouped in consecutive 10 min blocks, and the raw RTs were then analyzed with mixed-effects analysis of variance (ANOVA) for test of an effect of block. Analyses of interest involved comparing the first through third 10 min blocks of the simulated driving task; comparing the first and second 10 min blocks of the 20 min pre-driving PVT; and comparing the first 10 min block of the 20 min pre-driving PVT to the (only) 10 min block of the post-driving PVT. Furthermore, pre- and post-testing KSS scores were compared, using a paired t test. We hypothesized that RTs on the simulated driving task, RTs on the PVT, and sleepiness scores on the KSS would all increase over time in the experimental session.

![Graph showing reaction time (ms) over 3 blocks of the simulated driving task](image)

**Figure 1.** Braking RTs (mean ± s.e.) over the three 10 min blocks of the simulated driving task, reflecting a significant time-on-task effect.

**RESULTS AND DISCUSSION**

There was a significant effect of block on the simulated driving task ($F_{2,27} = 6.5, P = 0.002$); average RTs became progressively slower towards the end of the 30 min task (Figure 1). There was also a significant effect of block on the 20 min pre-driving PVT ($F_{2,27} = 23.9, P < 0.001$); average RTs were significantly slower (by 19.7 ms) during the second 10 min block than during the first 10 min block. RTs during the 10 min post-driving PVT were slower yet (by another 9.2 ms), and significantly different from the first 10 min of the 20 min pre-driving PVT ($F_{2,27} = 11.4, P < 0.001$). Post-driving KSS scores were significantly higher (by 2.1 units on a scale from 1 to 9) than pre-driving KSS scores ($t_{10} = -4.6, P = 0.001$).

These results are consistent with our hypotheses. There was a significant time-on-task effect in the simulated driving task (Figure 1). As expected, there was also a significant time-on-task effect in the pre-driving PVT. This effect appeared to persist for 30 min (i.e., during the driving task) and to carry over to the post-driving PVT. Thus, unlike what has been reported in other task-switching paradigms, in this study interspersal of the PVT with another task did not provide relief of the PVT time-on-task effect, but rather seemed to maintain (or perhaps even enhance) it. The build-up of cognitive fatigue over time was experienced subjectively as well, as evidenced by the increase in KSS sleepiness scores.

A recent theory posits that the time-on-task effect may stem from activity-dependent induction of a sleep-like state in cortical columns used during the performance task at hand. In this view, the observation that post-driving PVT performance was degraded relative to pre-driving PVT performance implies that the intervening 30 min task entailed continued activation of cortical columns used during both the PVT and the driving task, perhaps related to a common attentional system in the brain. This supports the notion that the PVT captures cognitive deficits—implicated in sustained attention—that are also relevant for automobile driving (and vice versa).
CONCLUSIONS

Building on the work of Drews and colleagues, we successfully developed a simulated driving task that shows sensitivity to the time-on-task effect. Implemented on a high-fidelity driving simulator, the new task has a high level of face validity. It involves frequent braking while driving at relatively high speed, and demands sustained attention. This also occurs in real-world driving, such as during bad weather, on roads with potholes, and in busy traffic. The time-on-task effect is similar to the effect of sleep deprivation on cognitive performance, and the two effects exacerbate each other. We therefore plan to further validate the task in a sleep deprivation study. Our ultimate goal is to establish the task as a cognitive assay that will be widely recognized as directly relevant for real-world operational impairment.

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CAN SLOW MELATONIN METABOLISM BE ASSOCIATED WITH A SINGLE NUCLEOTIDE POLYMORPHISM IN THE CYP1A2 GENE? - A PILOT STUDY

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INTRODUCTION

The majority of patients suffering from a biological clock sleep disorder have a Delayed Sleep Phase Syndrome (DSPS). In DSPS, patients tend to fall asleep later than desired and/or have difficulty waking up in the morning. Usually, in such cases, the Dim Light Melatonin Onset (DLMO) has shifted to a later moment. Exogenous melatonin is able to advance the endogenous melatonin rhythm and its associated circadian rhythms, including sleep-wake, temperature and cortisol rhythms, maximally when it is administered 5 hours before DLMO. Melatonin in the usual pharmacotherapeutic doses (1-5 mg), cannot be found in blood or saliva within 12 hours after its administration. When exogenous melatonin is metabolized slowly it will remain present 24 hours after its administration. Subsequent doses of melatonin will give a steady-state melatonin level. Consequently, exogenous melatonin loses its chronobiological effect as the 24 hour melatonin rhythm disappears resulting in the return of the sleep disturbance after several weeks of treatment. A metabolisation test performed in suspected slow metabolizing patients showed that high levels of melatonin were the probable cause of the disappearing effectiveness of exogenous melatonin. This might be caused by decreased activity / inducibility of the CYP1A2 enzyme. Melatonin is metabolized in the liver by Cytochrome P450 1A2 (CYP1A2) to its primary metabolite 6-hydroxymelatonin, conjugated with a sulphate group and subsequently excreted in urine. About 90% of melatonin is metabolized by CYP1A2 and in a lesser extent by CYP2C19, CYP1A1 and CYP1B1. Several reports indicate that a Single Nucleotide Polymorphism (SNP) in the CYP1A2 gene might cause decreased activity or inducibility of the CYP1A2 enzyme. Putative allelic variants with decreased activity or inducibility are: CYP1A2*1C, CYP1A2*1K, CYP1A2*3, CYP1A2*4 and CYP1A2*6. The CYP1A2*1F allelic variant is associated with a higher inducibility. In this clinical pilot study we investigated whether a specific SNP in the CYP1A2 gene can be associated with slow melatonin metabolism.

METHODS

Patients participating in this study underwent a metabolisation test: patients started at 12 PM (t=1) with collection of the first salivary sample immediately followed by oral intake of melatonin (1 mg Fagron BV, The Netherlands). Additional salivary samples were collected at 2 PM (t=2), 4 PM (t=4) and 8 AM the following morning (t=20). Patients were asked to refrain from coffee and intensive exercise during the test. Saliva was collected with

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