

Fighting Sleep at Night: Brain Correlates and Vulnerability to Sleep Loss

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Objective: Even though wakefulness at night leads to profound performance deterioration and is regularly experienced by shift workers, its cerebral correlates remain virtually unexplored.

Methods: We assessed brain activity in young healthy adults during a vigilant attention task under high and low sleep pressure during night-time, coinciding with strongest circadian sleep drive. We examined sleep-loss-related attentional vulnerability by considering a *PERIOD3* polymorphism presumably impacting on sleep homeostasis.

Results: Our results link higher sleep-loss-related attentional vulnerability to cortical and subcortical deactivation patterns during slow reaction times (i.e., suboptimal vigilant attention). Concomitantly, thalamic regions were progressively less recruited with time-on-task and functionally less connected to task-related and arousal-promoting brain regions in those volunteers showing higher attentional instability in their behavior. The data further suggest that the latter is linked to shifts into a task-inactive default-mode network in between task-relevant stimulus occurrence.

Interpretation: We provide a multifaceted view on cerebral correlates of sleep loss at night and propose that genetic predisposition entails differential cerebral coping mechanisms, potentially compromising adequate performance during night work.

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Sleep-loss-related decrements in cognitive performance are most severe during the biological night.¹ They often originate from a misalignment of circadian and sleep-wake regulatory mechanisms, rendering night work particularly challenging for humans. At the end of the biological night, the endogenous circadian timing system no longer promotes wakefulness, but facilitates sleep with maximal sleep propensity.² The circadian system interacts with a homeostatic process tracking previous sleep-wake history by increasing sleep pressure levels during wakefulness and dissipating during sleep.³ Thus, at night, as both the circadian and homeostatic processes promote

sleep,² adequate performance levels are compromised by lapses, slower reaction times (RTs), and greater response variance.⁴ Especially in tasks with relatively infrequent stimuli, it is most difficult to sustain appropriate attentional levels over time, whereas phasic adequate recruitment of attentional resources still remains possible.^{4,5} In vigilant attention tasks, the nonoptimal domain (i.e., lapses or slow RTs) is thus more affected by sleep loss and adverse time of day than the optimal domain (i.e., fast responses).⁶ The cerebral basis of attentional processes under sleep deprivation (SD), and in particular how attentional vulnerability to sleep loss becomes evident at

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the cerebral level at this very critical time (i.e., during the individual biological night), has not yet been investigated. Crucially, up to 92% of variance in neurobehavioral performance can be explained by systematic, trait-like interindividual variability.⁷ Accordingly, the search for genetic influences of vulnerability to the negative effects of SD was fostered. A variable-number-tandem-repeat (VNTR) polymorphism in the human clock gene *PERIOD3* (*PER3*) was associated with susceptibility to total SD at the physiological and behavioral level,^{8–11} most likely through influence on the sleep homeostatic process.¹² Notably, so far, *PER3*-related neurobehavioral modulation was detected under total SD during the night and early morning hours, but not when sleep was merely restricted to a few hours per night.¹³ At the cerebral level, a previous study already revealed that the *PER3* polymorphism affected brain activity underlying working memory performance after 24 hours of total SD.¹⁴ However, like in other SD studies investigating cerebral activity,¹⁵ data were collected during the biological day following the SD night. Furthermore, sleep-loss-related drifts into task-inactive brain networks might be most likely detected during tasks with relatively low stimulus frequency¹⁶ at adverse circadian phase during the biological night. Thus, our aim was to investigate the neural bases of vigilant attention during night-time by considering vigilance-specific genetic vulnerability to total SD based on the *PER3* polymorphism. We combined a 40-hour SD and a multiple nap protocol (NP) to compare brain activity at the same critical circadian time point under high versus low sleep pressure levels,¹⁷ with the aim to disentangle sleep homeostatic and circadian influences at the cerebral level. The functional magnetic resonance imaging (fMRI) sessions were scheduled at 21 hours after habitual wake time during each participant's biological night. Based on the link between the *PER3* polymorphism and SD vulnerability via the impact on the homeostatic process,¹² we expected group differences between homozygous short- (*PER3*^{4/4}) and long-allele (*PER3*^{5/5}) carriers to occur mainly under high sleep pressure. We hypothesized that the *PER3*-related differences will mainly emerge in brain responses associated with slow RTs, given that behavioral⁶ and cerebral¹⁸ changes in this RT range are considerably prominent after sleep loss. In between the phasic occurrence of stimuli, when attention has to be sustained in the absence of a stimulus, a stronger drift into task-inactive networks¹⁹ was predicted in *PER3*^{5/5} carriers. Notably, vulnerability to total SD comprises many domain-specific aspects (e.g., reference 7). Given that we have recently shown that *PER3*^{5/5} carriers are particularly vulnerable to the detrimental effects of total SD in subjective and objective measures of sleepiness and vigilant attention,⁹ we consider this group as the more vulnerable participants here.

Patients and Methods

Participants

Thirty-three healthy volunteers participated in the study. One subject was excluded because of fMRI data loss, 2 subjects dropped out of the study, and 2 subjects were not included in this sample because of matching criteria (final N = 28; mean age \pm standard deviation: 24.9 \pm 3.3 years). Details on recruitment and exclusion criteria can be found in a previous work.⁹ Fourteen (7 males, 7 females, 1 left-handed) were homozygous carriers of the short repeat allele (*PER3*^{4/4}) and 14 (5 males, 9 females) homozygous carriers of the long repeat allele (*PER3*^{5/5}, all right-handed). The genotyping procedure has been described in previous reports.^{9,20} Women without contraceptives (2 of 16) participated during the luteal phase of their menstrual cycle. The groups did not significantly differ in terms of gender ratio, age, body mass index, bed times during study weekends, and questionnaire scores (Table 1). The local ethics committee (Ethikkommission beider Basel, EKBB, Switzerland) approved the study, and all procedures conformed to the standards of the declaration of Helsinki. Written informed consent was given.

Procedure

The study procedure is illustrated in Figure 1. Behavioral, melatonin, and electrophysiological data of this design characterizing our sample according to genotype have been published before,⁹ where details on the study procedure can be found. Here, the most important aspects will be reproduced. Each volunteer completed two study blocks (56-hour duration each) in the laboratory, in a pseudo-randomized, balanced, crossover order. We implemented stringently controlled conditions, which are semi-recumbent posture in bed during wakefulness, regularly scheduled light meals, dim light (<8 lux) during scheduled wakefulness, and zero lux with supine body posture during scheduled sleep episodes (i.e., naps), as well as no time-of-day indication. Participants were continuously monitored by electroencephalography (EEG) except during fMRI acquisition. Both protocols started with a baseline night (8 hours time in bed at respective habitual bedtimes, which were held regular during the week before study blocks). In the SD, participants were awake for 40 hours after habitual wake-up time. In the NP, they underwent 10 alternating cycles of 160 minutes of scheduled wakefulness and 80 minutes of scheduled sleep (i.e., naps). Both blocks ended with a recovery night (minimum 8-hour time in bed at usual bedtimes). The combination of the two protocols allows for investigating a continuous rise in homeostatic sleep pressure on one hand, whereas on the other hand, by multiple naps, sleep pressure remains at relatively low levels (see also previous works^{9,17,21}).

Here, we focus on the functional imaging data acquired during the night, that is, 21 hours after wake up (approximately 4 AM for a 7 AM wake-up time). The dim-light melatonin offset (DLMO_{off}), indicative for the passage into the biological day, occurred, on average, at 23.55 \pm 1.3 hours after wakeup in the NP protocol and 23.47 \pm 1.4 hours in the SD protocol. DLMO_{off} was determined at the 50% level of the maximal

TABLE 1. Means (\pm Standard Deviation) of Demographic Data and Questionnaire Scores by *PER3* Genotype

	<i>PER3</i> ^{4/4}	<i>PER3</i> ^{5/5}	<i>p</i>
N [M, F]	14 [7, 7]	14 [5, 9]	0.44
Years of age	24.3 (3.0)	25.6 (3.6)	0.31
BMI [kg/m ²]	21.9 (1.9)	22.7 (2.8)	0.38
Wake time [clock time]	07:10 (61 min)	07:10 (44 min)	1.00
Sleep time [clock time]	23:10 (61 min)	23:10 (44 min)	0.97
PSQI	3.3 (1.1)	3.0 (1.4)	0.54
ESS	3.6 (1.9)	4.3 (2.7)	0.47
MEQ	58.1 (9.5)	53.5 (10.2)	0.23
MCTQ Sleep duration [hours]	7.8 (0.7)	7.9 (1.0)	0.69
MCTQ MSFsc	4.3 (1.0)	4.4 (1.3)	0.81
MCTQ MSFscac	7.5 (2.7)	7.2 (2.5)	0.54
BDI-II	2.6 (2.5)	1.3 (1.9)	0.13

p values were derived from X^2 (gender) and *t* tests (all other).

M, male; F, female; BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index⁴⁹; ESS = Epworth Sleepiness Scale⁵⁰; MEQ = Morningness-Eveningness Questionnaire⁵¹; MCTQ = Munich Chronotype Questionnaire⁵²; MSFsc = Midsleep free days sleep corrected; MSFscac = Midsleep free days sleep and age corrected; BDI = Beck Depression Inventory-II⁵³. Wake and sleep times refer to baseline and recovery nights during the study.

melatonin secretion. Figure 1 illustrates the overlap of the acquisition point with highest levels of physiological sleepiness (slow eye movements and unintentional sleep episodes assessed and analyzed as described in a previous work⁹), especially under high sleep pressure (Fig 1A) and peak levels of melatonin secretion during our study.

Behavior

PSYCHOMOTOR VIGILANCE TASK. We assessed vigilant attention during both the NP and SD protocol with a psychomotor vigilance task (PVT) of 10 minutes duration.²² The original PVT design²² was modified to suit fMRI admission. A white fixation cross was presented on a black screen, and at random intervals (2–10 seconds) a millisecond counter started (clock event). Participants were instructed to press a button to stop the counter as fast as possible with their dominant hand. Null events, where the clock event is replaced by the fixation cross, were included at random in the task (25% of the trials, 2–10 seconds duration). Feedback of RT performance was displayed for 1 second after the response. RTs >500ms were classified as lapses, which were transformed by $\sqrt{x + \sqrt{x + 1}}$ ⁶. Time-on-task (ToT) was considered by comparing RTs or number of lapses during the first vs. the last 3 minutes on the task (as previously published²⁰). Errors of commission (i.e., random or anticipatory button presses) were not registered.

SUBJECTIVE SLEEPINESS. Participants regularly indicated their subjective sleepiness levels on the Karolinska Sleepiness Scale (KSS²³). Here, we report an average value (mean sam-

pling time \pm standard deviation: 03:22 AM \pm 10 minutes) of three night-time samplings during SD (approximate times: 02:30, 03:30, and 04:00 AM; similar for the two genotypes, *p* > 0.05) preceding the fMRI acquisition within the biological night.

BEHAVIORAL DATA ANALYSIS. Group analyses of the behavioral data (i.e., PVT performance and subjective sleepiness) were performed with the statistical package SAS (version 9.3; SAS Institute Inc., Cary, NC). We used *t* tests or mixed-model repeated measures analysis of variance (PROC MIXED), where appropriate, and *p* values were based on Kenward-Roger's corrected degrees of freedom.²⁴ Contrasts were assessed with the LSMEANS statement. The factors *genotype* (*PER3*^{5/5} vs. *PER3*^{4/4}), *condition* (NP vs. SD), and *ToT* (last vs. first part) were used. For the PVT, RTs were classified as follows for each participant in each session: RTs lower than the 25th percentile (fast RTs); RTs higher than the 75th percentile (slow RTs); and RTs in the range between the 25th and 75th percentile (intermediate RT), and lapses (RTs >500ms). Unlike our and other previous studies,^{6,9,18,20} we chose this RT range classification to enhance the number of events for fMRI analysis (mean no. of events \pm standard deviation: 14.8 \pm 3.7). Regression analyses were calculated with STATISTICA 9 (StatSoft Inc., Tulsa, OK).

fMRI

DATA ACQUISITION. A 3T MR Scanner (MAGNETOM Verio; Siemens Healthcare, Malvern, PA) with a standard

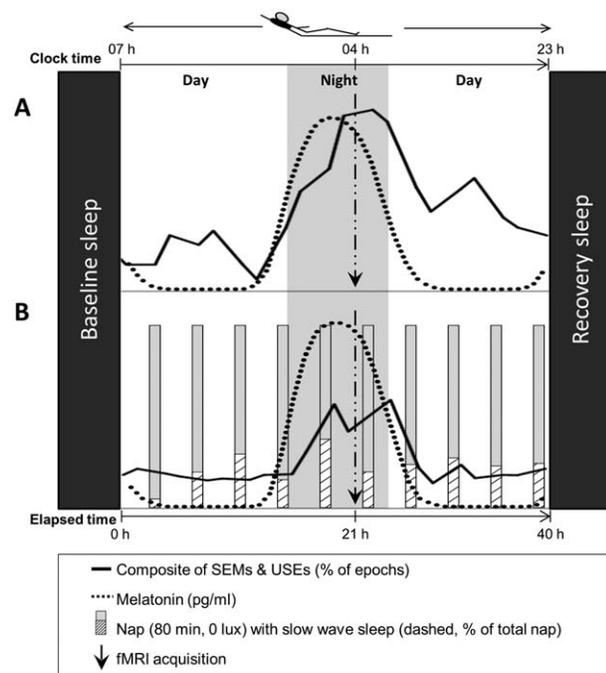


FIGURE 1: Schematic illustration of the laboratory part. (A) 40-hour sleep deprivation (SD). (B) 40-hour multiple nap protocol (ten 80/160-minute sleep/wake cycles). Clock time indication is relative to a 7 AM wake time. In (A) and (B), the solid line shows the 40-hour time course of physiological sleepiness represented by the averaged amount of slow eye movements (SEMs) and unintentional sleep episodes (USEs; mean % of 20-second epochs containing slow eye movements or any sleep stage, plotted from zero, SD_{max} 22.7%, NP_{max} 13.5%; $N = 28$; time binned and analyzed as described previously⁹). Dotted lines represent the 40-hour time course of melatonin secretion (pg/ml, plotted from zero, maximal levels: SD 14.5 pg/ml, NP 13.8 pg/ml; $N = 28$, hourly intervals modeled as described previously⁹); the gray bars in (B) depict the 10 naps, in dashed the respective percentage of slow-wave sleep (see our previous publication 9 for details on analysis of these data). The course of slow-wave sleep illustrates presumable sleep pressure dissipation depending on time of nap. The time of functional magnetic resonance imaging (fMRI) data acquisition is marked with the arrow and coincides with peaking melatonin secretion and highest sleepiness levels in SD.

12-channel head coil was used to acquire fMRI time series. Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation (32 slices; voxel size: $3 \times 3 \times 3$ mm³ with 0.75 mm interslice gap; matrix size $76 \times 76 \times 32$; repetition time [TR] = 2,200 ms; echo time [TE] = 32 ms; flip angle [FA] = 82°). Structural T1-weighted images were acquired for anatomical reference with a magnetization-prepared rapid gradient echo sequence (TR = 2,000 ms; TE = 3.37 ms; FA = 8°; field of view = 25.6 cm; matrix size = $256 \times 256 \times 176$; voxel size = $1 \times 1 \times 1$ mm³). One hundred seventy-six contiguous axial slices covering the entire brain were assessed in sagittal direction.

Data Analysis

GENERAL APPROACH. Data were analyzed with SPM8 (<http://www.fil.ion.ucl.ac.uk>) implemented in MATLAB 2012 (MathWorks, Natick, MA). Scans were realigned with iterative rigid body transformations, corrected for head motion and spatially normalized (standard SPM8 parameters). In a two-step analysis, we took into account the intra- and interindividual variance, respectively. Brain responses were modeled for each subject at each voxel using a general linear model (GLM). Our model included four regressors for each condition: events associated with RTs lower than the 25th percentile (fast RTs); events associated with RTs higher than the 75th percentile (slow RTs); events linked to the RT range between the 25th and 75th percentile (intermediate RTs) as well as lapses (RTs >500ms). For each trial type, we additionally added a time modulation regressor (first-order polynomial) to account for ToT effects. Every event of each trial type was modeled as a function representing its onset (i.e., at the time of presentation of stimulus). The ensuing vector was convolved with the canonical hemodynamic response function (HRF) and used as a regressor in the individual design matrix. The main effect of task performance during the different test sessions was estimated with linear contrasts. We focused on the RT range encompassing the mean of the slowest 25% of RTs. This RT range is very sensitive to increased sleep pressure^{6,18,25} and its neural basis has been previously described.¹⁸ Please note that unlike other authors,^{6,18} we separated lapses (RT >500ms) from the slowest RTs (thus, maximal duration of a slow RT was 500ms) in our study. This ensures that we only investigate brain activity when participants were awake and able to respond. Furthermore, at the between-subject level, we separately included subjective sleepiness as well as the mean speed difference between each slowest and its subsequent RT as covariates to investigate the relation to cerebral activity during SD.

Statistical inferences were performed at a threshold of $p = 0.05$ after correction for multiple comparison over the entire brain (family-wise error correction) or over small spherical volumes (radius, 10 mm) around regions of interest (ROIs) at locations a priori derived from the literature (small volume correction, svc). These ROIs were based on two studies that previously investigated the neural correlates of the PVT,^{18,26} one study reporting cerebral patterns after SD in the two *PER3* genotypes,¹⁴ and three studies reporting the effects of SD on different attentional components.^{27–29} For task-inactive network regions, we identified ROIs based on references previously reporting default mode activity.^{19,30–33}

FUNCTIONAL CONNECTIVITY ANALYSIS. To assess functional connectivity between ROIs, we conducted a psychophysiological interaction analysis^{34,35} implemented in SPM8. Based on an a posteriori hypothesis established on the GLM analysis described above, we defined a seed ROI within a region in the brainstem compatible with a part of the reticular formation (see Table S1 and Fig 2), activity in a similar area was previously described to be negatively correlated with deep sleep.³⁶ In this

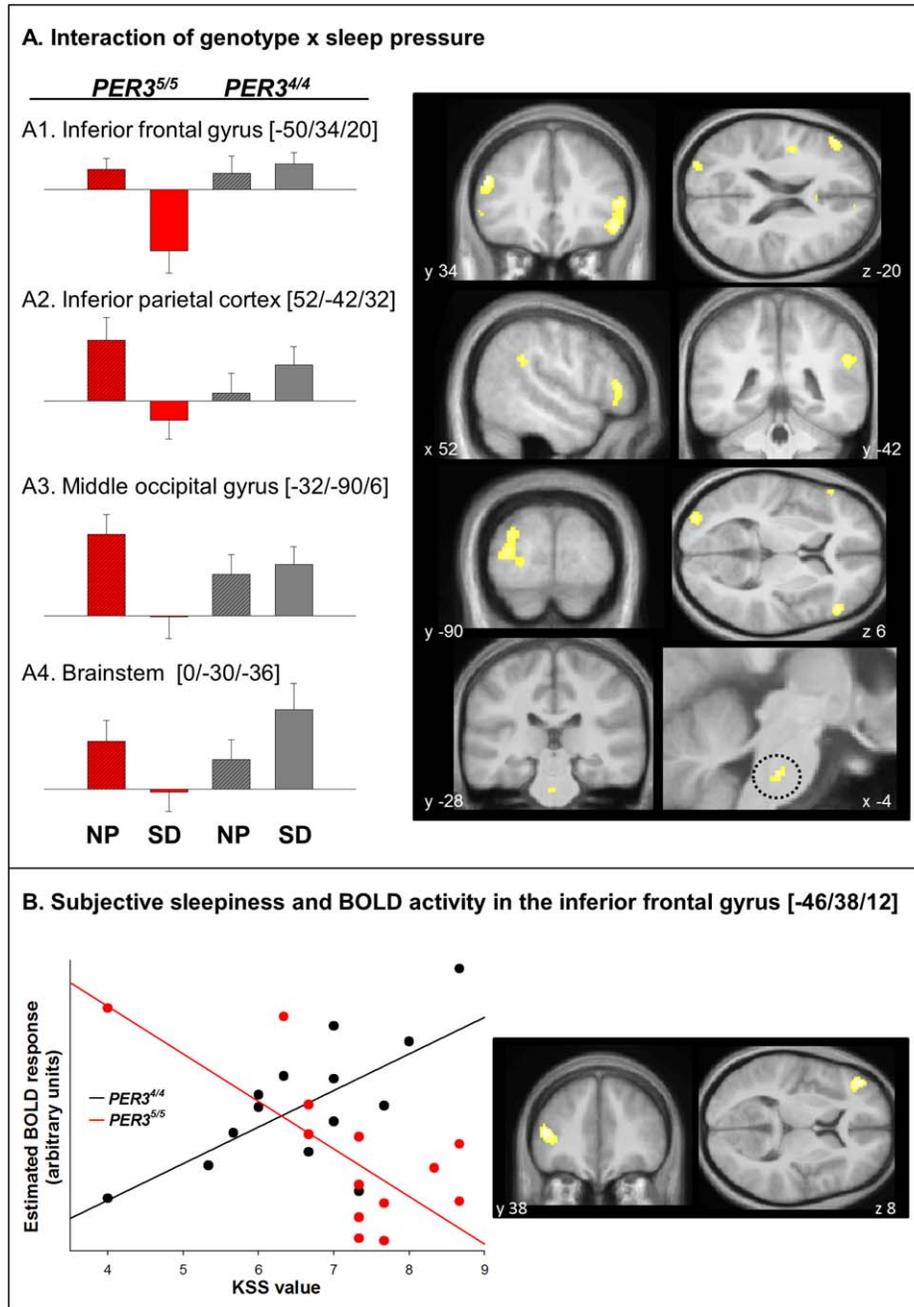


FIGURE 2: BOLD activity during SD vs. NP, *PER3*^{4/4} vs. *PER3*^{5/5} and relation to subjective sleepiness. (A1–A4) Selected brain areas during slowest reaction times showing a significant condition × genotype interaction (*PER3*^{4/4} vs. *PER3*^{5/5}, SD vs. NP) see also Table 3 and S1). Bar plots display parameter estimates for BOLD activity in regions A1–A4 by genotype and condition on the left. On the right, the corresponding activity overlay on study population mean structural image show higher activations under high sleep pressure (sleep deprivation; SD) compared to low sleep pressure (nap protocol; NP), depending on genotype (display at $p = 0.001$ uncorrected). The observed pattern in regions A1–A4 is representative for brain areas listed in Table 3 and S1: The *PER3*^{5/5} group consistently shows a decrease in activation in SD compared to NP, whereas the *PER3*^{4/4} group shows the opposite pattern. Red bars: *PER3*^{5/5}; black bars: *PER3*^{4/4} carriers; dashed bars: NP; filled bars: SD. (B) Left panel: Regression analysis of the relation between estimated BOLD responses during slowest RTs in the left inferior frontal gyrus and the Karolinska Sleepiness Scale (KSS) values (the higher, the sleepier) during the biological night preceding fMRI acquisition ($R^2 = 0.56$; $p < 0.001$; $n = 28$). Right panel: Display of the brain area showing a significant covariance pattern with subjective sleepiness depending on genotype: left inferior frontal gyrus [peak voxel: $-46/38/12$]; $p_{\text{corrected}} < 0.000$; $Z = 3.8$, display at $p = 0.001$ uncorrected). Exclusion of outliers visible on left panel did not change the observed pattern. Activity overlay on study population mean structural image on the right. BOLD = blood-oxygen-level dependent; fMRI = functional magnetic resonance imaging.

seed region, the first eigenvariate of the blood-oxygen-level-dependent (BOLD) time series was extracted from voxels within a 6-mm radius sphere around the peak voxel (1 male *PER3*^{5/5} carrier was excluded from this analysis because the individual activation mask did not cover this brain area, i.e., no data available).

BOLD ACTIVITY BEFORE STIMULUS APPEARANCE. To assess brain activity immediately before stimulus appearance, we further added finite-impulse-response (FIR³⁷) regressors for each RT range and its time modulation (fastest, slowest, and intermediate RTs) to our initial model described above. With FIR analysis, the BOLD signal is modeled without assumption of its shape by using successive boxcar functions (miniboxcars or “sticks”). Here, in order to capture BOLD signal right before stimulus appearance, we added one single prestimulus stick with a duration of 2.2 seconds (i.e., one TR). Although stimulus appearance was not synchronized to the TR, with this approach, it is assured that we are capturing prestimulus BOLD activity, given that the HRF associated with the stimulus per se has a 4- to 6-second lag.

Results

Time Course of Sleepiness and Vigilant Attention Over the Entire 40 Hours

The typically observed¹⁷ circadian- and sleep-pressure-level-dependent time course for subjective and physiological sleepiness was detected throughout the 40-hour SD and multiple nap protocol, as published in a previous work.⁹ As depicted in Figure 1, slow rolling eye movements and unintentional sleep episodes as a physiological correlate for sleep drive increased when passing into the biological night. Maximal levels were reached toward the end of the night to the beginning of the biological day, stabilizing on the second day under SD and decreasing again under NP (related statistics are found in a previous work⁹). A similar pattern was observed for lapses (RT >500ms) during psychomotor vigilance task (PVT) performance (see our previous publication⁹ for details). Importantly, over the 40 hours of SD, *PER3*^{5/5} participants felt sleepier and had more slow eye movements and unintentional sleep episodes as well as attentional lapses under SD, compared to NP.⁹ According to these findings, clearly revealing different responses to sleep loss in sleepiness and vigilant attention measures, we considered our *PER3*^{5/5} carriers as the more SD-vulnerable group hereafter.

Subjective Sleepiness and Vigilant Attention During Night-time

Participants tended to be subjectively sleepier (assessed with the KSS²³; $t_{54} = -1.74$; $p = 0.08$) and had significantly more lapses and longer RTs in the slow domain (25 % slowest RTs) during the night under SD, com-

pared to NP. ToT effects in the night session were similar in both conditions for the 25% slowest RTs and lapses; results are listed in Table 2. Between genotypes, subjective sleepiness levels were similar during night-time ($t_{26} = -1.49$; $p = 0.15$; mean \pm standard error [SE]: *PER3*^{4/4} 6.6 ± 0.3 *PER3*^{5/5} 7.3 ± 0.3). However, the *PER3*^{5/5} carriers produced significantly more attentional lapses (number of RTs >500) than the *PER3*^{4/4} carriers ($p = 0.03$; mean \pm SE: *PER3*^{4/4} 4.6 ± 0.7 *PER3*^{5/5} 7.2 ± 1.1) at this time window under SD, irrespective of ToT. RTs did not differ in the slow RT range between genotypes (mean RT \pm SE during SD: *PER3*^{4/4} 403.9 ± 3.7 , *PER3*^{5/5} 409.1 ± 4.6 ; mean RT \pm SE during NP: *PER3*^{4/4} 373.9 ± 4.1 , *PER3*^{5/5} 381.8 ± 3.9 ; mean number of slow responses: *PER3*^{4/4} SD 14.9; NP 16.4, *PER3*^{5/5} SD 11.9; NP 16.1), nor was the interaction with condition (i.e., SD and NP) significant. ToT affected *PER3*^{5/5} carriers similarly for the slow RT range (slower in the last test part).

fMRI Data

SLEEP PRESSURE MODULATES NIGHT-TIME BRAIN RESPONSES UNDERLYING SLOW REACTION TIMES. Under high sleep pressure, a bilateral thalamic region ([0, 10, 6], $Z = 3.55$, $p_{svc}^{26} = 0.0002$) as well as the putamen ([22, 10, 12], $Z = 3.78$, $p_{svc}^{26} = 0.0001$) showed higher BOLD activity compared to NP (SD > NP). During NP, several cortical regions, that are, the left cuneus ([6, 94, 20], $Z = 3.49$, $p_{svc}^{28} = 0.0002$), right middle temporal gyrus ([64, 30, -4], $Z = 3.91$, $p_{svc}^{14} < 0.0000$), as well as insular regions ([42, 18, 8], $Z = 3.2$, $p_{svc}^{26} = 0.0007$) were more active than during SD (NP > SD).

GENETIC VULNERABILITY TO SLEEP LOSS ACUTELY AFFECTS SLEEP-PRESSURE-DEPENDENT BOLD ACTIVITY AND FUNCTIONAL CONNECTIVITY TO AROUSAL-PROMOTING SUBCORTICAL REGIONS DURING NIGHT-TIME VIGILANCE. The *PER3* polymorphism significantly modulated brain responses to the task according to sleep pressure level (interaction condition \times genotype; see Fig 2; Table S1, significant interaction terms are marked by an asterisk). Generally, *PER3*^{4/4} individuals had increased activation during SD compared to NP in multiple attention-related cortical and subcortical brain areas, whereas the *PER3*^{5/5} carriers showed the opposite pattern (see Fig 2 for selected regions with corresponding parameter estimates, Table S1 details the corresponding post-hoc contrasts). More precisely, higher BOLD activity under SD was observed for *PER3*^{4/4} compared to *PER3*^{5/5} carriers (SD 44 > 55) in frontal, temporal, and parietal areas as well as in a brainstem region. No regions were activated more in *PER3*^{5/5} than *PER3*^{4/4} carriers during SD

TABLE 2. Results of Mixed-Model Analysis of Variance for the Slowest Reaction Time (RT) Range and Lapses in the Psychomotor Vigilance Task; F Values (df), and p values

RT range	Cond	PER3	ToT	Cond × PER3	Cond × ToT	PER3 × ToT	PER3 × Cond × ToT
25% slowest	$F(1,75.4) = 21.87$ $p < 0.001$	$F(1,26.2) = 0.76$ $p = 0.4$	$F(1,75.4) = 0.74$ $p = 0.4$	$F(1,75.4) = 1.06$ $p = 0.31$	$F(1,75.4) = 0.04$ $p = 0.84$	$F(1,75.4) = 0.00$ $p = 1$	$F(1,75.4) = 2.29$ $p = 0.13$
Lapses	$F(1,78) = 17.1$ $p < 0.001$	$F(1,26) = 5.49$ $p = 0.03$	$F(1,78) = 5.36$ $p = 0.02$	$F(1,78) = 10.67$ $p = 0.002$	$F(1,78) = 3.31$ $p = 0.07$	$F(1,78) = 0.71$ $p = 0.4$	$F(1,78) = 0.25$ $p = 0.6$

Time-on-task (ToT) refers to mean values during first versus last 3 minutes on the 10-minute task. Significant results are printed in bold.
No significant difference in post-hoc testing between genotypes after correction for multiple comparison.
RT = reaction time; Cond = condition; PER3 = PERIOD3 genotype.

(SD 55>44). Furthermore, separate analyses by genotype revealed that the *PER3*^{4/4} group showed BOLD activity increases in SD compared to NP in a series of cortical and thalamic structures as well as areas of the basal ganglia and the cerebellum (44 SD>NP). The *PER3*^{5/5} group yet showed the opposite pattern: None of the areas showed higher activations during SD compared to NP (55 SD>NP), but a series of areas were more activated during NP (55 NP>SD), that is, frontal, temporal, parietal, and several occipital areas as well as a brainstem area compatible with the location of the reticular formation (midline pons). A functional connectivity analysis revealed that under sleep loss, the latter region was more connected to cortical and thalamic structures and a more superior located brainstem region (Table 3) in *PER3*^{4/4} compared to *PER3*^{5/5} carriers.

Our data indicated that the more resistant individuals (*PER3*^{4/4}) responded to sleep loss by increasing task-related cortical BOLD activity and by additionally recruiting thalamic resources. Activity in a subset of these areas also covaried with speed during the subsequent RTs (Table S1, common activity identified by inclusive masking). In these areas, the higher the BOLD activity during a slowest RT, the faster the subsequent RT. The more vulnerable genotype (*PER3*^{5/5}), however, mainly responded by activity decreases and reduced functional connectivity between brainstem, thalamic, and task-related cortical regions.

BRAIN RESPONSES UNDERLYING TIME-ON-TASK MODULATION: GREATER STATE INSTABILITY BY DECREASED THALAMIC RECRUITMENT? According to the state-instability hypothesis,^{4,5} SD strongly affects the ability to maintain appropriate attentional levels continuously over time. In a previous report,²⁰ we observed that *PER3*^{5/5} carriers presented higher response variability and stronger ToT decrements (lapses) in vigilant attention under sleep loss. We detected that the time course of BOLD activity throughout the 10-minute PVT differed between genotypes in the anterior and posterior thalamus as well as the anterior cingulate cortex (Table 4; Fig 3A) under SD for the slow RT range. *PER3*^{5/5} carriers showed activity decreases in these brain areas over the course of the task ($p < 0.05$), whereas activation in *PER3*^{4/4} carriers remained stable ($p > 0.05$; Fig 3B schematically depicts the course of thalamic brain activity for two representative subjects of each genotype). In fact, the group presenting higher state instability at the behavioral level²⁰ was hallmarked at the cerebral level by reduced task-related cingulate and thalamic recruitment with increasing ToT.

TABLE 3. Significant Differences in Functional Connectivity With a Brainstem Area During SD Between Genotypes

Brain Area	Side	Z Score	p_{svc}	x	y	z	Ref.
Brain areas with greater connectivity to the seed region in $PER3^{44}$ compared to $PER3^{55}$ carriers (SD 44 > 55)							
IFG	L	3.12	0.0009	-44	28	-4	14
Thalamus	R	3.70	0.0001	26	-30	-4	14
	R	3.40	0.0003	20	-18	-10	14
	R	3.23	0.0006	18	-14	-10	14
	B	3.97	<0.0001	0	-8	2	26
Thalamus/pineal gland	B	3.84	0.0001	-6	-32	2	18
	B	3.50	0.0002	2	-32	6	18
Brainstem	L	3.28	0.0005	-10	-22	-16	26
Brain areas with greater connectivity to the seed region in $PER3^{55}$ compared to $PER3^{44}$ carriers (SD 55 > 44)							
n.s. at $p = 0.001$ uncorrected level							
Coordinates (x, y, z) are expressed in mm in the Montreal Neurological Institute (MNI) space. p_{svc} : p value after correction for multiple comparisons over small volumes of interest taken from the literature. SD = sleep deprivation; Ref. = references for coordinates; IFG = inferior frontal gyrus; R = right; L = left; B = bilateral; n.s. = not significant.							

SUBJECTIVE SLEEPINESS MODULATES BRAIN RESPONSES UNDERLYING SLOW RTs DEPENDING ON VULNERABILITY TO SLEEP LOSS. Depending on genotype when sleep deprived, BOLD activity associated to slow RTs was significantly related to subjective sleepiness in the left inferior frontal gyrus (IFG; peak coordinates: -46,

38, 12; $Z = 3.8$, $p_{svc} < 0.001$): $PER3^{55}$ carriers showed a negative relation (the sleepier they felt, the less they recruited this region), whereas in $PER3^{44}$ carriers, the relation was positive (the sleepier they felt, the more they activated this region; Fig 2E).

TABLE 4. Brain Activity Modulated by Time-on-Task During Sleep Deprivation

Brain Area	Side	Z Score	p_{svc}	x	y	z	Ref.
44 > 55							
Anterior cingulate cortex	B	3.39	0.0004	0	32	14	18
	R	3.23	0.0006	4	26	22	18
Insula	L	3.33	0.0004	-30	-26	14	27
Midbrain/CMN	R	3.41	0.0003	8	-22	-8	27
Midbrain/N. ruber	R	3.29	0.0005	10	-18	-6	26
Midbrain/MDN	L	3.32	0.0004	-8	-16	-4	26
Midbrain/N. ruber	L	3.29	0.0005	-6	-20	-6	14
55 > 44							
n.s. at $p = 0.001$ uncorrected level							
Coordinates (x, y, z) are expressed in mm in the Montreal Neurological Institute (MNI) space. p_{svc} : p value after correction for multiple comparisons over small volumes of interest taken from the literature. Ref. = references for coordinates; R = right; L = left; B = bilateral; N. = nucleus; CMN = central medial nucleus of the thalamus; MDN = medial dorsal nucleus of the thalamus.							

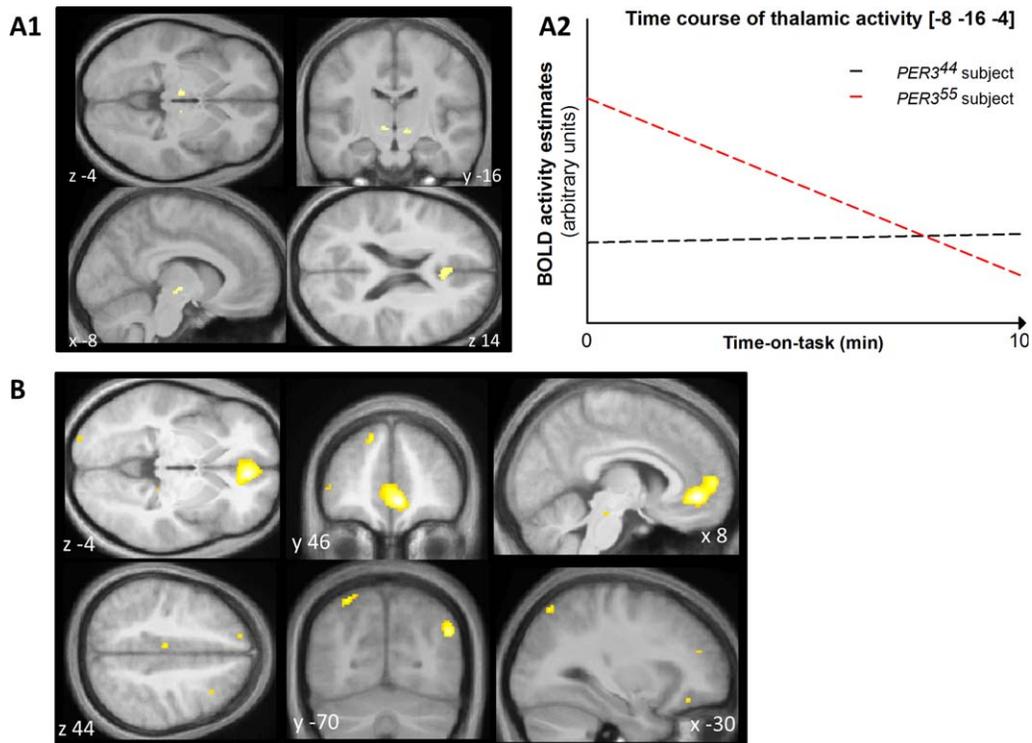


FIGURE 3: Sleep-loss-related time-on-task effects in the slowest RT domain and brain activity before stimulus appearance. (A1) Brain areas showing a significantly different time-on-task effect in the slowest RT domain between genotypes during sleep deprivation. (A2) Schematic display of the time course of thalamic brain activity [-8/-16/-4] over the task for a representative subject of each $PER3$ group. (B) Brain areas showing significantly more activation 2.2 seconds (equals 1 TR) before stimulus appearance with a subsequent slow response in $PER3^{5/5}$ than $PER3^{4/4}$ carriers during sleep deprivation. (A1) and (B): Overlay of statistical results on study population mean structural image, display at $p = 0.001$ uncorrected. RT = reaction time; TR = time of repetition.

KEY STRUCTURES OF THE DEFAULT MODE NETWORK ARE MORE ACTIVATED BEFORE THE SLOW EVENTS UNDER SD IN THE VULNERABLE GENOTYPE. Given that it has been shown previously that brain activity before stimulus appearance is predictive for subsequent lapses in attention,¹⁹ we analyzed brain activity immediately before stimulus appearance. Our results showed that immediately before slow RTs and compared to $PER3^{4/4}$, $PER3^{5/5}$ carriers had higher activation in regions commonly assigned to the default mode network (DMN)^{30,38,39} (Table 5; Fig 4). No areas were more active in the $PER3^{4/4}$ compared to the $PER3^{5/5}$ (Table 5). Importantly, before fastest RTs, we did not observe any genotype-related differences (SD 55 > 44 n.s. at $p = 0.001$ uncorrected level, data not shown). Please note that in this analysis, we did not test for functional connectivity of the DNMT, but merely observed greater activity in regions that were assigned to this network in previous reports.^{30,38,39}

Discussion

In the present study, we investigated cerebral correlates underlying performance during individually scheduled

night-time (i.e., after 21 hours after wake-up time), when detrimental effects of sleep loss on cognition are strongest. For the first time, a SD and a multiple nap protocol was combined in order to quantify the impact of differential sleep pressure conditions at this critical circadian time window. By considering a polymorphism in the clock gene $PER3$, we stratified our group according to genetic susceptibility to total sleep loss. Performing the PVT, an attention-demanding task,²⁵ more SD-vulnerable^{9,20} participants ($PER3^{5/5}$) showed a consistent pattern of brain activity decreases under high sleep pressure, whereas in the more resilient participants ($PER3^{4/4}$) brain activity increased. In addition, arousal-promoting areas were progressively less recruited with ToT in vulnerable subjects and less functionally connected to other arousal- and attention-related brain structures under SD. Vulnerable participants were additionally more prone to activate structures associated with the default mode network when no stimulus was present.

Similar to earlier SD studies,^{15,28,40} we observed that SD during night-time is associated with increased activation in subcortical structures, whereas under low sleep pressure, several cortical regions were more active.

TABLE 5. Differences in Brain Activity Before Slowest RTs During Sleep Deprivation According to Genotype

Brain Area	Side	Z score	p_{svc}	x	y	z	Ref.
Areas with greater activity one TR (2.2 seconds) before stimulus appearance in $PER3^{55}$ than $PER3^{44}$ carriers (SD 55 > 44)							
Superior/middle frontal gyrus	R	3.40	0.0003	32	22	46	19
Superior occipital gyrus	L	3.18	0.0007	-38	-78	28	19
Medial frontal gyrus	R	4.20	0.0000	8	46	-4	31
	R	3.48	0.0002	2	54	10	30
	L	3.48	0.0002	-2	56	10	30
	L	3.48	0.0003	-6	58	14	30
	L	3.33	0.0004	-2	50	8	30
Dorsal ACC	R	4.26	0.0000	6	40	-6	30
Dorsal ACC	R	3.93	0.0000	2	42	-8	30
Posterior/middle cingulate	L	3.39	0.0004	-6	-20	44	32
Superior parietal gyrus	R	3.93	0.0000	46	-66	32	31
Gyrus angularis/preuncuneus	L	3.56	0.0002	-28	-70	56	14
	L	3.29	0.0005	-24	-68	60	14
	L	3.25	0.0006	-20	-66	60	14
Medial temporal gyrus	L	3.70	0.0001	-62	-14	-22	33
	R	3.85	0.0001	56	-6	-16	33
Areas with greater activity one TR (2.2 seconds) before stimulus appearance in $PER3^{44}$ than $PER3^{55}$ carriers (SD 55 > 44)							
n.s. at $p = 0.001$ uncorrected level							
Coordinates (x, y, z) are expressed in mm in the Montreal Neurological Institute (MNI) space. p_{svc} : p value after correction for multiple comparisons over small volumes of interest taken from the literature. TR = time of repetition; SD = sleep deprivation; Ref. = references for coordinates; R = right; L = left; B = bilateral; ACC = anterior cingulate cortex.							

Notably, many SD studies reported higher activations in frontoparietal areas when performance was preserved, and activity decreases when performance declined (reviewed in reference¹⁵). Although we observed significantly lower slowest RTs in the SD, these deactivations were located in the middle temporal gyrus, in the insula and the cuneus under high versus low sleep pressure when pooling both genotype groups. This discrepancy is likely due to the difference in circadian phase and duration of sleep loss, when compared to daytime SD studies, or alternatively, divergent task characteristics.

The consistent decreases in brain areas under high sleep pressure in the more vulnerable group ($PER3^{55}$), and the increased brain activity in the more resilient group ($PER3^{44}$) support data from Vandewalle et al.,¹⁴ who investigated the impact of the $PER3$ genotype on cerebral correlates of working memory in the morning after SD. According to Drummond et al.,¹⁸ activity

increases underlying slow RTs after SD may reflect attentional recovery, given that compensatory behavior (e.g., anticipatory or fast responses) often follows slow RTs or lapses.⁴ In our data, a set of the brain regions showing higher activity in $PER3^{44}$ carriers during SD was positively associated with faster responses to the subsequent stimulus. This favors the assumption of compensatory recruitment, potentially leading to attentional recovery in the more resilient group. Similarly, Chee and Tan⁴⁰ showed that in contrast to more resilient, the cognitively more vulnerable participants were unable to increase frontoparietal activation during a selective attention task under SD. The same authors showed that the ability to raise activation in response to lapses was lower under SD, and during lapses, visual cortex and thalamic activation was reduced in comparison to lapses in well-rested conditions, which was interpreted as deactivations indicative for a loss of top-down control.⁴¹ Remarkably, we

observed a similar pattern in the *PER3*^{5/5} carriers, whereas the activity of our *PER3*^{4/4} carriers better matched the well-rested pattern observed by Chee et al. In regard to sleepiness, a study by Czisch et al.⁴² showed compensatory activations within insular regions comparing a physiologically more alert to a more sleepy state (EEG-derived during task) after SD in an oddball task. This parallels our findings of the physiologically sleepier group (*PER3*^{5/5} carriers, see a previous work⁹), which also shows less task-related activation in an insular region. With respect to subjective sleepiness, our more SD-resilient participants increased activation in the left IFG, whereas the more vulnerable decreased activity in this region with increasing subjective sleepiness, which confirms previous reports of a positive relation of activation in this region with subjective sleepiness under SD.^{43,44}

RTs did not significantly differ between genotypes in the slowest range, although *PER3*^{5/5} carriers had significantly more lapses (RTs >500ms) across the entire SD, particularly also with increasing ToT.^{9,20} Notably, genotypes did not differ in the slowest 25% of RTs with increasing ToT. However, on the cerebral level, the genotypes had different BOLD activity time courses, such that *PER3*^{5/5} carriers decreased thalamic and ACC activity, supposedly mirroring a greater ToT-related vigilance decrement, whereas the *PER3*^{4/4} carriers show relatively stable levels of activation within these regions. Similarly, Chee and Tan⁴⁰ showed that vulnerable subjects suppress thalamic activity during lapses (defined as long RTs) after SD, whereas more resilient ones tended to elevate. Thus, the *PER3*^{5/5} genotype might be less able to sustain attention through “mental effort” mirrored on the cerebral level,⁴⁵ potentially leading to a greater number of lapses. Notably, the thalamus has numerous projections to cortical areas, but also receives input from ascending arousal systems, thereby mediating bottom-up arousal.⁴⁶ We observed increased functional connectivity between a part of the reticular formation (paramedian part of the mid-brain) and a more superior brainstem area, the thalamus, the left IFG, and an occipital area in the resilient genotype. Importantly, activity in a brainstem region close to our seed region was shown to negatively correlate with slow wave sleep,³⁶ further indicating that this area is potentially implicated in sleep-wake-related arousal promotion. This strengthens the plausibility that the differences between vulnerable and resilient genotypes result partly from a stronger ascending arousal promotion in *PER3*^{4/4}.

Considering the greater number of lapses and the higher amount of slow eye movements and sleep attacks in the more vulnerable *PER3*^{5/5} genotype during SD,⁹

it is tempting to interpret the failure to recruit “compensatory” brain areas during slowest RT as a greater tendency or even a precursor to drift into an “off-mode” or default mode when no stimulus is present. This is supported by the previous finding that areas of the DMN are more activated before lapses.¹⁹ Our data are conceptually in line with this observation, given that immediately before the appearance of a stimulus, areas commonly assigned to the DMN (e.g., dorsal anterior cingulate cortex, posterior cingulate cortex, precuneus, and medial frontal areas)^{30,33,39} were more activated in the vulnerable *PER3*^{5/5} carriers than in the resilient group under high sleep pressure. Interestingly, if taking into account the specific pattern during the slowest RT for each group separately, only *PER3*^{5/5} carriers showed deactivations under SD, mostly in areas compatible with the DMN.^{30,33,39} These participants are probably less able to sustain an active attentional network while they are waiting for stimuli, and thus switch into a more passive default mode,⁴⁷ which, in turn, needs stronger suppression as soon as the stimulus appears. This may reflect a coping strategy of the more vulnerable participants leading to similar RTs for both genotypes at the behavioral level. However, because the *PER3*^{5/5} carriers had more lapses, this coping process seems less successful or frailer to behavioral instability. These assumptions only account for nonoptimal performance, which is typically observed under SD and can be fatal, especially when appearing insidiously, eventually resulting in total lapses.

Finally, under low sleep pressure achieved by multiple naps, along with comparable vigilance levels and electrophysiological activity,^{9,20} brain activity was similar for both groups. Thus, the two genotypes did not differ substantially in their response to adverse circadian phase in the absence of high homeostatic sleep pressure levels. In this line, it is important to note that the *PER3*^{5/5} carriers have a roughly 10% higher nap sleep efficiency over the entire circadian cycle.⁹ Although sleep efficiency is not a classical marker of sleep homeostasis,³ this finding suggests that between the naps, the homeostatic buildup may have been faster in the *PER3*^{5/5} carriers, and that higher sleep efficiency might be necessary to reach equally low homeostatic levels compared to more resilient *PER3*^{4/4}. Homeostatic sleep pressure, operationalized here by a manipulation of the state (SD vs. NP), and presumably by trait (*PER3*^{4/4} vs. *PER3*^{5/5}),¹² seems thus to potentiate the harmful effects of adverse circadian phase at the cerebral level.

Our modest sample size presents a limitation in interpreting our results. Nevertheless, by selecting healthy participants without sleep complaints and controlling for confounding variables, we chose a homogenous phenotype

across both genotypes. By implementing stringently controlled laboratory conditions, we minimized potential masking factors. The present analysis does not include a well-rested condition (daytime after regular sleep), restricting our findings to the present circadian window. However, the focus of this study was to compare the same circadian phase under differential sleep pressure conditions, and our results relate to being awake at night. Finally, fMRI is an indirect brain activity measure assessing relative changes in BOLD activity. We thus cannot rule out whether activity changes observed here result from changes in absolute brain activity. However, a recent study suggested that neural consequences of SD are mainly observed in signals evoked in task-relevant brain regions.⁴⁸

By comparing two groups that were characterized with regard to vulnerability to SD with a multimethod approach (i.e., electrophysiology, subjective sleepiness, nap sleep, and vigilant attention^{9,20}), we were able to infer patterns of resilience and vulnerability at the cerebral level. Our study revealed that the sensitivity to SD observed for tasks with low stimulus predictability might be based on a shift into the task-inactive DMN between relevant stimuli. Given that some people seem to have a greater predisposition to drift into these networks competing with goal-directed attention under SD, our findings might have implications to optimally adapt environment or instructions for night workers.

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Authorship

M.M.: study design, data collection, analysis, and manuscript preparation; C.R.: study design, data collection, analysis, and manuscript preparation; V.G.: data collection and manuscript preparation; AV: manuscript preparation; C.P.: analysis and manuscript preparation; J.K.: data collection and manuscript preparation; K.S.: manu-

script preparation; M.K.: manuscript preparation and study design; WS: manuscript preparation; C.C.: study design, data collection, analysis, and manuscript preparation; CS: study design, data collection, analysis, and manuscript preparation.

Potential Conflicts of Interest

Nothing to report.

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