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Human fronto-parietal response scattering subserves vigilance at night

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ABSTRACT

Lack of sleep has a considerable impact on vigilance: we perform worse, we make more errors, particularly at night, when we should be sleeping. Measures of brain functional connectivity suggest that decrease in vigilance during sleep loss is associated with an impaired cross-talk within the fronto-parietal cortex. However, fronto-parietal effective connectivity, which is more closely related to the causal cross-talk between brain regions, remains unexplored during prolonged wakefulness. In addition, no study has simultaneously investigated brain effective connectivity and wake-related changes in vigilance, preventing the concurrent incorporation of the two aspects. Here, we used electroencephalography (EEG) to record responses evoked by Transcranial Magnetic Stimulation (TMS) applied over the frontal lobe in 23 healthy young men (18–30 yr.), while they simultaneously performed a vigilance task, during 8 sessions spread over 29 h of sustained wakefulness. We assessed Response Scattering (ReSc), an estimate of effective connectivity, as the propagation of TMS-evoked EEG responses over the fronto-parietal cortex. Results disclose a significant change in fronto-parietal ReSc with time spent awake. When focusing on the night-time period, when one should be sleeping, participants with lower fronto-parietal ReSc performed worse on the vigilance task. Conversely, no association was detected during the well-rested, daytime period. Night-time fronto-parietal ReSc also correlated with objective EEG measures of sleepiness and alertness. These changes were not accompanied by variations in fronto-parietal response complexity. These results suggest that decreased brain response propagation within the fronto-parietal cortex is associated to increased vigilance failure during night-time prolonged wakefulness. This study reveals a novel facet of the detrimental effect on brain function of extended night-time waking hours, which is increasingly common in our societies.

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Introduction

Modern lifestyle is associated with longer waking hours that perturb circadian rhythmicity and reduce sleep time. This negatively affects vigilance (Durmer and Dinges, 2005; Krause et al., 2017), a basic neuropsychological feature, yet essential to complex cognitive processes. It is defined as the ability to sustain attention on a series of stimuli over prolonged periods of time, or a state of readiness to detect and respond to certain small changes occurring at random time intervals in the environment (Oken et al., 2006; Posner and Petersen, 1990). Vigilance has been reported to suffer the most from insufficient sleep compared with complex cognitive aspects (Lim and Dinges, 2008; Lo et al., 2012). This is particularly the case when wakefulness is extended during the night, because the circadian timing system no longer opposes high sleep pressure, but rather promotes sleep, thereby amplifying the deleterious effects of high sleep pressure on waking performance (Cajochen et al., 1999). In fact, the misalignment between sleep-wake behavior and endogenous circadian time is a major cause of the night-time peak in errors and accidents (e.g. medical errors and car accidents) (Lim and Dinges, 2008; Philip and Akerstedt, 2006). Electrophysiology studies demonstrated that the drop of vigilance at night parallels a wake-dependent increase in the power of slow delta (0.75–4 Hz) and theta (4.5–7.5 Hz) frequency bands of the waking EEG, and a decrease in the power of faster alpha frequency band (8–12 Hz) (Aeschbach et al., 2001; Cajochen et al., 2002, 1999).

The brain substrates of vigilance encompass mainly frontal and parietal areas at the cortical level, and the thalamus at the subcortical level (Corbetta et al., 1993; Coull et al., 2004; Culham et al., 1998). Reduced fronto-parietal response to a vigilance task has been observed following a night of sleep deprivation (Poudel et al., 2013; Tomasi et al., 2009). Moreover, vigilance failures (lapses) were associated with reduced activation within these cortical and subcortical areas (Chee et al., 2008; Chee and Tan, 2010). Beyond abnormal brain activations, vigilance decline during sleep deprivation appears to be related to modifications in the cross-talk between brain areas. This is indicated by changes in spontaneous (i.e. task free) functional connectivity, showing reduced within-network connectivity (or integration) in the default mode and dorsal/ventral attention networks (including many frontal and parietal regions), and reduced segregation between these networks (De Havas et al., 2012; Sämann et al., 2010; Tüshaus et al., 2017; Yeo et al., 2015).

Functional connectivity is based on temporal correlations in brain activity, whereas effective connectivity refers to the ability of a set of neuronal elements to causally affect the firing of other neuronal groups within a system (Friston, 2011). Effective connectivity is therefore more directly related to the cross-talk between brain regions. Brain effective connectivity has been reported to change during sleep deprivation: Granger Causality measures of effective connectivity within the cingulate cortex decreased during task-free recordings of brain activity following sleep deprivation (Piantoni et al., 2013). Similarly to functional connectivity measures, the magnitude of this decrease in cingulate effective connectivity predicted vigilance performance, assessed after brain activity recording. However, variations in effective connectivity within the fronto-parietal cortex have not yet been assessed during prolonged wakefulness. Likewise, performance to a vigilance task has not yet been assessed *simultaneously* to effective connectivity measures.

Compared to wakefulness, effective connectivity sharply decreased during sleep, as probed by the propagation of a direct Transcranial Magnetic Stimulation (TMS) perturbation of neuronal activity (Massimini et al., 2005). This decrease in effective connectivity was associated with a reduction in the complexity of the cortical response: neuronal activity was less variable, more regular, i.e. neurons information content was impoverish during sleep compared to wakefulness (Casali et al., 2013). To our knowledge, a single study addressed variations of complexity driven by sleep loss (Abásolo et al., 2015), and found no significant changes. This study was however conducted on rat, and following 4 h of partial sleep deprivation. Whether effective connectivity changes induced by a full night of sleep deprivation in human fronto-parietal are accompanied by changes in response complexity remains unknown.

Here, we assessed variations in fronto-parietal Response Scattering (ReSc), based on TMS response propagation, during prolonged wakefulness while participants simultaneously performed a vigilance task. We hypothesized that wakefulness extension into the night is associated with a decrease in fronto-parietal ReSc, and consequently with a decrease in Response Complexity (ReC). Furthermore, since vigilance failures are more prominent at night, we anticipated that lower ReSc and ReC at night would be related to lower vigilance performance and lower markers of alertness.

Material and methods

Except for TMS Response Scattering (ReSc) and Response Complexity (ReC), data analyses are as in (Chellappa et al., 2016; Ly et al., 2016). The following section details nevertheless all aspects of the protocol and analyses.

Participants

The study was approved by the Ethics Committee of the Medicine Faculty of the University of Liège. Participants gave their written informed consent. Twenty four healthy Caucasian men (18–30 yr.) were enrolled. Women were excluded from the study as changes in ovarian hormones may influence cortical excitability in humans (Smith et al., 2002). Other exclusion criteria included: 1) Body Mass Index (BMI) ≤ 18 and ≥ 25; 2) psychiatric history, severe trauma, sleep disorders; 3) addiction, chronic medication; 4) smokers, excessive alcohol (>14 doses/week) or caffeine (>3 cups/day) consumption; 5) night shift workers during the last year; 6) transmeridian travel during the last two months; 7) anxiety or depression; 8) poor sleep quality; 9) excessive self-reported daytime sleepiness. One participant was excluded due to melatonin phase-delay > 6 h compared to the remainder of the sample. Thus, data presented here include 23 participants. Table 1 summarizes the demographic characteristics of the final study sample.

Anxiety was measured by the 21 item Beck Anxiety Inventory (BAI ≤ 14) (Beck et al., 1988); mood by the 21 items Beck Depression Inventory II (BDI-II ≤ 14) (Steer et al., 1997); sleep quality by the Pittsburgh Sleep Quality Index Questionnaire (PSQI ≤ 7) (Buysse et al., 1989); daytime propensity to fall asleep in non-stimulating situations by the Epworth Sleepiness Scale (ESS ≤ 11) (Johns, 1991); chronotype by the Horne-Östberg Questionnaire (lower than 42: evening types; 42–58: intermediate types; higher than 58: morning types) (Horne and Östberg, 1976).

Table 1
Sample demographics, questionnaires scores (mean ± SD).

N	23
Age (yr.)	22.74 (2.58)
Ethnicity	Caucasian
BMI (kg/m^2)	22.13 (2.07)
Right handed	17/23
Anxiety level (BAI)	1.17 (1.90)
Mood (BDI-II)	1.61 (2.10)
Caffeine (cups/day)	0.39 (0.50)
Alcohol (doses/week)	3.26 (3.21)
Sleep quality (PSQI)	4.10 (1.12)
Daytime propensity to fall asleep (ESS)	3.57 (2.78)
Chronotype (HO)	52.35 (4.92)
Sleep time (hh:min, sleep diary)	23:23 (47 min)
Wake time (hh:min, sleep diary)	7:24 (47 min)
Sleep time (hh:min, actigraphy)	23:29 (47 min)
Wake time (hh:min, actigraphy)	7:27 (46 min)

Experimental protocol

Participants first completed a pretest TMS-EEG session to determine optimal TMS parameters. The left or right supplementary motor area (SMA) was set as stimulation target for right or left-handed individuals, respectively. This brain area was chosen for the following reasons: 1) similar to the entire frontal lobe, the SMA is sensitive to sleep pressure (Huber et al., 2013; Ly et al., 2016); 2) it has extensive fronto-parietal cortico-cortical connections, making this area interesting for studying effective connectivity (Massimini et al., 2010, 2005; Rosanova et al., 2012); 3) it is engaged in continuous visuomotor vigilance task (Maquet et al., 2003; Poudel et al., 2013); 4) its stimulation does not trigger muscle activation artefact.

Participants completed a screening night of sleep to exclude major sleep disorders. During the 7 days preceding the study, they kept a regular 8 h sleep-wake schedule (±15 min; verified using wrist actigraphy -Actiwatch, Cambridge Neurotechnology, UK- and sleep diaries). Participants were requested to abstain from all caffeine and alcohol-containing beverages for 3 days preceding the study.

For the experiment *per se*, participants were maintained in dim-light for 6 h (<5 lux), prior to sleeping for 8 h at their habitual bedtime (in complete darkness). The TMS-compatible electrode cap was placed upon awaking prior to the 29 h of sustained wakefulness period under constant routine conditions (i.e. light <5 lux, temperature ~19 °C, regular isocaloric liquid meals and water, semi-recumbent position, no time-of-day information, sound proofed rooms). These conditions aim at minimizing external and internal factors masking circadian rhythmicity (Duffy and Dijk, 2002). Spontaneous quiet eyes-open waking EEG and TMS-evoked EEG potentials (TEP) were recorded 8 times during the prolonged wakefulness period to cover the entire near-24 h circadian cycle, with higher session frequency around the circadian wake maintenance (WMZ) and sleep promoting zones (SPZ) (Dijk and Czeisler, 1995) (1100, 1700, 2100, 2300, 0200, 0600, 0800, 1100, for a subject sleeping from 2400 to 0800; Fig. 1). Behavioral test batteries, including the psychomotor vigilance task (PVT), were carried out 12 times during the protocol in between TMS-EEG sessions (1200, 1400, 1600, 1800, 2000, 2200, 2400, 0300, 0500, 0700, 0900, 1200). Subjective sleepiness was assessed hourly using the Karolinska Sleepiness Scale (KSS) (Åkerstedt et al., 2014). Saliva samples were collected hourly for melatonin assays.

TMS-evoked EEG response acquisitions

TMS pulses were generated by a Focal Bipulse 8-coil (Eximia; Nexstim, Helsinki, Finland). Stimulation target (SMA) was located on individual structural MRI by means of a neuronavigation system (Navigated Brain Stimulation; Nexstim). This device allows for reproducible evoked EEG responses (Rosanova et al., 2012) and precise target location (FDA approval for presurgery). Each session included 250–300 trials. Inter-stimulus intervals were randomly jittered between 1900 and 2200 ms. TMS responses were recorded with a 60-channel TMS-compatible EEG amplifier (Eximia; Nexstim), equipped with a proprietary sample-and-hold circuit that provides TMS artifact free data from 5 ms post-TMS (Virtanen et al., 1999). Electrooculogram was recorded with two additional bipolar electrodes. Participants wore the EEG cap during the entire constant routine protocol, and electrodes impedance was set below 5 kΩ prior to each recording session. Signal was band-pass-filtered between 0.1 and 500 Hz and sampled at 1450 Hz. Each TMS-EEG session ended with a neuronavigated digitization of the location of each electrode. Auditory EEG potentials (AEP) evoked by TMS and bone conductance were minimized by diffusing a continuous loud white masking noise through earplugs, and applying a thin foam layer between the EEG cap and the TMS coil (Rosanova et al., 2012). Each session was followed by a sham session consisting in 30–40 TMS pulses delivered parallel to the scalp while white noise was diffused at the same level. Absence of AEP was checked online on Cz between 0 and 500 ms post-TMS (all sessions were AEP-free). Data of sham sessions were not considered any further in ReSc and ReC analyses.

Spontaneous waking EEG acquisition

Spontaneous quiet eyes-open waking EEG (WEEG) was recorded prior to each TMS session using the same 60-channel TMS-compatible EEG (+2 electro-occulogram - EOG - channels) amplifier (Eximia; Nexstim). Participants were instructed to fix a black dot during 2 min while relaxing and suppressing blinking.

Visuomotor vigilance task

While recording TMS-evoked EEG responses, participants performed a visuomotor compensatory tracking task (CTT) to monitor their vigilance as in (Huber et al., 2013). The task consisted of keeping a constantly randomly moving cursor on a target located in the center of a computer screen, using a trackball device. This task recruits the fronto-parietal cortex (Poudel et al., 2013) and was used for correlations with ReSc as a measure of vigilance level. The task was preferred to the PVT (see 2.6.) during TMS-EEG recording because it requires continuous smooth and limited movement of a single finger, compared to the burst-like muscular activity engaged by PVT that could be time-locked to TMS evoked EEG responses. Performance was computed as the average distance (in pixels) between the cursor and the target during TMS-EEG recordings. If signs of drowsiness were detected while performing the

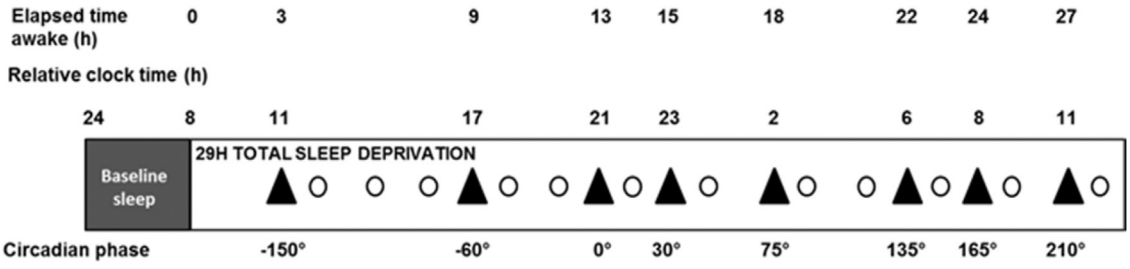

Fig. 1. Experimental protocol.
After an 8 h baseline night of sleep under polysomnographic recording, participants (N = 23) underwent 29 h of sustained wakefulness under constant routine conditions (no time-of-day information, dim light < 5 lux, temperature 19 °C, regular isocaloric liquid intake, semi-recumbent posture, sound proofed rooms). TMS-evoked EEG potentials (TEP) were recorded 8 times (~250 trials per session; black triangles) over the frontal cortex contralateral to the dominant hand (i.e. mostly left frontal cortex), while participants performed a visuomotor vigilance compensatory tracking task (CTT). Each TMS-EEG session was preceded by 2 min quiet eyes-open wake EEG recording (WEEG). In-between TMS-EEG sessions, 12 behavioural test batteries were administered (circles) - including the psychomotor vigilance task (PVT). Saliva samples were collected hourly for melatonin assays, allowing a posteriori data realignment based on individual endogenous circadian timing. Subjective sleepiness measures were collected hourly. Time is expressed in circadian phase (°) and equivalent elapsed time awake (h). Relative clock time displayed here is for a participant with a 2400–0800 sleep-wake schedule. For simplicity, elapsed time awake and clock time are given as integer values but 0.5 h should be added.

task during TMS-EEG sessions, the experimenter briefly touched the participant. Transitory lapses of vigilance resulted in temporary increases of the target-cursor distance, and could be automatically detected offline. A lapse was identified when the cursor was located outside a central 200 by 200 pixel box surrounding the target for >500 ms from the last trackball movement. The lapse period ranged from the last trackball movement until the lapse detection. TMS evoked responses occurring during and <1 s from a lapse period were discarded from analyses.

Psychomotor Vigilance Task (PVT)

In between TMS-EEG assessments, participants were required to press a computer space bar as soon as an auditory signal occurred (presented at a random interval of 3–7 s (Graw et al., 2004)). We opted for an auditory version, because it would lead to fewer lapses of vigilance and potential micro-sleep episodes, which would have biased our results (Jung et al., 2011). The PVT lasted 5 min (Roach et al., 2006). Performance was inferred from the median reaction time following removal of lapses (>500 ms), anticipation (<100 ms) and error (>3000 ms) (Dinges and Powell, 1985).

Melatonin

Saliva samples were first placed at 4 °C, prior centrifugation and congelation at −20 °C within 12 h. Salivary melatonin was measured by radioimmunoassay (Stockgrand Ltd, Guildford, UK), as previously described (English et al., 1993). The limit of detection of the assay for melatonin was 0.8 ± 0.2 pg/ml using 500 μL volumes.

TMS-EEG data pre-processing and source reconstruction

TMS-EEG data were processed using SPM12 software package (Statistical Parametric Mapping 12, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab 2011a (The Mathworks Inc, Natick, MA). Continuous EEG recordings were re-referenced to the average of all good channels, low-pass filtered at 80 Hz, resampled from 1450 to 1000 Hz, and high-pass filtered at 1 Hz, split into epochs between −100 and 300 ms around TMS pulses, and baseline corrected (−100 to −1 ms pre-TMS). Robust averaging was applied to compute the mean evoked response of each session (Leonowicz et al., 2005). Source reconstruction was computed on the averaged TMS-evoked EEG response of each recording session (up to 300 ms post-TMS), to obtain a spatio-temporal history of the significant cortical sources responsible for the observed EEG pattern. Sensor and fiducial positions were used for realistic head model based on individual structural image (conductive head volume model based on Boundary Element Method (BEM), i.e. 3 compartments of fixed conductivities: scalp, skull, brain). All analyses were performed within the individual subject space. The cerebral cortex was modeled using 5124 dipoles oriented normally to the cortical surface. For the inverse reconstruction, "Multiple Sparse Prior" (MSP) was adopted, because (i) it produces more accurate localizations (Friston et al., 2008), and (ii) model comparison (computed as the difference of log model evidence (Mattout et al., 2006)) indicated that "MSP" was more appropriate than the "Loreta" approach for our dataset (i.e. difference in log evidence higher than 3). MSP source reconstruction resulted in patches of currents that were transformed in a binary spatio-temporal distribution of statistically significant sources over the 300 ms post-TMS. To determine source electrical activity that was "truly" induced by TMS, standardization was performed. A source electrical activity higher than 4 standard deviation from the mean TMS baseline activity was considered as significant and allocated 1 (0 if non-significant). The cut-off of 4 Z-Score allows a false positive rate of less than 0.01% (i.e. $p < 0.0001$) (Casali et al., 2010). This procedure was applied to each source and to each time bin. The resulting binary spatio-temporal matrix allowed the identification of statistically significant sources over the 300 ms post-TMS. The matrix was then masked with a fronto-parietal 3D mask (WFU PickAtlas; http://fmri.wfubmc.edu/software/PickAtlas, based on Talairach Daemon database, implemented in SPM12), i.e. all significant sources outside the fronto-parietal 3D mask were set to zero. This approach did not include the thalamus and focused solely on the cortical mantel.

During TMS acquisitions, participants were performing a continuous visuomotor vigilance task, recruiting fronto-parietal regions (Poudel et al., 2013) as well as the occipital cortex (Chee et al., 2011). However, TMS by-passes afferent sensory systems to trigger brain responses, and TMS-evoked responses were not time-locked to any particular event related to the task. Our protocol allowed therefore to focus only on core vigilance cortical regions -i.e. the fronto-parietal cortex- without considering areas involved in sensory processing. For completeness, we computed a supplementary analysis including the occipital areas, i.e. fronto-parietal-occipital (FPO) mask (refer to Supplementary Fig. 1).

Synthetic indices of Response Scattering (ReSc) and Response Complexity (ReC)

Indices were computed based on the binary spatio-temporal source matrix *ST* (x,t) (Fig. 2). For computation of both indices the first 5 ms were discarded to avoid possible artefacts contamination. *Response Scattering (ReSc)* was measured based on the scattering of significant current, i.e. the spatial spreading of the significant electrical activity elicited by TMS pulses. ReSc is a measure of effective connectivity: it originates at the stimulation hotspot and propagates over an ensemble comprised within the fronto-parietal cortex. It is however distinct from other types of effective connectivity measures between specific brain regions (Moran et al., 2013). ReSc was computed as the sum of the geodesic distance between any significant sources within the fronto-parietal cortex and the TMS target, averaged either over the entire 5–300 ms period post-TMS, or in 50 ms bins over the 300 ms (first bin: 5–50 ms post-TMS). A higher ReSc index means that the initial perturbation reaches more sources and/or more distant sources over the cortical brain surface. *Responses Complexity (ReC)* (first conceptualized by (Tononi et al., 1994)) was derived by applying the Lempel-Ziv compression algorithm on the fronto-parietal binary matrix of significant sources followed by normalization, as in (Casali et al., 2013). It is therefore a proxy of the neuronal information content following stimulation (Aboy et al., 2006). A lower ReC means that the brain response is more stereotypical, less variable over time and space, but is not directly related to the scattering of the response. A large and widespread response could still contain little pattern variations and have low ReC. Importantly, in the current study, source reconstruction model (MSP instead of Loreta) and significant sources determination (*ST* (x,t) matrix), which precede ReSc and ReC computation, were different than the original publications (Casali et al., 2013, 2010): direct comparison of absolute values between studies is therefore not pertinent.

Spontaneous waking EEG analyses

Data preprocessing was performed using SPM12. Continuous EEG recordings were band-pass filtered between 0.1 and 500 Hz and resampled from 1450 to 500 Hz. Data were then manually and visually scored offline for artefacts and microsleep episodes (eye blinks, body movements, and slow eye movements), using FASST toolbox (http://www.montefiore.ulg.ac.be/~phillips/FASST.html). Power spectral densities were computed using a fast Fourier transform on artifact-free 4 s windows, overlapping by 2 s, using the Welch's method (pwelch function in MATLAB 2011a) (Welch, 1967). EEG activity was computed over frontal-parietal regions for delta (0.75–4 Hz), theta (4.5–7.5 Hz), alpha (8–12 Hz), sigma (12.5–18 Hz) and beta (18.5–30 Hz) frequency bands over the entire 2 min recording.

Statistics

Statistical analyses were performed with SAS version 9.3 (SAS

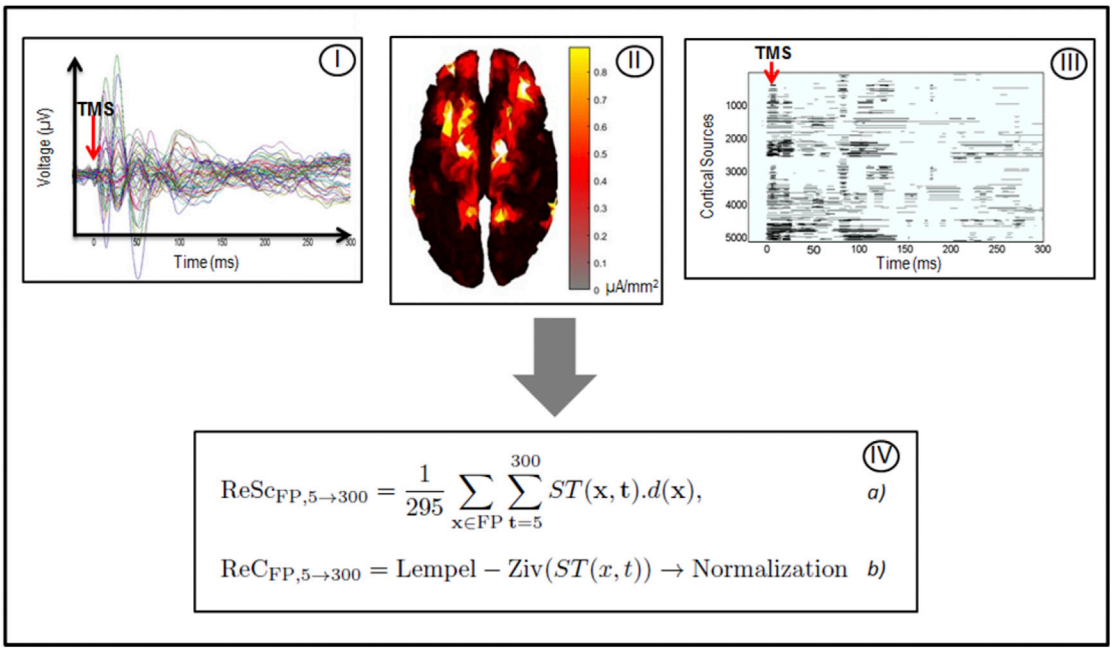

Fig. 2. TMS-EEG data processing.
I.) Butterfly plot of the average TMS-evoked response in all 60 EEG channels over 300 ms post TMS. **II.)** EEG source reconstruction showing the inferred spatio-temporal history of the electrical activity over the cortical surface. **III.)** The spatio-temporal history is transformed into a binary spatio-temporal matrix ST (x,t): for each time bin, significant fronto-parietal sources were allocated 1 (resp. 0 when non-significant/outside fronto-parietal cortex). **IV.)** Equations underlying the synthetic indices of cortical responsiveness. *a) Response Scattering (ReSc)*, where ST (x,t) is the binary spatio-temporal matrix, with x = [1:5124] indexing the cortical source dipoles and t = [0:300] the post-TMS interval in ms, and d(x) being the geodesic distance between the TMS hotspot and source (x). ReSc is the sum, from 5 to 300 ms, of the geodesic distances between all significant fronto-parietal sources ($x\varepsilon FP \wedge x = 1$) and the TMS stimulation area, averaged over 295 ms of the 5–300 ms post-TMS period. *b) Response Complexity (ReC):* derived by applying the Lempel-Ziv algorithm to the binary matrix ST (x,t), followed by normalization.

Institute, Cary, NC, USA). Fronto-parietal ReSc, ReC, PVT and KSS values were standardized by computing z-scores at the individual level across circadian phases (PROC STANDARD). CTT was normalized by dividing the performance to the task duration, and then z-scored (technical issues prevented CTT to be properly recorded for one participant that was discarded, $N_{CTT} = 22$). WEEG activity was averaged across channels within the fronto-parietal region, and normalized by dividing each power band by the sum of all frequencies within 0.75 and 30 Hz (i.e. relative activity). The time-course of all variables was examined with mixed-model analyses of variance for repeated measures (PROC MIXED), with "circadian phase" as fixed factor and "subject" as random factor. For two within-subject factors, i.e. "circadian phase" and "bin" a general linear model was used (PROC GLM, predictors based on type III SS). Differences between circadian phases were assessed with LSMEANS statement. All P-values were based on Kenward-Roger's corrected degrees of freedom and were adjusted for multiple testing with Tukey's procedure.

All data were realigned to individual dim light melatonin onset (DLMO). Estimation of circadian phase (where 0° = individual DLMO) was determined based on raw values. The 4 first samples were disregarded and maximum secretion level was set as the median of the 3 highest concentrations. Baseline level was set to be the median of the values collected from "wake-up time +5 h" to "wake-up time +10 h". DLMO was computed as the time at which melatonin level reached 20% of the baseline to maximum level (linear interpolation). All data points were grouped in the following circadian phase bins: −150° [-180° to −130°], −60° [-105° to −15°], 0° [-15°–15°], 30° [15°–45°], 75° [45°–105°], 135° [120°–150°], 165° [150°–180°], 210° [180°–240°] (i.e. each data point was attributed to its closest bin).

Pearson's Correlations (PROC CORR) were performed between ReSc, WEEG markers and CTT performance. Values distribution was checked for normality by visual inspection and based on Shapiro-Wilk test. Non-parametric equivalent tests were used for non-normally distributed variables (Spearman's rank correlations). Correlations were first considered only for night-time data points, when one should be asleep, i.e. the first circadian point that belongs to the night (75°) until the end of it (165°, around wake up time). The difference between the last (165°) and first (75°) night-time data point was also computed to assess the night-time decline in ReSc, and CTT performance. Six participants (missing data for one of these circadian phases) and one outliner (+3 SD) were discarded. Correlation analyses for night-time decline included 16 participants. Similar correlations were also computed using daytime values (circadian phases: −150°, −60°, 0°) to assess whether the significant correlations were specific to the night-time period.

Results

Time course of objective and subjective measures of sleepiness and vigilance performance

In all analyses data were realigned according to the circadian phase 0°, which corresponds to the onset of melatonin secretion.

As expected, EEG recordings of spontaneous waking fronto-parietal activity showed that relative theta (4.5–7.5 Hz) and alpha power (8–12 Hz) -objective physiological markers of sleepiness and alertness (Strijkstra et al., 2003)- significantly varied during the protocol (Fig. 3B–C) ($n = 23$; PROC MIXED main effect of circadian phase; theta: $F(7, 118) = 5.99$; $P < 0.0001$; alpha: $F(7, 117) = 5.45$; $P < 0.0001$). Likewise, relative fronto-parietal delta power (0.75–4 Hz) displayed a trend (Fig. 3A) ($n = 23$; PROC MIXED, main effect of circadian phase; $F(7, 119) = 2.03$; $P = 0.057$). Hourly subjective sleepiness scores (KSS) significantly varied with circadian phase (Fig. 3D) ($n = 23$; PROC MIXED, main effect of circadian phase; $F(25, 437) = 6.57$; $P < 0.0001$). The time course of these subjective and objective measures of sleepiness and alertness reflects the expected dual influence of sleep homeostasis and circadian phase (Dijk and Czeisler, 1995): a fairly stable profile during the day compared to the night (−150°, −60°, 0°, or 30° vs. 135° or 165°:

$P_{corr} < 0.048$). Importantly, within the night-time period (75° vs. 165°), Tukey post-hoc test revealed a significant increase in relative theta power ($P_{corr} = 0.049$), and decrease in relative alpha power ($P_{corr} = 0.044$), as well as a tendency for an increase in relative delta power ($P_{corr} = 0.09$).

As expected also, the progressive intrusion of WEEG slow frequencies during the night-time period was accompanied by a drop in PVT performance, assessed *in between* TMS-EEG recordings (Fig. 3E) (n = 23; PROC MIXED, main effect of circadian phase; F (11, 224) = 6.24; $P < 0.0001$). Vigilance was also assessed *simultaneously* to TMS-EEG recordings using a visuomotor vigilance task (compensatory tracking task, CTT). CTT displayed a pattern similar to PVT (Fig. 3F) (n = 22; PROC MIXED, main effect of circadian phase; F (7, 122) = 13.78; $P < 0.0001$): good performance during day compared to night time (−150°, −60°, 0°, or 30° vs. 135° or 165°: $P_{corr} < 0.003$), contrasting with a sharp overnight decrement (75° vs. 165°: $P_{corr} = 0.003$), and a partial recovery the subsequent morning (165° vs. 210°: $P_{corr} = 0.0025$).

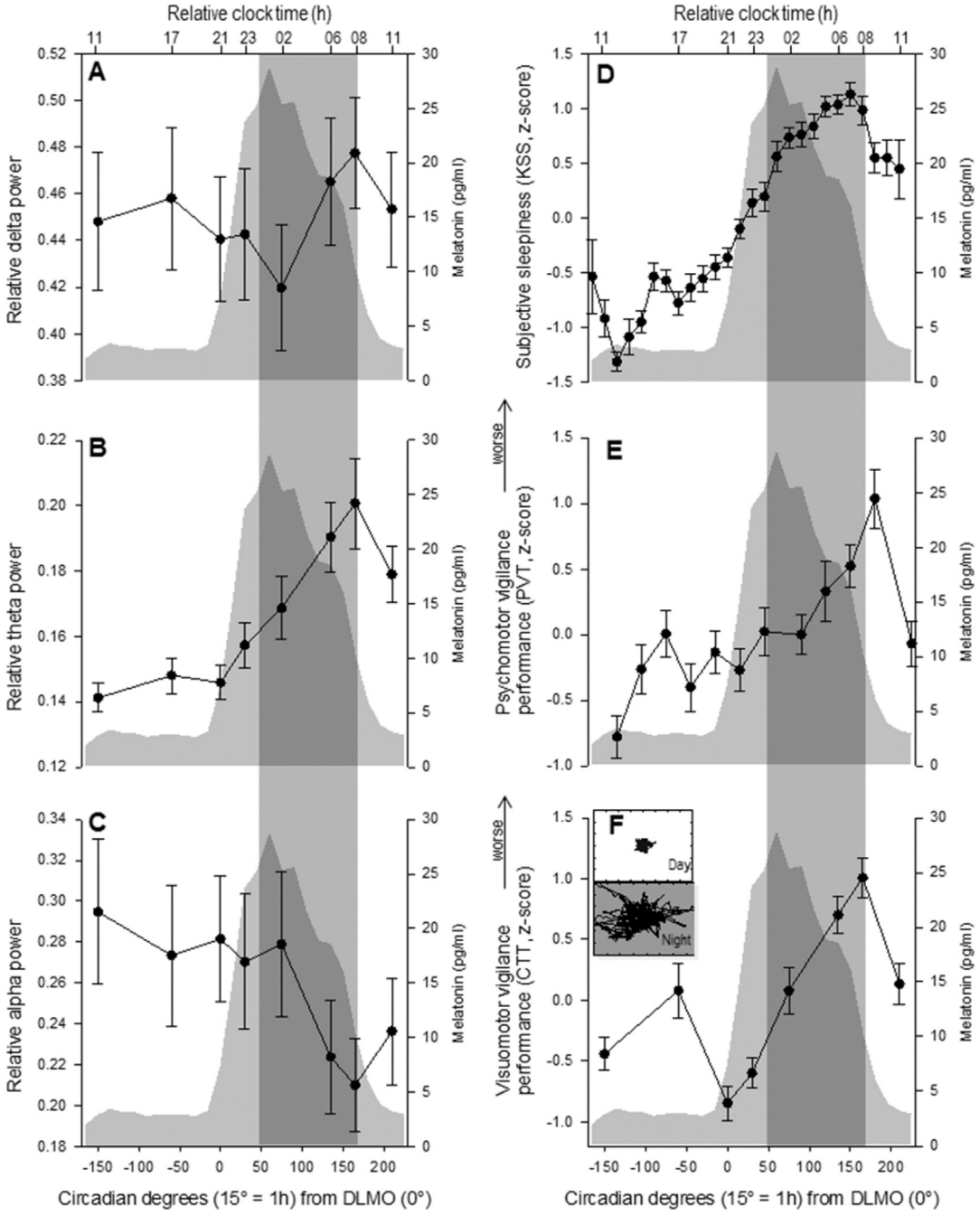

Fig. 3. Time courses of objective and subjective measures of sleepiness and vigilance performance (means and standard errors). **A.** Relative fronto-parietal delta power (0.75–4 Hz) (n = 23; PROC MIXED, main effect of circadian phase; F (7, 119) = 2.03; P = 0.057). **B.** Relative theta power (4.5–7.5 Hz) (n = 23; PROC MIXED, main effect of circadian phase; F (7, 118) = 5.99; $P < 0.0001$). **C.** Relative alpha power (8–12 Hz) (n = 23; PROC MIXED, main effect of circadian phase; F (7, 117) = 5.45; $P < 0.0001$). **D.** Subjective sleepiness (n = 23; PROC MIXED, main effect of circadian phase; F (25, 437) = 6.57; $P < 0.0001$). **E.** PVT performance (median reaction times; n = 23; PROC MIXED, main effect of circadian phase; F (11, 224) = 6.24; $P < 0.0001$). **F.** Compensatory tracking task performance (CTT; n = 22; PROC MIXED, main effect of circadian phase; F (7, 122) = 13.78; $P < 0.0001$). Insets: representative performance to the task; cursor remains close to target (screen centre) during the day, while it deviates during night-time wakefulness. The light gray area represents the average melatonin profile (0° = dim light melatonin onset (DLMO)). All variables are plotted in degree (15° = 1h) relative to DLMO. The dark gray bars indicate night-time period for a participant with 2400–0800 sleep-wake schedule.

Fronto-parietal response scattering varies during prolonged wakefulness but not cortical response complexity

Following these first analyses, we turned to fronto-parietal ReSc, our main focus of interest. The scattering of the electrical current significantly varied with circadian phase (Fig. 4A) (n = 23; PROC MIXED, main effect of circadian phase; F (7, 135) = 2.09; P = 0.049). Tukey post-hoc tests between the different circadian phases were non-significant following correction for multiple comparisons ($P_{corr} > 0.05$). However, qualitative inspection of the data, as well as uncorrected post-hoc tests, suggest that ReSc increased from day to evening and early night (−150° or −60° vs. 0°, 30° or 75°: $P_{uncorr} < 0.04$), and from the first morning session up to the last morning session (i.e. 24 h later; −150° vs. 210: $P_{uncorr} = 0.03$). During the night, a visual decline was perceptible (75° vs 135° or 165°: $P_{uncorr} > 0.05$). A similar pattern was observed when considering the occipital cortex within the fronto-parietal-occipital mask (Supplementary Fig. 1).

Since ReSc varied with circadian phases, we also investigated whether the within session temporal dynamics differed according to the circadian phase. We decomposed ReSc in six bins of 50 ms over the 300 ms post-TMS period. This additional analysis showed that fronto-parietal ReSc significantly varied from bin to bin and between circadian phases, but without a bin x circadian phase interaction (Fig. 4B) (n = 23; PROC GLM, model: F (47) = 2.79, P < 0.0001, R^2 = 0.11; circadian phase: F

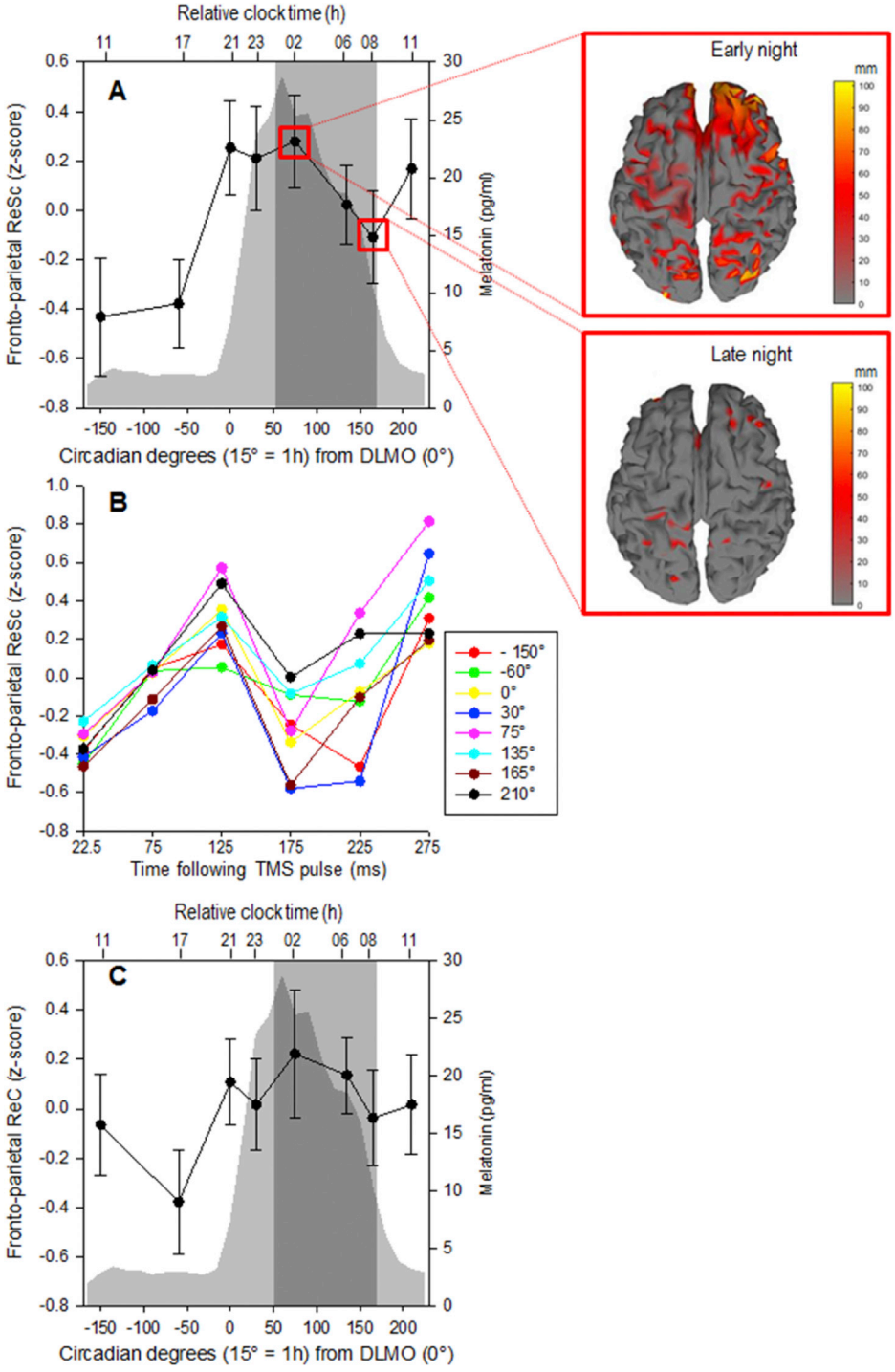

Fig. 4. Response Scattering (ReSc) and Response Complexity (ReC) during 29 h of sustained wakefulness (means and standard errors, z-scores). **A.** Fronto-parietal ReSc significantly varied during the protocol (n = 23; PROC MIXED, main effect of circadian phase; F (7, 135) = 2.09; P = 0.049). The right panels are displayed as representative examples of ReSc in the early and late night for a representative subject. Colour code corresponds to the distance from the supplementary motor area (SMA) stimulated by TMS. **B.** When divided in six bins of 50 ms over the 300 ms post-TMS (midpoint of bin plotted; first bin: 5–50 ms post-TMS), fronto-parietal ReSc significantly varied from bin to bin and between circadian phases, but the bin x circadian phase interaction was not significant (n = 23; PROC GLM, model: F (47) = 2.79, P < 0.0001, R^2 = 0.11; circadian phase: F (7) = 2.21, P = 0.03; bin: F (5) = 18.54, P < 0.0001; bin*circadian phase: F (35) = 0.69, P = 0.9). Standard errors were omitted for clarity. **C.** Fronto-parietal ReC did not significantly vary during prolonged wakefulness (n = 23; PROC MIXED, main effect of circadian phase; F (7, 137) = 0.83; P = 0.56). The light gray area represents the average melatonin profile (0° = dim light melatonin onset (DLMO)). All variables are plotted in degree (15° = 1h) relative to DLMO. The dark gray bars indicate night time period for a participant with 2400–0800 sleep-wake schedule.

(7) = 2.21, P = 0.03; bin: F (5) = 18.54, P < 0.0001; bin*circadian phase: F (35) = 0.69, P = 0.9). The within session temporal dynamics appears therefore to remain similar across sessions.

Given that the power in slower spontaneous waking EEG oscillations and ReSc significantly varied during the protocol, we further asked whether fronto-parietal response complexity (ReC) would change as well. Contrary to our hypothesis, ReC did not vary significantly during prolonged wakefulness (Fig. 4C) (n = 23; PROC MIXED, main effect of circadian phase; F (7, 137) = 0.83; P = 0.56).

Worse vigilance correlates with lower fronto-parietal response scattering at night

Our analyses then focused on how fronto-parietal ReSc translated to *simultaneous* vigilance performance during night-time period, when vigilance is mostly affected by prolonged wakefulness. A significant correlation between ReSc and performance at the visuomotor vigilance task was found (Fig. 5A) (rs (54) = −0.35, P = 0.01), suggesting that lower fronto-parietal ReSc was associated with worse vigilance performance

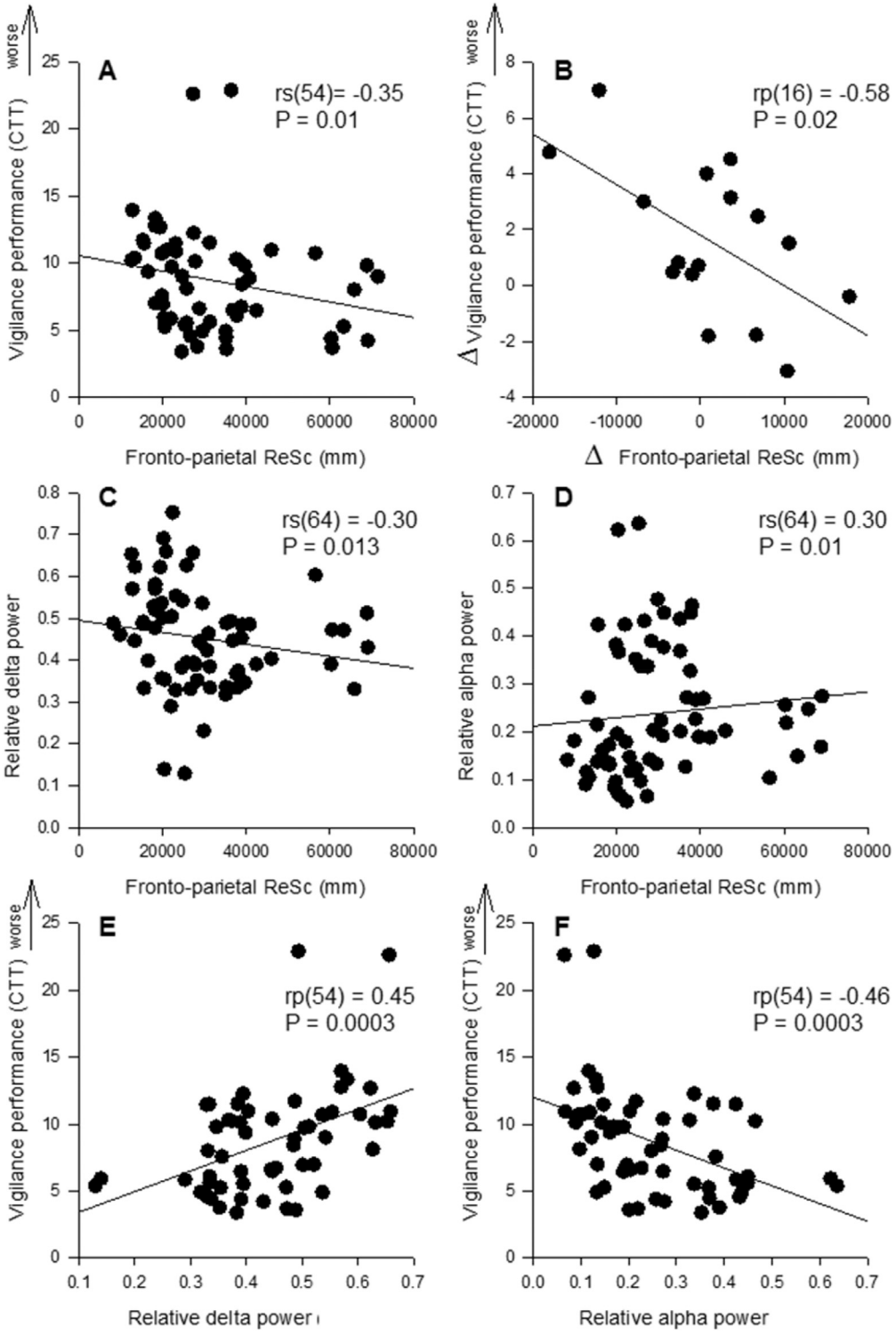

Fig. 5. Associations between fronto-parietal response scattering, vigilance performance and relative wake EEG power spectra at night.
The following correlations include data collected at 75°, 135°, 165°, which were considered together irrespective of circadian phase. For each plot, the correlation coefficient [Pearson: rp; Spearman: rs; (degree of freedom)] and the corresponding P-value are reported. A. Significant correlation between fronto-parietal ReSc and CTT performance at night. Higher ReSc is associated to better vigilance performance. B. Significant correlation between decrease in fronto-parietal ReSc and decrement in CTT performance from the beginning to the end of the night-time period (Δ = 165°–75°). C. Significant negative correlation between fronto-parietal ReSc and relative delta power (0.75–4 Hz) of the spontaneous WEEG recordings. D. Significant positive correlation between fronto-parietal ReSc and relative alpha power (8–12 Hz) of the spontaneous WEEG recordings. E. Significant positive correlation between relative delta power and CTT performance. F. Significant negative correlation between relative alpha power and CTT performance.

during night-time wakefulness. Importantly, ReSc did not correlate with CTT performance during a normal waking day (−150°–30°; rs (74) = −0.09, P = 0.45).

In a next step, we computed the difference between the first and last point within our night-time window (Δ = 165°–75°). The night-time period is indeed a heterogeneous window: important neurobehavioral impairments start at the end of a normal waking day and reach the peak at the end of the night, around the circadian sleep promoting zone (SPZ) (Wright et al., 2012). A marked decrease in ReSc was significantly associated with a marked decline in CTT performance over this time window (Fig. 5B) (rp (16) = −0.58, P = 0.02). This indicates that participants maintaining or increasing ReSc overnight were those having better vigilance performance.

ReSc measure was also significantly and negatively associated with relative delta (Fig. 5C) (rs (64) = −0.30, P = 0.013), but not theta power (rs (64) = 0.17, P = 0.16) of the spontaneous night-time waking EEG recordings, while it was significantly and positively correlated with relative alpha power (Fig. 5D) (rs (64) = 0.3, P = 0.01). These latter results suggest that higher fronto-parietal ReSc at night is associated with lower sleepiness and higher alertness. Further correlations showed that higher delta and lower alpha power were associated with worse performance to the visuomotor vigilance task at night (Fig. 5E–F) (delta: rp (54) = 0.45, P = 0.0003; theta: rp (54) = 0.25, P = 0.06; alpha: rp (54) = −0.46, P = 0.0003).

Discussion

In this study, we tested whether a reduction of fronto-parietal response scattering (ReSc) and response complexity (ReC) could contribute to the vigilance impairment typically observed during night-time wakefulness. We perturbed brain activity with TMS and recorded the propagation of the triggered response over the cortical surface with EEG. Fronto-parietal TMS response scattering, as assessed following EEG source reconstruction, significantly changed with circadian phase, while, contrary to our expectations, response complexity did not. Data further suggest that ReSc tended to decrease during night-time wakefulness and, in line with our prediction, lower night-time level was correlated with worse vigilance performance and lower alertness. Furthermore, the extent of the night-time decrease in ReSc was correlated to the decline of vigilance performance.

The fronto-parietal cortex includes many polymodal associative areas and is very active during wakefulness. Beyond vigilance regulation, it is heavily involved in higher cognitive processes and in the top-down control of attention (Chee and Tan, 2010). This region shows substantial variations in the amount of slow activity rhythms during both wakefulness and sleep, indicating that it is a site of important homeostatic sleep pressure accumulation and dissipation (Cajochen et al., 1999). Although variations between circadian phases did not reach post-hoc statistical significance, fronto-parietal ReSc profile seemed to change non-linearly as a function of prolonged wakefulness, suggesting a dual influence of sleep homeostasis together with the circadian timing system (Borbély et al., 2016). Moreover, fronto-parietal ReSc seemed to increase from the first recording in the morning after sleep to the last recording in the morning after a night without sleep (24 h later). A period of night-time sleep appears therefore necessary to bring back ReSc to baseline level. Thus, although this should be formally tested, we assume that ReSc after recovery sleep would be similar to the first session. After the night time period, ReSc seems to increase again, i.e. it increased accross the last 2 sessions of the protocol (i.e. from 0800 to 1100). This might suggest a circadian influence that switches from sleep to wake promotion around that period (Dijk and Czeisler, 1994).

Our data suggest that fronto-parietal ReSc increased during a normal waking day, which is reminiscent of a previous study reporting significant MRI-based functional connectivity alterations from morning to evening of a normal waking day (Kaufmann et al., 2016). This daytime variation does not seem detrimental for the visuomotor vigilance performance, which is typically good and stable during a normal waking day (Gaggioni et al., 2014). It is only at night that visuomotor vigilance performance drops, when both sleep homeostatic and circadian processes greatly challenge cognitive abilities. In line with our hypothesis, we found a significant correlation between night-time fronto-parietal ReSc and simultaneous measures of vigilance, indicating that a relative reduction in fronto-parietal ReSc at night is associated with worse vigilance performance. In addition, individuals showing marked vigilance impairment over the night-time period had a more important decline in ReSc. Importantly, even resilient participants at night had lower CTT performance compared to daytime, reminding that sleep is necessary for assuring optimal performance. Nocturnal modifications in ReSc were accompanied by the intrusion of slow brain activity rhythms, typical of sleepiness and lower alertness level (Cajochen et al., 1999; Slater et al., 2017): we found that the relative decrease in ReSc at night was related respectively to increase of slower (delta), and decrease of faster (alpha) brain activity rhythms.

A relative reduction of ReSc at night suggests that fronto-parietal areas, sustaining vigilance, are less connected, or are less integrated when compared to the end of a normal waking day. It also implies that night-time integration level directly affect vigilance. This observation is similar to the previously reported link between increased spontaneous eyelid closures following sleep deprivation, as proxy for sleepiness level, and reduced functional connectivity within the default mode and dorsal/ventral attention networks (Wang et al., 2016). Using resting state functional MRI, a recent study (Ben Simon et al., 2017) also reported a reduced functional connectivity of the brain following sleep deprivation based on Graph modularity measures, and subsequent behavioral impairment. Our finding recalls the link between the decrease in effective connectivity within the cingulate cortex following sleep deprivation, and subsequent worse vigilance performance (Piantoni et al., 2013). Here we confirm and extend the latter observation to the fronto-parietal cortex and simultaneous vigilance assessment.

Effective connectivity is close to the intuitive notion of a connection (Büchel and Friston, 1997). Changes in effective connectivity may therefore reflect changes in structural brain connectivity. A day of wakefulness was associated with widespread increases in white matter fractional anisotropy ((FA), reflecting changes in axonal microstructure), whereas sleep deprivation triggered widespread FA decreases (Elvsåshagen et al., 2015), reminiscent of the ReSc variations we observed. In addition, higher FA within the fronto-parietal cortex while well rested was associated with better PVT performance during sleep deprivation (Cui et al., 2015). In contrast, participants with lower FA values within multiple brain regions while well rested had worse performance to a visuomotor task after sleep deprivation (Rocklage et al., 2009).

If effective connectivity allows insight about cortico-cortical interaction, cortical excitability informs about the responsiveness of the cortex. We previously showed that local cortical reactivity (i.e. measured at the electrode closest to the area stimulated by the TMS pulse) was stable during a normal waking day prior to increasing sharply during overnight wakefulness, and was correlated to CTT performance (Ly et al., 2016). With the present results, it seems that, following the initial responses, the degree of effective connectivity of the fronto-parietal cortex is also important for night-time vigilance performance. Thus, these results bring together different facets of the changes in neuronal response triggered by extended wakefulness: spatio-temporal changes in local excitability and in global fronto-parietal effective connectivity negatively affect behavior at night, and may thus represent a form of “neuronal tiredness” (Fisher and Vyazovskiy, 2014). During extended wake (beyond normal sleep time), neurons can undergo off periods similar to sleep, although the EEG shows signals typical of wakefulness (Vyazovskiy et al., 2011). Neuronal activity is therefore more synchronous. In our data, this is confirmed by an increase in the prevalence of slower EEG rhythms, which are associated with poorer performance. Delivering TMS pulses during sleep deprivation results in an increased local excitability (Huber et al., 2013; Ly et al., 2016), either because neurons reply more synchronously or

because more neurons respond to an external perturbation. Our results suggest that effective connectivity, as indexed by ReSc, increases first during the day, before local excitability increases, and then seems to show a relative decrease at night. Our results are in line with a recent paper showing that short and long range signal characteristics can differ importantly: the intrusion of off-period can compromise long range signal propagation during sleep deprivation (Meisel et al., 2017). One could therefore posit that the increased prevalence of off-line periods contribute in part to this disruption of long range response scattering. Likewise, since the thalamus plays an important role in vigilance regulation (Killgore et al., 2015), changes in thalamo-cortical loops could contribute to effective connectivity variation during prolonged wakefulness.

Sleep is characterized by a sharp reduction in effective connectivity (Massimini et al., 2005), and TMS-evoked response complexity (Casali et al., 2013). Given that our data showed changes in ReSc and in slow oscillation power, we expected changes in cortical response complexity: a simplification of the neuronal information content, concomitant with the night-time vigilance state instability. However, we did not find a significant difference, suggesting that cortical response complexity does not change during prolonged wakefulness. This result is in line with another study showing no significant variation of complexity during a partial sleep deprivation in rats (Abásolo et al., 2015).

Conclusions

Overall, our study shows that TMS applied over the frontal lobe triggers responses within the fronto-parietal cortex that vary as a function of wakefulness duration. It reinvigorates the concept that cortico-cortical transmission varies during prolonged wakefulness (Piantoni et al., 2013; Verweij et al., 2014; Yeo et al., 2015), and that lower effective connectivity is linked to worse vigilance performance and lower alertness level at night.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.03.055.

Authors' contribution

GG acquired and analyzed the data, wrote the paper. JQLM and SLC acquired and analyzed the data. MR and SS provided expertise for TMS-EEG acquisitions. MM designed the experiment, provided expertise for TMS-EEG acquisitions. BM performed melatonin assays. CS, AL and ES provided expertise for statistical analysis. DC, AC provided expertise for EEG data analyses. CP provided expertise and analysed EEG data and wrote the paper. GV designed the experiment, acquired and analyzed the data, wrote the paper. All authors edited the manuscript.

Disclosure statement

The authors declare no competing financial interests.

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