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The brain functional connectome is robustly altered by lack of sleep

Tobias Kaufmann [a,*,1], Torbjørn Elvsåshagen [a,b,c,1], Dag Alnæs [a,d], Nathalia Zak [a,b], Per Ø. Pedersen [b], Linn B. Norbom [d], Sophia H. Quraishi [e], Enzo Tagliazucchi [f,g], Helmut Laufs [f,g], Atle Bjørnerud [h,i], Ulrik F. Malt [b,j], Ole A. Andreassen [a], Evangelos Roussos [k], Eugene P. Duff [k], Stephen M. Smith [k], Inge R. Groote [d,h], Lars T. Westlye [a,d,*]

[a] NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Norway
[b] Department of Psychosomatic Medicine, Oslo University Hospital, Norway
[c] Department of Neurology, Oslo University Hospital, Norway
[d] Department of Psychology, University of Oslo, Norway
[e] Barnard College, Columbia University, NY, USA
[f] Department of Neurology and Brain Imaging Center, Goethe University Frankfurt am Main, Frankfurt am Main, Germany
[g] Department of Neurology, University Hospital Schleswig Holstein, Kiel, Germany
[h] The Intervention Centre, Oslo University Hospital, Norway
[i] Department of Physics, University of Oslo, Norway
[j] Department of Research and Education, Oslo University Hospital, Norway
[k] FMRIB Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, UK

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ABSTRACT

Sleep is a universal phenomenon necessary for maintaining homeostasis and function across a range of organs. Lack of sleep has severe health-related consequences affecting whole-body functioning, yet no other organ is as severely affected as the brain. The neurophysiological mechanisms underlying these deficits are poorly understood. Here, we characterize the dynamic changes in brain connectivity profiles inflicted by sleep deprivation and how they deviate from regular daily variability. To this end, we obtained functional magnetic resonance imaging data from 60 young, adult male participants, scanned in the morning and evening of the same day and again the following morning. 41 participants underwent total sleep deprivation before the third scan, whereas the remainder had another night of regular sleep. Sleep deprivation strongly altered the connectivity of several resting-state networks, including dorsal attention, default mode, and hippocampal networks. Multivariate classification based on connectivity profiles predicted deprivation state with high accuracy, corroborating the robustness of the findings on an individual level. Finally, correlation analysis suggested that morning-to-evening connectivity changes were reverted by sleep (control group)—a pattern which did not occur after deprivation. We conclude that both, a day of waking and a night of sleep deprivation dynamically alter the brain functional connectome.

Introduction

Although we spend roughly one third of our lives sleeping, the neurobiological mechanisms of sleep and sleep deprivation remain poorly understood. Whereas the quality, intensity and functions of sleep vary across species (Siegel, 2008), the almost universal presence of some form of sleep behaviour strongly promotes sleep as an evolutionary conserved phenomenon of immense implications (Cirelli and Tononi, 2008). Lack of sleep has been associated with a long list of health-related and cognitive consequences which can only be compensated with sleep itself (Rogers et al., 2003). Although sleep deprivation affects whole-body functioning, it is evident that no other organ is as severely affected as the brain (Cirelli and Tononi, 2008).

Not only is sleep essential to consolidate memory acquired prior to sleep (Walker and Stickgold, 2004), but it is also needed to prepare the brain for acquiring next-day's memories (Yoo et al., 2007). In line with these important roles of sleep in memory functions, a single night of sleep deprivation has been shown to perturb functional connectivity in hippocampal circuits (Yoo et al., 2007). Furthermore, sleep deprivation is associated with mood alterations and biased emotional appraisal (Anderson and Platten, 2011). Recent imaging data illustrated disturbed functional connectivity in amygdala circuits, particularly connections between amygdala and executive control regions (dorsolateral prefrontal, anterior cingulate, inferior frontal; Shao et al., 2014), and increased connectivity between the dorsal nexus and dorsolateral prefrontal cortex, thereby suggesting a mechanism for the putative therapeutic utility in depression (Bosch et al., 2013). Importantly,

* Corresponding authors at: OUS Postboks 4956, Nydalen, 0424 Oslo, Norway.
E-mail addresses: tobias.kaufmann@medisin.uio.no (T. Kaufmann), l.t.westlye@psykologi.uio.no (L.T. Westlye).
[1] These authors contributed equally.

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emotional effects of sleep deprivation are not only associated with altered response patterns to negative stimuli but also enhanced reactivity toward pleasure-evoking stimuli (Gujar et al., 2011). Apart from its impact on memory and emotional processing, sleep deprivation strongly affects vigilance and attentional capacities (Lim and Dinges, 2008), likely in parts originating from decreased activation and altered patterns of connectivity of the attention and salience networks of the brain (Ma et al., 2014). In line with the notion that lack of sleep affects patterns of large-scale brain connectivity, sleep deprivation was found to reduce the frequently reported anti-correlation between the task-positive dorsal attention network (DAN) and the default-mode network (DMN) in addition to diminished within-DMN connectivity (De Havas et al., 2012; Yeo et al., 2015).

With this body of literature associating sleep deprivation with pronounced connectivity changes throughout the brain, it is important to distinguish connectivity changes that appear solely due to deprivation from those that appear due to morning-to-evening or morning-to-morning variability. Previous results suggest that, in the context of memory retrieval, functional connectivity of medio-temporal regions changes during a regular day from local within-regional connections to global across-regional connections (Shannon et al., 2013). These findings clearly emphasize the need to account for diurnal variability when studying sleep deprivation. Furthermore, imaging studies on sleep deprivation often lack a control group.

Thus, to help us understand the alterations inflicted on the functional organization of the brain by lack of sleep, we estimated patterns of large-scale between-network resting-state brain connectivity using fMRI data obtained at three time points: In the morning after a regular night's sleep, in the evening of the same day and the next morning after a night of total sleep deprivation. We included a control group that had another night of regular sleep between the evening and the second morning. Furthermore, we included behavioural assessments of vigilance and visual attention in a subgroup. This 2 group × 3 time points design allowed us to directly assess and differentiate diurnal variability from the effects of sleep deprivation. In order to assess the robustness and predictability of network alterations, we combined data-driven definitions of brain network nodes, large-scale network modelling by means of regularized partial correlations, and multivariate machine-learning techniques with cross-validation and permutation testing. Finally, we employed an automated wake and sleep staging using a previously validated connectivity-based classifier (Tagliazucchi and Laufs, 2014) to assess wakefulness probabilities based on connectivity profiles.

Materials and methods

Sample and ethical approval

We included 60 male, healthy participants and assigned them either to the *deprived group* (N = 41, mean age: 21.8 years, SD = 2.4, range 18–26) or *control group* (N = 19, mean age: 22.7 year, SD = 2.2, range 19–26). The groups did not differ in age ($t = 1.4$, $p = .16$). Before study inclusion, all subjects were screened for current and previous psychiatric and somatic illnesses, either by a medical doctor (TE or NZ) or a student in the final year of medical school (PØP). Exclusion criteria were any history of sleep disorder, neurological or other chronic and acute somatic disorder, including infections, psychiatric illness, alcohol or drug use disorder, previous head injury with loss of consciousness for more than one minute, metallic implants, and previous or current use of psychotropic drugs. Participants reported an average sleep duration of 7.4 ± 1.0 h per night the week prior to the study, 7.6 ± 0.9 h per night the month prior to the study, and 6.6 ± 1.2 h the night before the first scanning using a self-reporting questionnaire. The self-reported sleep durations of the participants the last week and month are consistent with average sleep duration in a recently published self-reporting-based sleep duration study of young Norwegian adults (Hayley et al., 2015). The sleep duration estimates did not differ between the two groups (all $p > .71$). Self-reported sleep duration the night before the study was significantly shorter than the self-reported average sleep duration per night the last month in both groups ($p < .001$). Furthermore, the control group reported an average sleep duration of 6.1 ± 0.9 h in the night before the third scan, which is significantly shorter than their reported sleep duration the last month ($p < .05$).

Appropriate ethical approval was obtained and all procedures were in line with the declaration of Helsinki. All participants signed informed consent prior to enrolment.

Study protocol

From each participant, we collected resting state fMRI scans at three time points (TP): TP1 (first morning after normal sleep), TP2 (evening after a regular day of waking) and TP3 (next morning). While TP1 and TP2 were similar for all participants in terms of waking length, TP3 differed between groups. Participants of the control group went home after TP2 and came back at TP3 after another night of regular sleep. In contrast, participants of the deprivation group were kept awake the entire night, continuously monitored by a research assistant. To control for light exposure, participants of the deprivation group stayed in the same room with constant, normal light intensity between TP2 and TP3. The room had no windows, measured approximately 5 × 4 m, had chairs and a table, and a TV set. During the night, participants of this group were playing video games, watching movies, reading books, and talking with the research assistant. Independent of group assignment, all participants had to refrain from any consumption of caffeine or energy drinks and had no exercise between TP1 and TP3.

Scan times were adjusted to the participants' usual sleep–wake cycles. Average scan times per time point were 8:15 AM (SD: 37 min) for TP1 (across groups), 10:05 PM (SD: 44 min) for TP2 (across groups) and for TP3 average scan times were 6:47 AM (SD: 27 min) for the sleep deprivation group and 8:03 AM (SD: 56 min) for the control group. For the morning scans, participants came to the scanning facilities immediately after waking up.

In order to explore the effects of sleep deprivation on attentional functions and vigilance, and its associations with large-scale brain network connectivity changes, subjects performed the attention network task (ANT; (Fan et al., 2002)) at each session, directly after MRI acquisition. ANT yields reaction time (RT) measures in three different conditions by flankering target stimuli with congruent, incongruent or neutral stimuli, thereby altering the difficulty of the task (neutral < congruent < incongruent). Since we were mainly interested in vigilance and attentional lapses as markers of sleep deprivation (Lim and Dinges, 2008), we primarily targeted the inter-individual variability in reaction time (IIV-RT), known to increase substantially with tiredness (Corfitsen, 1994), defined as the coefficient of variation in response time across all correct trials across conditions. In addition, we investigated changes in mean reaction time in addition to the conflict, orienting and alerting scores based on differences in mean reaction times between conditions (Fan et al., 2002; Westlye et al., 2011). Both IIV-RT and reaction times were assessed within and across the 3 ANT flanker conditions (congruent, incongruent and neutral).

Furthermore, we assessed subjective sleepiness using the self-reported Karolinska Sleepiness Scale (KSS; (Akerstedt and Gillberg, 1990)), a nine-point Likert-type scale ranging from “Extremely alert” (score = 1) to “extremely sleepy, fighting sleep” (score = 9). The KSS was administered immediately after the ANT. IIV-RT and KSS data was available for N = 39 subjects (all 19 controls, 20 of the deprived group).

MRI data collection

MRI scans were obtained from a Philips Achieva 3.0 T scanner (Philips Healthcare, The Netherlands) with an 8-channel head coil at Oslo University Hospital. We acquired structural MRI with a T1-

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