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Introduction: Caffeine is a stimulant often taken to reduce sleepiness and improve cognitive performance. The effect of caffeine on glucose metabolism during sleep deprivation is less well understood. This double-blind laboratory study examined the impact of caffeine on glucose metabolism, self-reported hunger and mood state during 50h of wakefulness.
Methods: Participants were assigned to caffeine (n=9, 6M, age 21.3 ± 2.1y; BMI 21.9 ± 1.6kg/m^2) or placebo conditions (n=8, 4M, age 23.0 ± 2.8y; BMI 21.8 ± 1.6kg/m^2). Following a baseline sleep opportunity from 22:00h-08:00h, participants commenced 50h of extended wake. Caffeine (200mg) or placebo gum was administered at 01:00h, 03:00h, 05:00h and 07:00h during each night of extended wake. Continual glucose monitoring was used to capture interstitial glucose 2h post-breakfast, from which area under the curve (AUC) was calculated. Hunger and mood state were assessed at 10:00h, 16:30h, 22:30h and 04:30h.
Results: A significant rise in glucose AUC, in response to breakfast, was seen following the second night of extended wakefulness (p=0.003, $\eta^2_{partial}$=0.32, large effect). Caffeine did not alter the glucose response, with no difference shown between conditions (p=0.680, $\eta^2_{partial}$=0.01, small effect). Participants reported significant (p<0.020) increases, with large effect sizes, for tiredness ($\eta^2_{partial}$=0.68), mental exhaustion ($\eta^2_{partial}$=0.61), irritability ($\eta^2_{partial}$=0.35) and stress ($\eta^2_{partial}$=0.48) on the second night of extended wakefulness compared to the first night. On the first, but not the second night (p<0.044), caffeine mitigated the rise in impairment, with medium-large effect sizes for the condition*night interaction for tiredness ($\eta^2_{partial}$=0.40), mental exhaustion ($\eta^2_{partial}$=0.14) and irritability ($\eta^2_{partial}$= 0.23). Self-reported hunger was not affected by extended wake or caffeine.
Conclusion: Caffeine improved performance and reduced self-reported tiredness, mental exhaustion, and irritability under conditions of extended wake. However, the effectiveness appeared to be limited after 45 hours. Caffeine did not alter glucose metabolism over and above the effect of extended wakefulness.
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0217

RESISTANCE TO SLEEP DEPRIVATION IS PREDICTED BY GRAY MATTER VOLUME IN THE POSTERIOR BRAIN STEM

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Introduction: There are consistent trait-like inter-individual differences in vulnerability/resistance to sleep deprivation (SD). Thus far, it has been difficult to identify biomarkers or stable behavioral traits that may confer this resistance capacity. We recently reported the ability to sustain overnight psychomotor vigilance speed was associated with a linear combination of functional brain activation, cortical volume, and white matter integrity. Here, we report multimodal neuroimaging findings that predict lapses in vigilance during an overnight sleep deprivation session.
Methods: Thirty-eight healthy adults (17 male, 21 female; Mean Age= 25.8, SD=5.6 years), completed neuroimaging scans at 3T, including structural MRI, diffusion tensor imaging (DTI), task-based functional magnetic resonance imaging (fMRI), resting state functional connectivity (rsFC). One to four days later, participants completed a 28-hour SD session during which they completed the psychomotor vigilance task (PVT) every hour. A linked independent components analysis was used to fuse the various data sources, which were then regressed against the log of lapses (i.e., reaction times ≥ 500 msec).
Results: After controlling for age and gender, the LICA revealed a single component that was significantly predictive of fewer lapses throughout the night (R^2=.21, p=.005). This component was comprised almost exclusively by modulated gray matter volume within the posterior brainstem, corresponding to the region of the ascending reticular activating system (ARAS).
Conclusion: These finding suggest that individuals with greater gray matter volume within the ARAS demonstrated fewer attentional lapsed during the overnight SD session. These findings are consistent with the putative role of the ARAS in sustaining alertness and further suggest that the volume of this system may serve as a measurable biomarker of trait vulnerability or resistance to SD.
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0218

EFFECTS OF SLEEP DEPRIVATION AND RECOVERY SLEEP ON HUMAN BRAIN NETWORK ORGANIZATION

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Introduction: Sleep plays a key role in the restoration and preservation of optimal brain function, whereas sleep loss causes fatigue and impairs a range of neurobehavioral functions. Accumulating evidence suggests that the human brain can be characterized as a small-world network. However, the effects of sleep deprivation (SD) and recovery sleep on human brain network organization remain unclear. Here we used resting-state functional magnetic resonance imaging (fMRI) to evaluate changes in brain network topology after sleep deprivation.
Methods: We used graph theory to analyze resting-state fMRI data from 51 health adults (34.1 ± 9.0y, 29 males) who participated in a 5-day and 4-night in-laboratory controlled study. Thirty-eight participants completed an experimental protocol including 36-hour acute total SD (TSD) after one night of 9-hour baseline sleep, and followed by two nights of recovery sleep. They were scanned three times on the mornings of day 2 after baseline sleep, day 3 during SD, and day 5 after recovery sleep. Thirteen participants completed a non-SD control protocol and were scanned three times on the equivalence days. Three network metrics, including small-worldness (σ), global efficiency, and local efficiency were calculated for each subject using GRETNA toolbox and compared between baseline, SD, and recovery conditions.
Results: All three brain network metrics were significantly reduced after one night of TSD compared to baseline (all p<0.001). After two nights of recovery sleep, network small-worldness and global efficiency returned to baseline level, whereas local efficiency was not fully restored to baseline level. Brain network small-worldness and global efficiency changes correlated with self-reported fatigue level increases during sleep loss (both p<0.005). No changes in brain network metrics were found among the fMRI scans in the control group.
Conclusion: Our results suggest that one night of TSD significantly impairs topological properties of brain small-world network. Two nights of recovery sleep fully restored global but not local properties of brain network organization.

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0219

ACUTE SLEEP DEPRIVATION DURING LATE PREGNANCY RAPIDLY ELEVATES MATERNAL CORTICOSTERONE AND FETAL BRAIN KYNURENIC ACID IN RATS

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Introduction: While loss of sleep during pregnancy adversely affects brain development, the mechanisms underlying the lasting physiological and behavioral consequences in the offspring remain unknown. The present study was designed to investigate the hypothesis that sleep deprivation (SD) during pregnancy impacts tryptophan metabolism via the kynurenine pathway in the *in utero* environment. Elevations in kynurenine pathway metabolism, specifically kynurenic acid (KYNA), an endogenous astrocyte-derived antagonist of α7 nicotinic acetylcholine (α7nACh) and NMDA receptors, *in utero* have been demonstrated to induce long-lasting negative behavioral consequences relevant to the study of psychiatric disorders including schizophrenia (reviewed in Notarangelo and Pocivavsek, *Neuropharm.* 2017).
Methods: Pregnant Wistar rat dams were sleep deprived by gentle handling for 5 h from zeitgeber time (ZT) 0 to ZT 5. Experimental cohorts included: A) one session of SD on embryonic (ED) 18 or B) three sessions of SD on ED 16 to ED 18. Maternal (plasma, brain) and fetal (placenta, plasma, brain) tissues were collected immediately after the last session of SD or after 24 h of recovery from SD. Respective controls were euthanized at ZT 5 on ED 18 and ED 19.
Results: Maternal plasma tryptophan and kynurenine, and fetal brain KYNA, were significantly elevated only after one session of SD on ED 18. Importantly, plasma corticosterone, a measure of the endocrine stress response, was significantly elevated in maternal plasma after one day of SD, and this measure, as well as maternal tryptophan, correlated significantly with fetal brain KYNA.
Conclusion: Collectively, our results demonstrate that sleep loss during pregnancy can adversely impact kynurenine pathway metabolism and impact fetal brain KYNA levels. We introduce KYNA as a novel molecular target influenced by sleep loss during pregnancy. Future experiments are designed to unravel the contribution of kynurenine pathway changes during maternal sleep loss on long-lasting biochemical and behavioral outcomes in developing offspring.
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0220

ROLE OF CRF SIGNALING IN THE DISRUPTION OF SLEEP HOMEOSTASIS DURING CHRONIC SLEEP RESTRICTION

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Introduction: CSR alters hypothalamic-pituitary-axis (HPA) axis function and can be viewed as a chronic mild stress. Homeostatic responses to sleep loss are present in rats during 1–2 days of CSR, but are attenuated or absent during subsequent days. We hypothesize that elevated corticotropin releasing factor (CRF) signaling in the brain contributes to the attenuation of sleep homeostasis during CSR. In this study we examined the effects of ICV infusion of CRF receptor-1 (CRF-R1) antagonist, in rats subjected to CSR.
Methods: CSR was achieved by a forced locomotion on a treadmill (speed=8cm/sec), with a 3/12 sec on/off sequence. This sequence was repeated for 3 hrs, followed by 1 hr sleep opportunity. This 3:1 hr schedule was applied continuously for five days. On CSR day 4, control rats (n=5) received ICV infusion of vehicle (1% DMSO in aCSF) while experimental rats received infusion of either 10 µg (n=7) or 1 µg (n=5) antalarmin (ANT) (0.2 µl/min over 3 hrs starting at ZT6). SWA in NREM sleep (% change from baseline) and time asleep during the 1 hr sleep opportunity at ZT9-10 were analyzed.
Results: Compared to baseline, EEG slow-wave activity (SWA) increased in all groups on CSR day 1 (Vehicle; 204 ± 27%, 1ug ANT; 209 ± 9% and 10ug ANT; 216 ± 11). SWA was reduced on CSR day 4 versus day 1 in Vehicle- (144 ± 10% vs 204 ± 27%) and 1 ug ANT- (153 ± 9% vs 209 ± 9% versus) treated rats. Infusion of 10ug ANT on day 4 partially restored the EEG SWA response (187 ± 20% versus 216 ± 11%). Total Sleep Time (TST) on CSR day 1 (in min) was Vehicle; 34.6 ± 3.1, 1ug ANT; 35.6 ± 3.7 and 10ug ANT; 36.7 ± 2.8. On CSR day 3 values were 27.2 ± 2.8, 27.7 ± 6.2, and 28.6 ± 2.7. Infusion of 10 ug ANT on CSR day 4 restored the TST response to sleep loss compared to Vehicle and 1 ug ANT infusion (36.9 ± 2.9 vs 28.7 ± 2.5 vs 27.9 ± 6.3).
Conclusion: Findings support the hypothesis that increased CRF signaling in the brain contributes to the suppression of sleep homeostasis during CSR.
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0221

CORTISOL LEVELS IN RAT URINE FOLLOWING CHRONIC SLEEP DEPRIVATION IN FORCED EXERCISE WHEELS AND GENTLE HANDLING CHAMBERS

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Introduction: Chronic sleep restriction and its adverse effects on overall health is a pervasive issue in our industrious society. The most common method of sleep restriction in rodents is gentle handling, but this procedure is non-automated, time consuming, and costly. The automated methods currently available to simulate sleep restriction in animals include forced exercise wheels and a newly developed automated gentle handling chamber. A large concern for researchers using automated methods is that these techniques can be inherently stressful for the animal. Therefore, the environment in which sleep deprivation takes place becomes a confounding variable that may alter the results of a study. The aim of the current study was to use peripheral cortisol levels in rat urine as a measure of stress when exposed to two different automated sleep deprivation techniques.
Methods: Male wistar rats (N=18) were exposed to six hours of sleep deprivation every day for seven consecutive days. Half of the rats were sleep deprived in a forced exercise wheel while the other half were in a gentle handling simulation chamber. On the last day of sleep deprivation urine samples were collected from each rat. Cortisol concentration in urine samples was analyzed using an enzyme-linked immunosorbent assay (ELISA).
Results: A between subjects t-test revealed a significant difference between cortisol concentrations in urine samples of the two groups ($p < .01$). Samples from rats that were sleep deprived in forced exercise wheels had significantly higher cortisol concentrations than those in gentle handling chambers.
Conclusion: These results indicate that gentle handling chambers offer a less stressful method of sleep deprivation than a forced exercise wheel. These findings can be useful for any sleep research requiring a sleep deprivation protocol that may minimize the confounding effects of stress.
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