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Effort During Prolonged Wakefulness Is Associated With Performance to Attentional and Executive Tasks but Not With Cortical Excitability in Late-Middle-Aged Healthy Individuals

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Objective: Sleep loss negatively affects brain function with repercussion not only on objective measures of performance but also on many subjective dimensions, including effort perceived for the completion of cognitive processes. This may be particularly important in aging, which is accompanied by important changes in sleep and wakefulness regulation. We aimed to determine whether subjectively perceived effort covaried with cognitive performance in healthy late-middle-aged individuals. ***Method:*** We assessed effort and performance to cognitive tasks in 99 healthy adults (66 women; 50–70 years) during a 20-hr wake extension protocol, following 7 days of regular sleep and wake times and a baseline night of sleep in the laboratory. We further explored links with cortical excitability using transcranial magnetic stimulation coupled to electroencephalography. ***Results:*** Perceived effort increased during wake extension and was highly correlated to subjective metrics of sleepiness, fatigue, and motivation, but not to variations in cortical excitability. Moreover, effort increase was associated with decreased performance to some cognitive tasks (psychomotor vigilance and two-back working memory task). Importantly, effort variations during wakefulness extension decreased from age 50 to 70 years, while more effort is associated with worse performance in older individuals. ***Conclusion:*** In healthy late-middle-aged individuals, more effort is perceived to perform cognitive tasks, but it is not sufficient to overcome the performance decline brought by lack of sleep. Entry in the seventh decade may stand as a turning point in the daily variations of perceived effort and its link with cognition.

Key Points

Question: Does perceived effort for completion of cognitive tasks vary with advancing age and how is associated to performance? ***Findings/Importance:*** Increase in the perceived effort is associated with cognitive performance, and more effort is associated with worse performance in older individuals. The daily variations of perceived effort and its link with cognition seems to vary according to age in a healthy late-middle-aged population. Changes in effort across the protocol were not associated with changes in

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Gilles Vandewalle and Fabienne Collette had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Charlotte Mouraux played supporting role in formal analysis and equal role in writing of original draft and writing of review and editing. Maxime Van Egroo played equal role in data curation, investigation and writing of review and editing. Daphne Chylinski played equal role in data curation, investigation and writing of review and editing. Justinas Narbutas played equal role in data curation, investigation and writing of review and editing. Christophe Phillips played equal role in data curation, funding acquisition, methodology and writing of review and editing. Eric Salmon played equal role in funding acquisition, project administration, resources and writing of review and editing. Pierre Maquet played equal role in conceptualization, funding acquisition, methodology, project administration, resources and writing of review and editing. Christine Bastin played equal role in funding acquisition, project administration and writing of review and editing. Fabienne Collette played lead role in writing of original draft and writing of review and editing, supporting role in visualization and equal role in conceptualization, funding acquisition, methodology, project administration, supervision and validation. Gilles Vandewalle played lead role in formal analysis, methodology, writing of original draft and writing of review and editing and equal role in conceptualization, funding acquisition, project administration and supervision.

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cortical excitability concomitantly assessed using TMS-EEG. ***Next Steps:*** Future studies should assess whether effort variation is an useful measure for early diagnosis of Alzheimer's disease.

Keywords: aging, effort, wake extension, cognitive performance

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Stable cognitive efficiency across the day–night cycle is regulated through interactions between sleep homeostasis, keeping track of time awake, and the circadian system, organizing physiology over the 24 hr day/night cycle (Dijk & Czeisler, 1995; Schmidt et al., 2012). Under normal sleep condition, the circadian signal counteracts the homeostatic build-up of sleep need during the day to maintain relatively stable cognitive performance up to the next sleep episode. Any disruption of this fine-tuned interplay is detrimental to performance (Lo et al., 2012; Schmidt et al., 2012). If wakefulness is extended into the biological night, performance sharply decreases because the circadian signal turns into a sleep-promoting signal while sleep pressure is high (Dijk & Czeisler, 1995). Likewise, chronic sleep loss leads to performance decrement over the course of a normal waking day (Lo et al., 2012; Schmidt et al., 2012).

Healthy aging is characterized by marked changes in cognitive functioning. These changes are however variable across individuals with some older people showing performance very close to or similar to younger individuals (Hale et al., 1988; Hultsch et al., 2002; Nyberg et al., 2012). Healthy aging is also associated to important changes in the regulation of sleep and wakefulness (Craik & Salthouse, 2008; Dijk et al., 1999; Klerman & Dijk, 2008; Schmidt et al., 2012; Van Cauter et al., 2000). Sleep quality decreases in aging, while the build-up of sleep need (Landolt et al., 2012; Schmidt et al., 2012) and the strength of the circadian signal (Dijk et al., 1999; Kondratova & Kondratov, 2012; Münch et al., 2005) also appear to be dampened as one gets older. This results in a more stable cognitive performance in older individuals during sleep deprivation: despite a potentially lower performance during the well-rested day, the decrease in performance detected if wakefulness is extended into the night is reduced in older than younger individuals (Landolt et al., 2012; Sagaspe et al., 2012; Schmidt et al., 2012).

The negative effect of sleep loss on performance spans across multiple cognitive domains (Lim & Dinges, 2010; Pilcher & Huffcutt, 1996) with larger deficits observed on alertness and sustained attention and smaller and less consistent deficits on executive functions or other complex tasks including memory tasks (Lim & Dinges, 2010; Lowe et al., 2017). When investigating the effect of sleep deprivation on specific processes within the same task, (Tucker et al., 2010) observed that the executive components of working memory scanning efficiency, resistance to proactive interference, and switching between phonemic clusters were not significantly degraded by sleep deprivation, contrary to nonexecutive ones. These results suggest that the effect of prolonged wakefulness is more detrimental for the automatic aspects of cognition. Critically, the largest effects of insufficient sleep during prolonged wakefulness are detected over subjective domains, such as motivation, fatigue, or effort perception (Lo et al., 2012; Odle-Dusseau et al., 2010; Pilcher & Huffcutt, 1996). This may be particularly important because subjective dimensions, such as motivation, can mitigate or amplify the negative effect of insufficient sleep on cognitive performance, particularly when wakefulness is extended beyond habitual sleep time (Hull et al., 2003).

Effort is considered as a regulator of the cognitive workload level used to perform a task depending on its specific characteristics (e.g., task difficulty, duration) and individual processing capacity (Kool & Botvinick, 2018; Shenhav et al., 2017). Effort is also tightly associated with motivation and fatigue. For instance, cognitive fatigue may appear when motivation is impaired and effort increases, leading to performance decrement and attentional impairment (Boksem & Tops, 2008; Hopstaken et al., 2015). Yet, whether effort varies during prolonged wakefulness and how it relates to cognitive performance is not established. Based on theories on the management of cognitive fatigue (Hockey, 1997, 2011, 2013), Massar, Lim, and Huettel (2019) discussed an integrated framework in which sleep-related performance decrement may result from a voluntary decision to withdraw effort. Indeed, performance goals that may be readily attained by exploiting lower-level noncostly processes under normal conditions need a compensatory effort that may be experienced as a strain under sleep deprivation. Active monitoring systems would control how much effort would be allocated to performance maintenance, depending on the felt strain, and the goal value (i.e., motivation related to the importance of task).

While brain mechanisms underlining subjective affect changes during prolonged wakefulness have been partially elucidated (Minkel et al., 2012; Mullin et al., 2013; Venkatraman et al., 2007; Yoo et al., 2007), the brain mechanisms underpinning the link between effort and cognitive performance during prolonged wakefulness are not established (Massar, Lim, Sasmita, et al., 2019). Likewise, how the brain creates the effort signal and manages effort involvement according to motivation and task goals is still debated. Neuroimaging research has indicated the role of the ventral striatum and ventromedial prefrontal cortex for the valuation of effort and reward (see Massar, Lim, & Huettel, 2019). The dorsal anterior cingulate cortex (dACC) was ascribed a role in the implementation of a general signal that is necessary to energize many effortful cognitive control actions (Holroyd & Yeung, 2012) and to integrate the internal estimates of values and effort costs to determine whether or not to allocate effort to an action (Shenhav et al., 2017; Verguts et al., 2015). In agreement with these proposals, Chong et al. (2017) observed that making choices about different cognitive or physical tasks involving effort is associated to brain activity in the dorsolateral prefrontal cortex, anterior insula, dorsal anterior cingulate, and dorsomedial prefrontal cortex.

Only few studies focused on how aging is associated to changes in effort perception and whether inefficient effort management is related to a risk of cognitive decline. Devine et al. (2021) observed that older adults seem to modulate effort investment over time differently from young adults and adolescents, with an expended effort to accumulate reward as quickly as possible. Oren et al. (2019) reported that the performance of demanding cognitive tasks led to subsequent changes in functional connectivity between anterior and posterior parts of the

hippocampus and that these changes predict cognitive decline at a 2-year follow-up.

To address the issue of effort management in healthy aging, we investigated the variation of perceived effort during 20 hr of continuous wakefulness under strictly controlled conditions in a large sample ($N = 99$) of healthy late-middle-aged adults (50–70 years), following 7 days of regular sleep and wake times, and baseline night of sleep in the laboratory. We capitalized on existing data from the data set Cognitive fitness in aging (COFITAGE), devoted to the identification of biological, sleep, and lifestyle characteristic influencing cognitive changes in healthy aging. We assessed subjective effort, together with sleepiness, fatigue, and motivation, and objective performance measures during tasks probing sustained attention, inhibition, and working memory. Because our results indicated that aging was not linearly associated with effort and performance, we further explored how aging in the 6th and 7th decades would modulate effort and its association with cognition. We hypothesized that effort would rise during wakefulness extension, particularly in the younger individuals of our sample that are more sensitive to sleep homeostasis and circadian signal. We further anticipated that effort would mitigate the effect of lack of sleep and would, therefore, be associated with better performance during the night.

Finally, to explore some of the potential brain mechanism underlying effort regulation, we assessed cortical excitability using transcranial magnetic stimulations coupled to an electroencephalogram (TMS-EEG) apparatus. Cortical excitability can be defined as the strength of the response of cortical neurons to a given stimulation. It reflects neuron reactivity and response specificity and is, therefore, a fundamental aspect of human brain function that contribute to cognition and behavior (Ly et al., 2016). Since cortical excitability varies with time awake and circadian phase, is related to subjective dimension such as motivation (Ly et al., 2016) and changes in aging (Gaggioni et al., 2019), we further explored whether variations in effort would be related to changes in cortical excitability during prolonged wakefulness.

Method

Participants

101 healthy participants aged 50–70 years (68 women; $M \pm SD = 59.4 \pm 5.3$ years) were enrolled between June 15, 2016, and October 2, 2019 for a multimodal cross-sectional study taking place at the GIGA-Cyclotron Research Centre/In Vivo Imaging of the University of Liège (COFITAGE—study; EudraCT: 2016-001436-35. The current list of publications streaming from this data set is provided in Supplemental Material). They gave their written informed consent and received financial compensation. This research was approved by the ethical committee of the Faculty of Medicine at the University of Liège, Belgium.

Exclusion criteria were as follows: body mass index (BMI) < 18 and > 29; smoking; excessive alcohol consumption (>15 units/week); excessive caffeine consumption (>6 cups/day, two subjects were unintentionally included while drinking 6.5 and 9 cups/day respectively); clinical symptoms of cognitive impairment; Dementia Rating Scale < 130 (Mattis, 1988) and Mini-Mental State Examination ≤ 27 (Folstein et al., 1975); recent severe brain trauma; shift work in the past 6 months; transmeridian travel in the past 2 months; high levels of anxiety (21-item self-rated Beck Anxiety Inventory ≥ 17; Beck, Epstein, et al., 1988) and depression (21-item self-rated Beck Depression Inventory ≥ 17; Beck, Steer, & Carbin, 1988); recent psychiatry history; chronic medication affecting the central nervous system (stable treatment for more than 6 months for hypertension or hypothyroidism were included). Participants with sleep apnea (apnea–hypopnea index ≥ 15/hr) were screened and excluded during an in-lab screening night of polysomnography. One study participant was excluded due to missing melatonin assay value at the time of completing the analyses and another for undosable melatonin in saliva samples. Demographic characteristics of the final 99 participants are shown in Table 1.

Wake Extension Protocol

All procedures were previously reported (first in; Van Egroo et al., 2019). After one week of regular sleep–wake schedule verified by using wrist actigraphy (Actiwatch, Cambridge Neurotechnology,

Table 1
Sample Characteristics (M ± SD [Ranges])

Sample characteristic	$N = 99$
Sex (female/male)	66/33
Age (years)	59.4 ± 5.3 [50–69]
Education (years)	15.2 ± 3.0 [9–25]
Right-handed	86
Ethnicity	Caucasian
Dementia Rating Scale	142.1 ± 2.3 [134–144]
Raven's progressive matrices	51.1 ± 5.0 [32–59]
Mill Hill Vocabulary Scale	26.9 ± 3.6 [12–32]
Body mass index (kg/m^2)	24.7 ± 2.9 [18–29]
Anxiety	2.9 ± 3.2 [0–17]
Mood (depression)	5.3 ± 4.4 [0–17]
Caffeine (cups/day)	2.8 ± 1.7 [0–9][a]
Alcohol (doses/week)	3.5 ± 3.7 [0–15]
Treated for hypertension (stable > 6 months)	9
Treated for hypothyroidism (stable > 6 months)	20
Systolic blood pressure (mmHg)	119.97 ± 13.07 [92–165]
Diastolic blood pressure (mmHg)	74.69 ± 9.64 [60–102]
Sleep quality	4.8 ± 2.8 [0–13]
Daytime sleepiness	5.9 ± 4.0 [0–16]
Chronotype	53.5 ± 7.8 [31–67]
Clock time of dim light melatonin onset (hh:min)	20:15 ± 00:59 [18:10–22:40]
In-lab baseline sleep duration (hh:min, EEG)	08:02 ± 0:40 [6.5–9.5]
In-lab baseline sleep efficiency, including N1 stage (%, EEG)	82.9 ± 9.6 [54–96]
Baseline sleep time (hh:min)	20:54 ± 00:37 [21:25–1:00]
Baseline wake time (hh:min)	06:56 ± 00:45 [5:30–9:15]

Note. Anxiety was measured by the 21-item Beck Anxiety Inventory (Beck, Epstein, et al., 1988); mood by the 21-item Beck Depression Inventory-II (Beck, Epstein, et al., 1988); caffeine and alcohol consumption by self-reported questionnaires; sleep quality by the Pittsburgh Sleep Quality Index (Buysse et al., 1989); daytime sleepiness by the Epworth Sleepiness Scale (Johns, 1993); chronotype by the Horne–Östberg questionnaire (average value correspond to intermediate chronotype, no participants were extreme chronotypes, i.e., scores < 30 or > 70; Horne & Ostberg, 1976). Systolic and diastolic blood pressures were measured in bed after laying down for > 15 min and 1–2 hr prior to bedtime. Dim light melatonin onset was computed as described in the next sections. EEG = electroencephalography.
[a] Two subjects were unintentionally included while drinking 6.5 and 9 cups/day respectively.

U.K.) and sleep diaries, participants arrived at the lab 6 hr before usual bedtime. They were then placed in dim light ~6.5 hr before bedtime, had a light meal in the evening before sleeping the night in the laboratory under an electroencephalogram. The 20-hr wake extension protocol was initiated upon awakening which represents a moderate wakefulness extension challenge. After a light standardized breakfast and a shower, a transcranial magnetic stimulation (TMS) compatible EEG cap was placed and participants were kept under strictly controlled constant conditions (dim light < 5 lux; temperature around 19°; in-bed semi-recumbent position except for bathroom visits in scheduled time range; soundproofed rooms; no time information; regular isocaloric food intake; Duffy & Dijk, 2002).

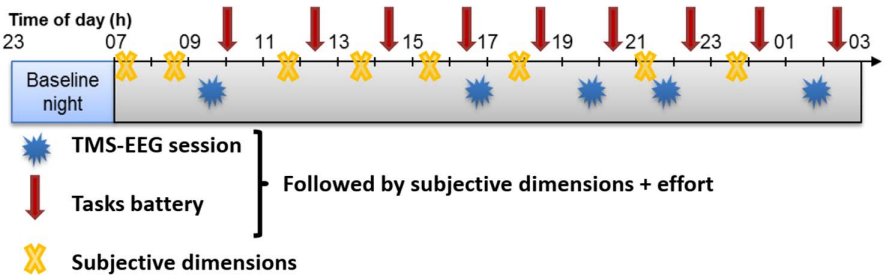
Saliva was collected hourly to assay melatonin concentration and detect the nocturnal initiation of its secretion, which is considered as a gold standard mean to assess the circadian phase (Duffy & Dijk, 2002). Melatonin assays consisted in radioimmunoassay (Department of Clinical Chemistry, Liège, Belgium), as previously described (English et al., 1993) with a limit of detection of the assay for melatonin at 0.8 ± 0.2 pg/ml using 500 µL volumes. Every 2 hr, participants had to complete a test battery on a laptop. Nine test batteries and five TMS-EEG sessions were completed over the wake extension protocol. The timing of the TMS-EEG sessions was set to increase session frequency around the so-called evening wake-maintenance zone, which corresponds to the time at which the circadian system maximally promotes wakefulness and opposes sleep need (Strogatz et al., 1987). After each test battery and TMS-EEG sessions, they had to fill in visual analogue scales (VAS) about subjective metrics including effort. They also had to fill in these scales (excluding effort) eight more times between batteries and TMS-EEG sessions so that subjective dimensions were assessed approximately every hour (Figure 1). Note that participants were not informed neither about the number of test batteries, saliva samples, and so forth nor about the exact duration of the wake extension protocol to avoid interference from motivational biases on wake-dependent effects on measurements (Hull et al., 2003).

Cognitive Test Batteries and VAS

A training session was completed upon arrival in the lab to ensure participants had correctly understood all task instructions. Test batteries of the wake extension protocol included four tasks, always in the same order. The first task was a visual Sustained Attention to Response Task (SART) where participants had to press; the right keyboard arrow when the number "4" was pseudorandomly appearing on the screen and the left one for any other numbers from 0 to 9 (228 items; ~10% of hits; item display duration: 250 ms; interstimulus interval [ISI]: 1,000 ms, task duration: 4 min 45 s). The task evaluates motor inhibition and attention (Sagaspe et al., 2012). Participants then completed the two-back and the three-back versions of a visual n-back task. Participants were instructed to state whether or not the current letter was identical to the consonant presented two and three stimuli earlier, respectively for the two-back and three-back tasks (60 items; 30% of hits; ISI: 2000 ms, task duration: 2 min 30 s). Both focus on a continuous update of information in working memory with a higher memory load in the 3-back task (Lo et al., 2012). Finally, a visual Psychomotor Vigilance Task (PVT), which probes sustained attention (Basner & Dinges, 2011), was completed. It requires pressing a computer space bar as soon as a chronometer pseudorandomly starts on the screen (~50 items; random interval of 2–10 s, task duration: 5 min). Test batteries ended with subjective assessments.

Subjective sleepiness was evaluated using a computerized version of the 9-point Karolinska Sleepiness Scale (KSS; Åkerstedt & Gillberg, 1990). VAS followed KSS assessments and included the following subjective dimensions: fatigue, motivation, joy, sociability, stress, and anguish, plus effort only when following test batteries or TMS-EEG session. VAS scores are expressed in arbitrary units representing the deviation to the left (negative value, up to −5) or to the right (positive value, up to +5) of a cursor which was initially centred. Specifically, the effort represents a subjective metric answering the question "did it take you a lot of effort to complete the previous tasks/TMS recording" (from left: less effort, to right: more effort).

Figure 1
Wake Extension Protocol



Note. Following baseline sleep under EEG, participants completed nine tasks batteries approximatively every 2 hr and five TMS-EEG sessions. Measures of effort and other subjective metrics were collected after each task battery and TMS-EEG session. Subjective dimensions excluding effort were also collected eight times in between batteries and TMS-EEG sessions. The protocol was conducted under strictly controlled constant routine conditions (dim light < 5 lux; temperature ~19°; in-bed semirecumbent position; soundproofed rooms; no time information; regular isocaloric food intake). EEG = electroencephalography. TMS-EEG = transcranial magnetic stimulation coupled to electroencephalography. See the online article for the color version of this figure.

TMS-EEG Sessions

All TMS-EEG procedures are as described in Van Egroo et al. (2019). A "pretest" TMS-EEG session was performed prior to the wake extension protocol to determine optimal stimulation parameters (i.e., location, orientation, and intensity) that allowed for EEG recordings free of muscular and magnetic artifacts. As in previous experiments (Gaggioni et al., 2019; Huber et al., 2013; Ly et al., 2016), the target location was in the superior frontal gyrus due to its sensibility to changes in sleep pressure and circadian phase (Huber et al., 2013; Ly et al., 2016), the reduced probability to elicit involuntary reaction such as muscular twitches or eye blinks when stimulated. For all TMS-EEG recordings, pulses were generated by a Focal Bipulse 8-Coil (Nexstim, Helsinki, Finland). ISIs were randomized between 1,900 and 2,200 ms. TMS-evoked responses were recorded with a 60-channel TMS-compatible EEG amplifier (Eximia, Helsinki, Finland), equipped with a proprietary sample-and-hold circuit which provides TMS artifact-free data from 5 ms poststimulation. Electrooculogram was recorded with two additional bipolar electrodes. EEG signal was band-pass filtered between 0.1 and 500 Hz and sampled at 1,450 Hz. Before each recording session, electrode impedance was set below 5 kΩ. Each TMS-EEG session included ˜250 single-pulse TMS ($M = 252 \pm 15$) with the same ISIs as for pretests. Auditory EEG potentials evoked by the TMS clicks and bone conductance were minimized by diffusing a continuous white noise through earphones and applying a thin foam layer between the EEG cap and the TMS coil. A sham session, consisting in 30 TMS pulses delivered parallel to the scalp with noise masking, was administered to verify the absence of auditory EEG potentials after at least one TMS-EEG session. Absence of auditory responses was confirmed in all participants. TMS-EEG data were preprocessed as previously described (Van Egroo et al., 2019) in SPM12 implemented in MATLAB2013a (The Mathworks Inc., Natick, MA). In brief, TMS-EEG data underwent semiautomatic artifacts rejection, low-pass filtering at 80 Hz, downsampling to 1,000 Hz, high-pass filtering at 1 Hz, splitting into epochs spanning −101 and 300 ms around TMS pulses, baseline correction (from −101 to −1 ms pre-TMS), and robust averaging. As described in Van Egroo et al. (2019), the actual stimulation site and the position of the EEG cap varied from subject to subject (due to head size and morphology, placement of the EEG cap, signal quality). In addition, the electrode signal could be of low quality at the closest location from the stimulation site. A full description of stimulation site variation is provided in Van Egroo et al. (2019). Cortical excitability was computed as the slope at the inflexion point of the first component of the TMS-evoked EEG potential on the electrode closest to the stimulation hotspot (in μV/ms). The electrode considered was constant across all sessions of the same volunteer.

Data Analysis and Statistics

To express time according to the internal circadian phase, which was meant to be the same for all aspects of the project in all subjects, rather than clock time, which varied across subjects depending to habitual sleep–wake schedule, all data were realigned with respect to the onset of melatonin secretion—dim light melatonin onset (DLMO)—, considered as a gold standard assessment of circadian phase (Duffy & Dijk, 2002). DLMO was determined based on assays in saliva using the hockey stick method, with ascending level set to 2.3 pg/ml (Hockey-Stick software V1.5) (Danilenko et al., 2014). The circadian phases of each test battery, TMS-EEG sessions, and KSS/VAS assessments were inferred from individual DLMO time (i.e., phase 0°; 15° = 1 hr). Results of cognitive tests and subjective assessments (including effort) were then resampled following linear interpolation at the planned/theoretical phases of test batteries (−140°, −110°, −80°, −50°, −20°, 10°, 40°, 70°, 100°). The same procedure was carried out for cortical excitability and subjective assessments—including effort—for planned/theoretical phases of TMS-EEG sessions (−145°, −60°, 0°, 30°,80°). Hourly subjective assessments—excluding effort—were resampled at the planned/theoretical hourly phases (−190°, −175°, −160°, −145°, −130°, −115°, −100°, −85°, −70°, −55°, −40°, −25°, −10°, 5°, 20°, 35°, 50°, 65°, 80°, 95°, 110°). Importantly, a constant routine approach is meant to unmask in part any circadian influence (Duffy & Dijk, 2002). One cannot, however, separate the effect of time spent awake and circadian phase, as any change with time spent awake will reflect their dual influences.

Performance to the PVT was inferred from the number of lapses (> 500 ms) and mean reaction time (mRT) following removal of anticipation (< 100 ms), lapses, and error (> 3,000 ms). Fast and slow RT were also computed for supplementary results as the 10% fastest and slowest RT, respectively, following the removal of anticipation and lapses. For the 2-back, 3-back, and SART, we used the D-prime (d') score to characterize performance to the task. d' takes into account hit and false alarm and thus represents a response discriminability index; that is, a measure of sensitivity, following the signal detection theory (Ingleby, 1967), with higher d' values meaning better performance.

Two subjects did not follow task instructions and were removed from the analyses. A few subjects had missing data due to technical issues. For each circadian phase, data that laid > 3 *SD* were considered as outliers (< 25 measures were removed per measure of interest, <3% of data). For each circadian phase, data that laid > 3 *SD* were considered as outliers (< 25 measures were removed per measure of interest, <3% of data). For the 3-back task, circadian phase 100° presented too many invalid/missing values (>25%) and was excluded from statistical analyses. The number of subjects included in each model is reported in the result tables.

Statistical analyses were performed using generalized linear mixed models (GLMMs) in SAS 9.4 (SAS Institute, Cary, NC, USA). Dependent variable distribution was first determined and GLMMs were adjusted accordingly. All GLMMs were adjusted for demographic variables of age, sex, and education. Subject (intercept) was included as a random factor. Circadian phase was included as a repeated measure together with an autoregressive estimation of autocorrelation of order 1 [AR (1)]. Degrees of freedom were estimated using Kenward–Roger's correction. In the search for associations between effort and other metrics, we included triple interactions between circadian phase, age, and the metric of interest. When nonsignificant, the triple interaction was removed from the model to assess separate circadian phase and age by metric of interest interactions. When GLMM yielded a significant interaction with age, the sample was split between subjects aged <60 and ≥60 years (median split) to test for significant differences between the younger and older subsample. This was meant to get a better understanding of the interaction effect. Statistical significance was set at $p < .05$. Semipartial R^2 ($R^2\beta^*$) values were computed to estimate the effect sizes of significant fixed effects and statistical

trends in all GLMMs (Jaeger et al., 2017). Two types of post hoc analyses were used: least square means (LS MEANS) procedure for simple contrasts of phase and ESTIMATE procedure for comparison of phases relative to each other. p values in post hoc contrasts (difference of LS MEANS) were adjusted for multiple testing with Tukey's procedure and t values obtained by ESTIMATE assessment were adjusted for multiple analyses with Sidak's procedure.

Optimal sensitivity and power analyses in GLMM remain under investigation (e.g., Kain et al., 2015). We nevertheless computed an a priori sensitivity analysis to get an indication of the minimum detectable effect size in our main analyses given our sample size. According to G*Power 3 (Version 3.1.9.4; Faul et al., 2009) taking into account a power of .8, an error rate α of .05, a sample size of 101 allowed us to detect small effect sizes $r > .29$ (2-sided; absolute values; 95% confidence interval: .1–.46; $R^2 > .08$, R^2 95% confidence interval: .01–.21) within a linear multiple regression framework including five covariates (effort, phase, age, sex, education).

Transparency and Openness

We report how we determined effect sizes associated to the sample, all data exclusions, all manipulations, and all measures in the study, and we follow journal article reporting standards (Kazak, 2018). All data, analysis code, and research materials are available upon request at the address email of the corresponding authors. Behavioral measures of interest were extracted using Matlab R2019 (Mathworks, Natick, MA) while EEG-TMS data were analyzed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Statistical analyses were computed using S.A.S, Version 9.4 (SAS Institute, Cary, NC, USA) and the package *proc glimmix*. This study's design and its analysis were not preregistered.

Results

Age-Related Dampening of the Variation of Effort During Wake Extension Protocol

For all analyses, we expressed time with respect to internal circadian phase, taking the onset of melatonin secretion as a gold standard mean to detect the anchor circadian phase 0° (Duffy & Dijk, 2002; see Methods). This procedure means that 15° represents 1 hr and that phase can be either negative or positive, if an event of the protocol was occurring before or after circadian phase 0°, respectively. Importantly, although, constant routine protocol unmasks in part any circadian influence, any changes we report arise from the dual influence of the increase in sleep need and of the circadian system.

We first investigated the variation of effort during wakefulness extension. To address this issue, we used effort values resampled according to tasks battery theoretical phases (−140°, −110°, −80°, −50°, −20°, 10°, 40°, 70°, and 100°; the same procedure was applied to all analyses, see Methods). A GLMM including age, sex, and education as covariates revealed a main effect of circadian phase; $F(8, 723.4) = 13.25$, $p < .0001$, $R^2\beta^* = 0.13$; Figure 2A. Post hoc analyses revealed a global increase of effort from the beginning to the end of the protocol (effort: −140°> −50° to 100°, −110° > −50° to 100°, −80° > −20° to 100°, −50° > 10° to 100°, −20° > 40° to 100°, 10° > 40° to 100°, 40° > 70° to 100°, 70° > 100°; $p < .05$; corrected for multiple tests). Consecutive phases were significantly different starting at 70° denoting a more abrupt change in effort during the biological night.

Interestingly, while the same GLMM did not yield a significant main effect of age; $F(1, 93.75) < 0.0001$, $p = .98$, it revealed that effort variations with circadian phase changed with age, even in our limited age range sample (Circadian Phase × Age interaction; $F(8, 725) = 9.08$, $p < .0001$, $R^2\beta^* = .09$). Post hoc analyses, at p-value threshold uncorrected for multiple comparisons, yielded a significant positive association between effort and age at phase −140°, $t(143.1) = 2.18$, $p = .03$, and a significant negative correlation at phase 100°, $t(179) = -2.15$, $p = .03$; Figure 2C. Additional post hoc contrasts showed that the relation between effort and age was significantly different from the beginning to the end of the protocol (Age × Circadian Phase interaction: −140° > 10° to 100°, −110° > 40° to 100°, −80° > 40° to 100°; $p < .05$; corrected for multiple tests), depicting reduced variations in effort in the older individuals of our sample. To visualize this, we split the sample between the younger (<60 years; $N = 50$) and older (≥ 60 years; $N = 49$) individuals on Figure 2B.

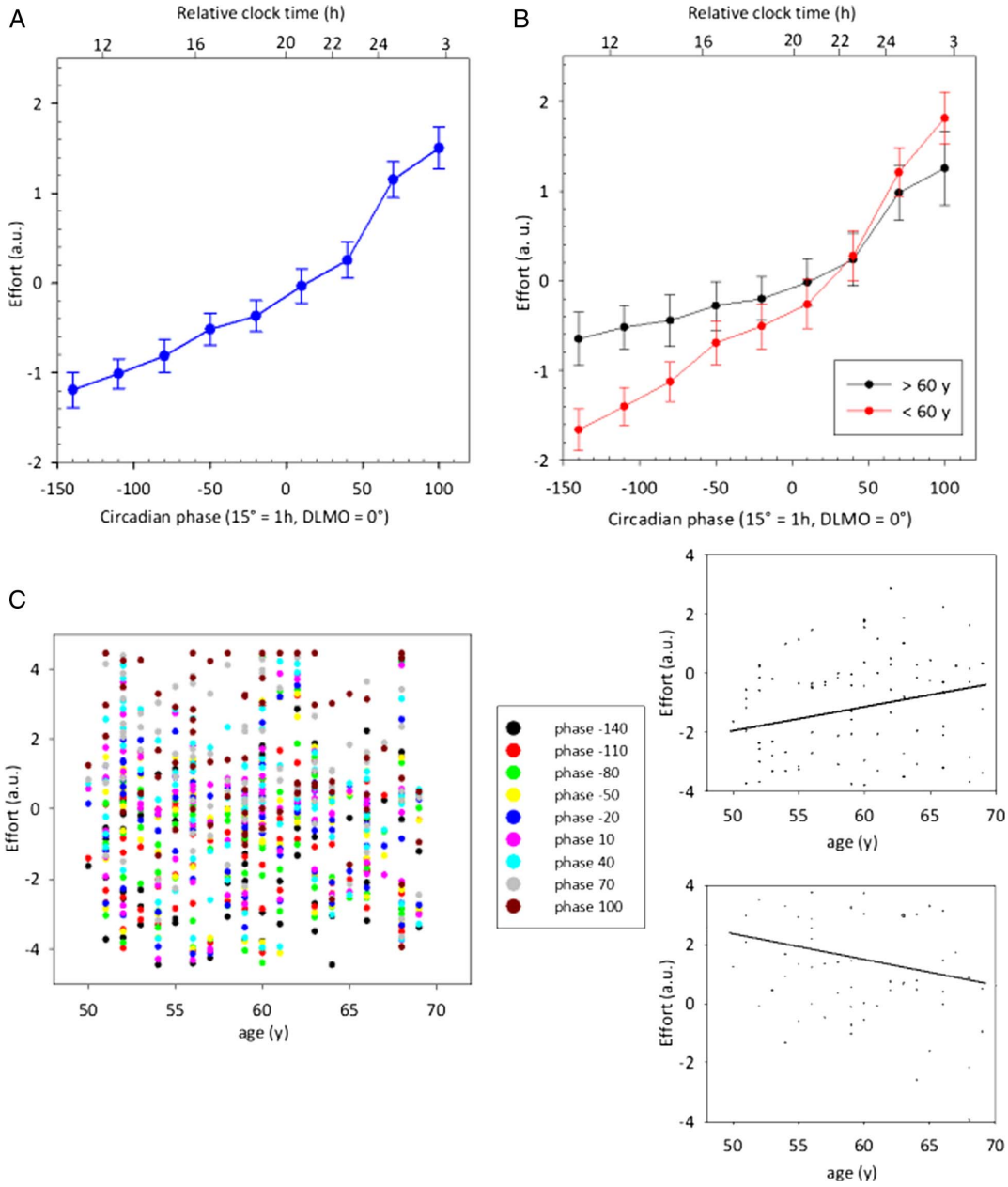
Effort Correlates With Variations in Other Subjective Measures

We then wanted to compare the time course of effort with other subjective metrics. We focused on subjective sleepiness, fatigue, and motivation as they are most related to effort; exploratory results for the other subjective dimensions can be found as Supplemental Information (Supplemental Figure S1; Boksem & Tops, 2008; Hopstaken et al., 2015). All three subjective measures underwent expected significant changes with circadian phase; $F(20, 1876) = 133.07$, $p < .0001$, $R^2\beta^* = 0.59$; fatigue: $F(20, 1877) = 90.23$, $p < .0001$, $R^2\beta^* = 0.49$; motivation: $F(20, 1854) = 20.63$, $p < .0001$, $R^2\beta^* = 0.18$; Figure 3A, D, G. Further analyses revealed that effort was significantly associated with all three measures (Table 2; Figure 3B, E, H) with effort positively associated with sleepiness and fatigue and negatively associated with motivation. A significant interaction between subjective metric and circadian phase was detected for sleepiness and fatigue but not for motivation (Table 2; Figure 3B, E, H). The associations between sleepiness/fatigue and effort are present at almost each circadian phase ($p < .05$ corrected for multiple post hoc tests; except sleepiness at phase −140°, $p < .2$ uncorrected, and fatigue at phase 10° and 40°, $p > .2$), but sleepiness and fatigue were more related to effort with variable magnitude during prolonged wakefulness (many post hoc comparisons between phases are significantly different—not shown).

Importantly, beyond a potential main effect of age, effort was significantly associated with the interaction between subjective metric and age for all three metrics (Table 2). To gain insight in these interaction, we again split the sample between the younger (<60 years; $N = 50$) and older (≥60 years; $N = 49$) individuals (Figure 3C, F, I) of the sample and find that the link between effort and subjective metrics decrease in the older compared to the younger group; Subjective Metric × Group; sleepiness: $F(1, 765.4) = 28.40$, $p < .0001$; fatigue: $F(1, 799.8) = 19.34$, $p < .0001$; motivation: $F(1, 807.7) = 11.43$, $p = .0008$.

Figure 2

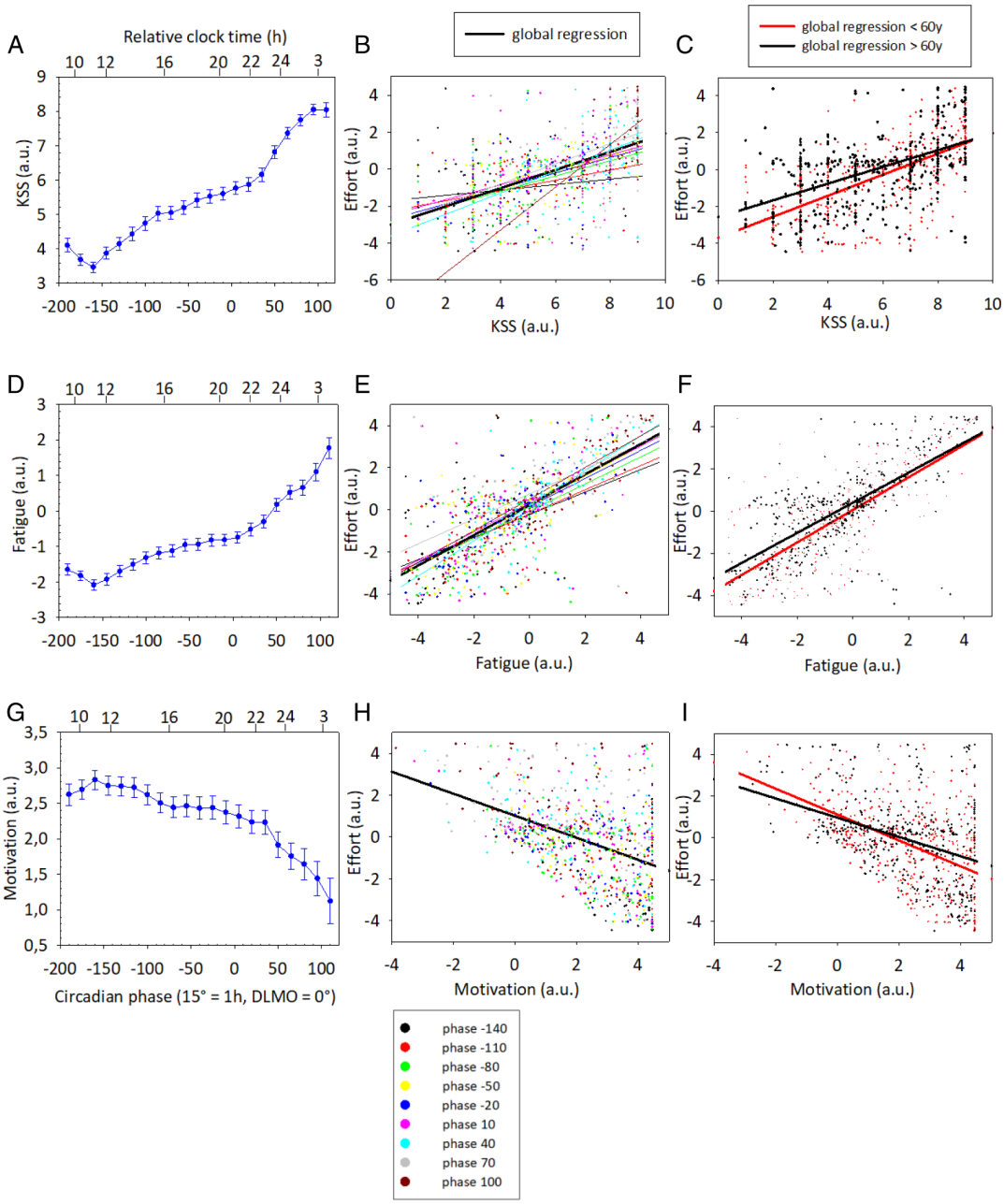
Variations of Effort During the Wake Extension Protocol and Link With Age



Note. Effort time course during 20 hr of prolonged wakefulness of the whole sample $N = 99$ (A) and according to age groups (<60 years or ≥ 60 years) (B). Regressions display of the association between effort and age at phase −140° (top, black) and 100° (bottom, marron) (C). Scatter plot of effort as a function of age over the different circadian phases of the protocol (color according to legend inset). Right insets show significant associations at phase −140° (top) and 100° (bottom). Regressions lines are displayed for illustration purposes of the significant associations yielded by the GLMM and do not substitute GLMM outputs. Effort is reported relative to individual melatonin onset which was used as reference time point for internal circadian phase (i.e., 0°; 15° = 1 hr) and effort assessment is expressed in arbitrary unit (a. u.). GLMM = generalized linear mixed model; DLMO = dim light melatonin onset. See the online article for the color version of this figure.

Figure 3

Association Between Effort and Variations in Other Subjective Measures



Note. Time course of subjective metrics (left panels), relationships with effort in all individuals (middle panels), and in younger (<60 years) and older (≥60 years) individuals of our sample (right panels): sleepiness (A–C), fatigue (D–F), and motivation (G–I). Colors of the dots correspond to the circadian phases of data collection during the 20 hr wake extension protocol as indicated in the inset legend. Regressions in middle panels display the associations between effort and cognitive metrics across all measurements, that is, irrespective of circadian phase (thick black line), when significant, and for each circadian phase (according to legend inset color code) when significant at least for one specific phase. Regressions lines are displayed for illustration purposes of the significant associations yielded by the GLMM and do not substitute GLMM outputs. A significant interaction between subjective metric and circadian phase was also detected for sleepiness and motivation but not for fatigue. All values are reported relative to individual melatonin onset which was used as reference time points for internal circadian phase (i.e., 0°, 15° = 1 hr) and subjective metrics, including effort, are expressed in arbitrary units (a. u.). GLMM = generalized linear mixed model; KSS = Karolinska Sleepiness Scale. See the online article for the color version of this figure.

Table 2
Associations Between Perceived Effort and Other Subjective Measures

Efforts vs. ...	SM	SM × Age	Phase	SM × Phase	Age	Sex	Education
Sleepiness (N = 99)	**F(1, 804.7) = 135.36**	**F(1, 792.2) = 35.39**	**F(8, 731.9) = 14.61**	**F(8, 724.3) = 7.87**	F(8, 180.9) = 18.00	F(1, 93.2)=.06	F(1, 92.1) = 1.61
	p < .0001	**p < .0001**	**p < .0001**	**p < .0001**	p < .0001	p = .81	p = .21
	$R^2\beta^*$ = .08	**$R^2\beta^*$ = .04**	**$R^2\beta^*$ = .025**	**$R^2\beta^*$ = .08**	$R^2\beta^*$ = 0.09		
Fatigue (N = 99)	**F(1, 790.4) = 65.08**	**F(1, 724.3) = 46.06**	**F(8, 765.4) = 2.3**	**F(8, 723.8) = 0.96**	F(1, 92.2) = .01	F(1, 90.7) = .07	F(1, 90.5) = 1.11
	p < .0001	**p < .0001**	**p < .02**	**p = .47**	p = .93	p = .8	p = .3
	$R^2\beta^*$ = .14	**$R^2\beta^*$ = .06**	**$R^2\beta^*$ = .14**				
Motivation (N = 99)	**F(1,804.6) = 14.81**	**F(1, 805.6) = 7.44**	**F(8, 721.6) = 16.32**	**F(8, 718.4) = 2.19**	F(1, 134) = 1.93	F(1, 94.2) = .04	F(1, 92.9) = .8
	p < .0001	**p = .006**	**p < .0001**	**p < .03**	p = .17	p = .85	p = .37
	$R^2\beta^*$ = .02	**$R^2\beta^*$ = .01**	**$R^2\beta^*$ = .15**	**$R^2\beta^*$ = .02**			

Note. Outputs of GLMM using effort measure as dependent variable and SM as independent variable. SM = subjective dimension (i.e., sleepiness, fatigue, or motivation); GLMM = generalized linear mixed model. Significant associations with p-value <.05 are in bold.

Effort Correlates With Some but Not All Cognitive Performance Metrics

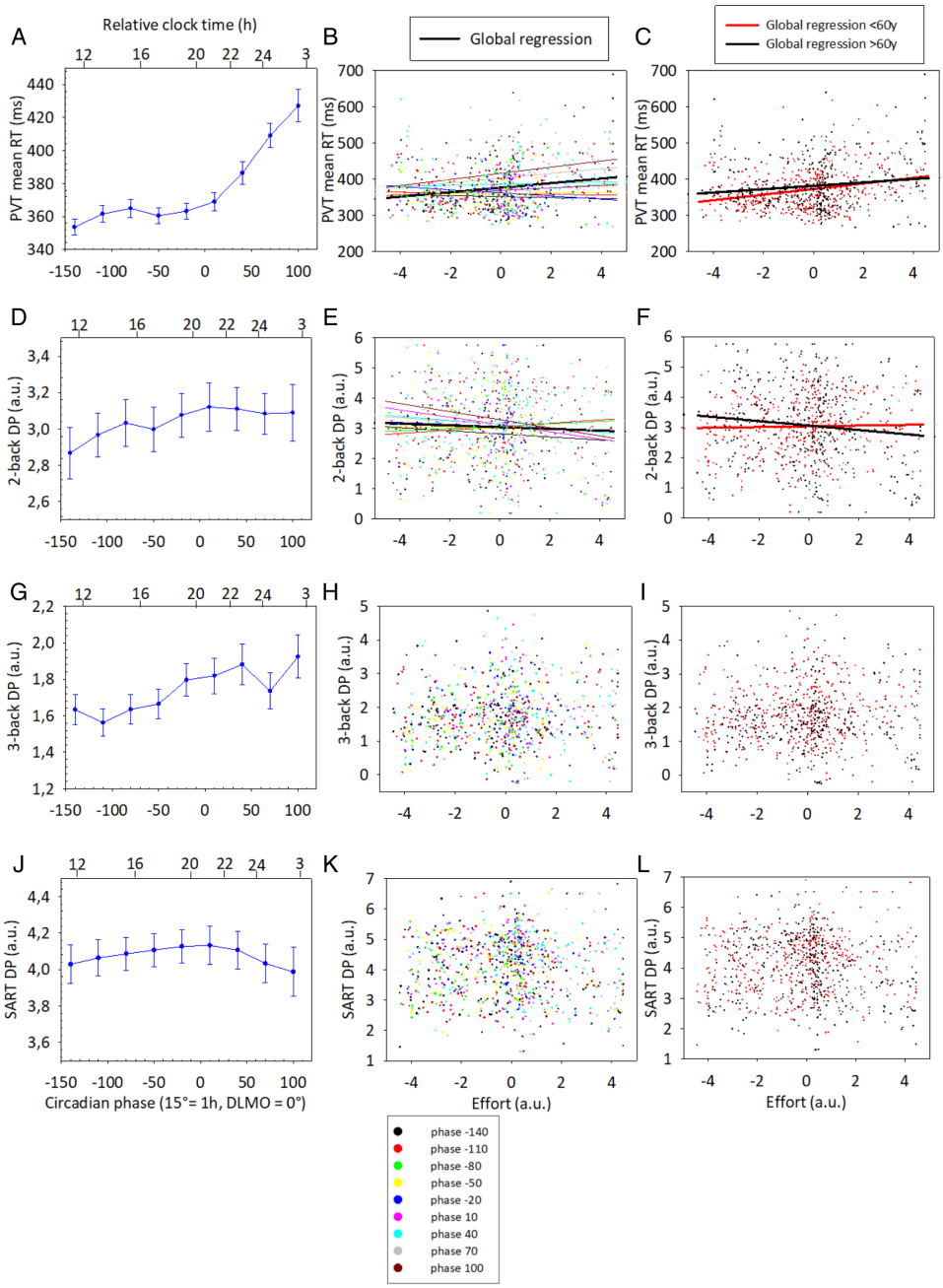
For the PVT, we focused on mRT. Analyses showed that PVT mRT (N = 99) significantly varied throughout the wakefulness extension; GLMM main effect of circadian phase; $F(8, 732.9) = 64.88$, $p < .0001$, $R^2\beta^* = 0.42$; Figure 4A. Post hoc analysis showed that performance worsens during wakefulness extension protocol with biological night measures slower than those collected during biological day (−140° < 10° to 100°, −110° < 40° to 100°, −80° < 40° to 100°, −50° < 40° to 100°, −20° < 40° to 100°, 10° < 40° to 100°, 40° < 70°, 70° < 100°, $p < .05$; corrected for multiple tests). PVT mRT showed a significant triple interaction between circadian phase, age, and effort; Circadian Phase × Age × Effort; mRT: $F(8, 696.1) = 2.47$, $p = .012$, $R^2\beta^* = 0.03$; which we further decomposed in simple interactions and main effects to get a full sense of it (Table 3). PVT mRT were significantly positively associated with effort, that is, more effort associated with slower RT, while the interaction between effort and circadian phase was also significant (Figure 4B; Table 3). Post hoc statistics revealed significant positive associations between effort and PVT mRT at phase 70° and phase 100°, 70°: $t(755.8) = 3.41$, $p = .0062$; 100°: $t(50.94) = 3.32$, $p = .0085$, and differences between phases (Effort × mRT: −140° < 100°, $p < .05$ corrected; 140° < −80° and 10° to 100°, −110° < 70° to 100°, −20° < 70° to 100°, $p < .05$ uncorrected; Figure 4B). These findings denote that more effort was associated with faster mRT, particularly toward the beginning of the protocol. Statistical analyses for other PVT metrics (slow/fast reaction times) can be found as Supplemental Information (Supplemental Figure S2) and lead to similar outputs. Interestingly, PVT lapses (RT > 500 ms) were not associated to effort (Table 3, Supplemental Figure S2).

Critically, while mRT was not significantly associated to age, the analysis yielded a significant interaction between effort and age group (Table 3). When decomposing our sample into the younger (< 60 years; $N = 50$) and older (≥ 60 years; $N = 49$) individuals, we find that more effort is associated with worse performance (i.e., slower mRT) in the older compared the younger group; mRT × Group; $F(1, 765.4) = 28.40$, $p < .0001$; Figure 4C.

Performance to the two-back task, as indexed by d' values, did not vary significantly during protocol, $N = 99$; GLMM main effect of circadian phase; $F(8, 686.5) = 1.74$, $p = .09$; Figure 4D. d' was both significantly related to effort as a main effect and in interaction with circadian phase (Figure 4E, Table 3). Post hoc analyses demonstrated that effort was significantly negatively associated with two-back d' at all phases (−140° to −20° & 70°, $p < .05$, corrected for multiple post hoc tests; 10°, 40°, 100°, $p < .05$ uncorrected) and the association at phase 100° was significantly different from the beginning of the protocol (d': 100° > −140° to −50° and 70°, $p < .05$, corrected for multiple tests; Figure 4E insets). This finding indicates that, except during the last session of the protocol, greater effort was associated with better performance to the two-back task. As for the PVT metric, two-back d' was not significantly associated to age as a main effect, but significantly varied in association with the interaction between effort and age (Table 3). When decomposing our sample into younger (< 60 years; $N = 50$) and older (≥ 60 years; $N = 49$) individuals, we observe that more effort is associated with worse performance (i.e., lower d') in the older group and with better performance (i.e., higher d') in the younger group without reaching

Figure 4

Association Between Effort and Cognitive Performance During the Wake Extension Protocol



Note. Time course of cognitive metrics (left panels) and their relationship with effort according to circadian phase (middle panels) and according to age groups (<60 years or ≥60 years; right panels). PVT mean reaction time –mRT (A–C), 2-back *d′* (D–F), 3-back *d′* (G–I), and SART *d′* (J–L). Regression in middle panels displays the associations between effort and cognitive metrics across all measurements, that is, irrespective of circadian phase (thick black line), when significant, and for each circadian phase (according to legend inset color code) when significant at least for one specific phase. Regressions lines are displayed for illustration purposes of the significant associations yielded by the GLMM and do not substitute GLMM outputs. All values are reported relative to individual melatonin onset, which was used as reference time point for internal circadian phase (i.e., 0°, 15° = 1 hr). Due to insufficient valid data points, circadian 100° for *d′* of three-back task was not included in the statistical analyses reported in the main text. PVT = psychomotor vigilance; GLMM = generalized linear mixed model; RT = reaction time; DP = d prime. See the online article for the color version of this figure.

statistical significance; d' × Group interaction; $F(1, 698.1) = 2.35$, $p = .12$, Figure 4F.

When considering the performance to the three-back task (excluding the last circadian phase of the protocol, see Methods) we find that d' did not significantly change during the protocol, $N = 99$; GLMM main effect of circadian phase; $F(7, 617.4) = 4.38$, $p = .63$; Figure 4G. Furthermore, 3-back d' performance was not associated with effort, both as a main effect of effort or in interaction with circadian phase or age (Table 3; Figure 4H, I). Similarly, performance on the SART, also indexed through d', did not significantly vary throughout the wake extension protocol, $N = 99$; GLMM main effect of circadian phase; $F(8, 739.6) = .55$, $p = .82$; Figure 4J. Again, SART performance was not associated with effort both as a main effect of effort or in interaction with circadian phase or age (Table 3, Figure 4K, L).

No Significant Associations Between Effort and Cortical Excitability

Our final analyses focused on cortical excitability, as indexed by the slope of the first component of the early EEG response to a TMS pulse, as a potential correlate of effort. As previously reported based on part of the current sample (Van Egroo et al., 2019), cortical excitability significantly changed during the protocol; GLMM main effect of circadian phase; $F(4, 372.1) = 6.29$, $p < .0001$, $R^2\beta^* = 0.06$; Figure 5A. Post hoc analyses revealed a cortical excitability decrease between the second and the fourth and last fifth sessions (slope: $-60° > 30°$, $-60° > 80°$, $p < .05$, corrected for multiple tests). We then sought for associations between effort and cortical excitability. No association was detected with cortical excitability; GLMM main effect of cortical excitability; $F(1, 391.2) = 0.04$, $p = .84$; neither with the interaction between cortical excitability and phase; GLMM Cortical Excitability × Phase; $F(4, 362.5) = 0.62$, $p = .65$; nor with the interaction between cortical excitability and age; GLMM Cortical Excitability × Age; $F(4, 391.8) = 0.03$, $p = .85$; Figure 5B, C.

Discussion

In this study, we first aimed to characterize variations of cognitive effort during 20 hr of wakefulness extension in a sample of 99 healthy late-middle-aged individuals aged 50–69 years. Prior reports found an increase in effort with time awake (Odle-Dusseau et al., 2010; Pilcher & Walters, 1997) while others did not find significant changes (Drummond, Meloy, et al., 2005). Our results are in line with the former, as we observe a significant increase in effort, potentially sharper during the biological night. Interestingly, this increase was reduced in the older participants of our sample. Effort increase was also directly correlated with other subjective metrics such as sleepiness and fatigue while it was opposite to motivation, which decreased with time awake in our study sample. Hence, similar to other subjective feelings (Odle-Dusseau et al., 2010), the effort is sensitive to wakefulness extension in individuals aged 50–70 years, particularly for individuals aged < 60 years. We further show that effort increase with time awake is significantly associated with decreased performance to a PVT task and a 2-back task, particularly during the biological night for the latter, while no significant links were detected when considering the 3-back task and SART. Importantly, we observe that the link between PVT and 2-back performance varies according to age, with more effort associated with worse performance in the older versus younger individuals of our sample. Finally, in an exploratory analysis, we find no significant association between effort and cortical excitability.

The sharpness of the increase in effort may appear surprising given the moderate challenge that the 20 hr wakefulness extension represents. Together with the relatively large size of our sample, the fact that we conducted our study under strictly controlled constant routine condition may have unmasked effort variations that could be otherwise hindered by physical activity, posture changes, or ambient light (Duffy & Dijk, 2002). This type of protocol is meant to unmask the influence of the circadian system on physiology and behavior so that circadian changes become more prominent. Any changes in the measures of interest remain, however, the reflection of the dual influence of the build-up of the need for sleep and of the influence of the circadian system. Interestingly, we observe a reduction in effort fluctuation with increasing age despite the limited age range of our sample. Qualitative inspection of the data indicates that effort may be higher at the beginning of the protocol as one gets older while its rise is shallower as wakefulness is extended. This pattern is in line firstly with higher cognitive effort in elderly under normal well-rested conditions to support optimal level of performance compared to younger (Hess & Ennis, 2012). In addition, the reduced effort rise during wakefulness extension is compatible with the previously reported decreases in homeostasic build-up of sleep need and circadian signal variation over the sleep–wake cycle (Landolt et al., 2012; Schmidt et al., 2012). In other words, because older people are less sensitive to the adverse effect of sleep loss, they are likely to exert less effort in an attempt to maintain performance during sleep deprivation. Alternatively, the lower effort could be explained by a potential ceiling effect for further effort enhancement; for example, due to lower brain reserve; (Cabeza et al., 2018). Further studies are needed to test these two interpretations.

Effort, as well as the other subjective dimensions we assessed, is among the first signs of the detrimental effects of wakefulness extension as it decreased early during the protocol. Therefore, the increase in the perceived amount of effort required to perform a certain task would be an alarm signal of the beginning of the effect of sleep deprivation with the impending arrival of performance decline (Odle-Dusseau et al., 2010). We find a direct link between effort and performance to the PVT, which is the only task showing a global decrease in performance during our moderate wake extension challenge, in agreement with a greater impact of sleep loss on attentional processes (Drummond, Bischoff-Grethe, et al., 2005; Lo et al., 2012). Also in line with a reduced impact of sleep need on executive tasks (Lo et al., 2012), performance to the 2-back task remains stable during the protocol. Yet, it was also associated with effort. It is only for the SART and 3-back task which did not show performance decline during the protocol, that no significant link with effort was detected. Performance to the 3-back was, as expected (De Beni & Palladino, 2004; Gaggioni et al., 2019), much poorer than for the 2-back, and that 3-back performance increased with time likely because of a learning bias in those that could overcome the initial difficulty of the task. The low performance at the 3-back in a

Table 3
Associations Between Perceived Effort and Cognitive Performance Metrics

Effort vs. ...	Effort	Effort × Age	Phase	Effort × Phase	Age	Sex[a]	Education
Mean RT (PVT) (N = 99)	**$F(1, 560.3) = 3.94$ $p = .047$ $R^2\beta^* = .01$**	**$F(1, 495.5) = 5.69$ $p = .017$ $R^2\beta^* = .01$**	**$F(8, 714.5) = 23.69$ $p < .0001$ $R^2\beta^* = .14$**	**$F(8, 702.7) = 2.38$ $p = .015$ $R^2\beta^* = .03$**	$F(1, 92.1) = 2.39$ $p = .13$	**$F(1, 92) = 8.59$ $p = .004$ $R^2\beta^* = .08$**	$F(1, 91.9) = .28$ $p = .6$
d' (2-back) (N = 99)	**$F(1, 639.1) = 7.07$ $p = .006$ $R^2\beta^* = .01$**	**$F(1, 594.9) = 8.22$ $p = .004$ $R^2\beta^* = .01$**	$F(8, 693.8) = 1.39$ $p < .2$	**$F(8, 683.3) = 3.10$ $p = .002$ $R^2\beta^* = .04$**	$F(1, 87.6) = .12$ $p = .73$	$F(1, 87.7) < .001$ $p = .95$	**$F(1, 87.7) = 11.79$ $p = .0009$ $R^2\beta^* = .12$**
d' (3-back) (N = 99)	$F(1, 647.2) = .63$ $p = .43$	$F(1, 641.6) = .46$ $p = .49$	$F(7, 613.6) = 1.00$ $p = .44$	$F(7, 603.6) = 1.95$ $p = .06$	**$F(1, 88.6) = 3.97$ $p = .05$ $R^2\beta^* = .04$**	$F(1, 88.1) = 1.26$ $p = .27$	$F(1, 87.4) = 1.31$ $p = .25$
d' (SART) (N = 99)	$F(1, 794.3) = .34$ $p = .56$	$F(1, 777.5) = .33$ $p = .57$	$F(8, 737.3) = .19$ $p = .99$	$F(8, 736.6) = 1.00$ $p = .43$	$F(1, 93.5) = .73$ $p = .39$	**$F(1, 93.2) = 4.73$ $p = .03$ $R^2\beta^* = .05$**	**$F(1, 93.4) = 8.22$ $p = .005$ $R^2\beta^* = .09$**

Note. Performance was set as the dependent variable and effort as independent variable. RT = reaction time; PVT = psychomotor vigilance; SART = Sustained Attention to Response Task. Significant associations with p-value <.05 are in bold.
[a] When significant, main effect of sex corresponds to women having better performance than men.

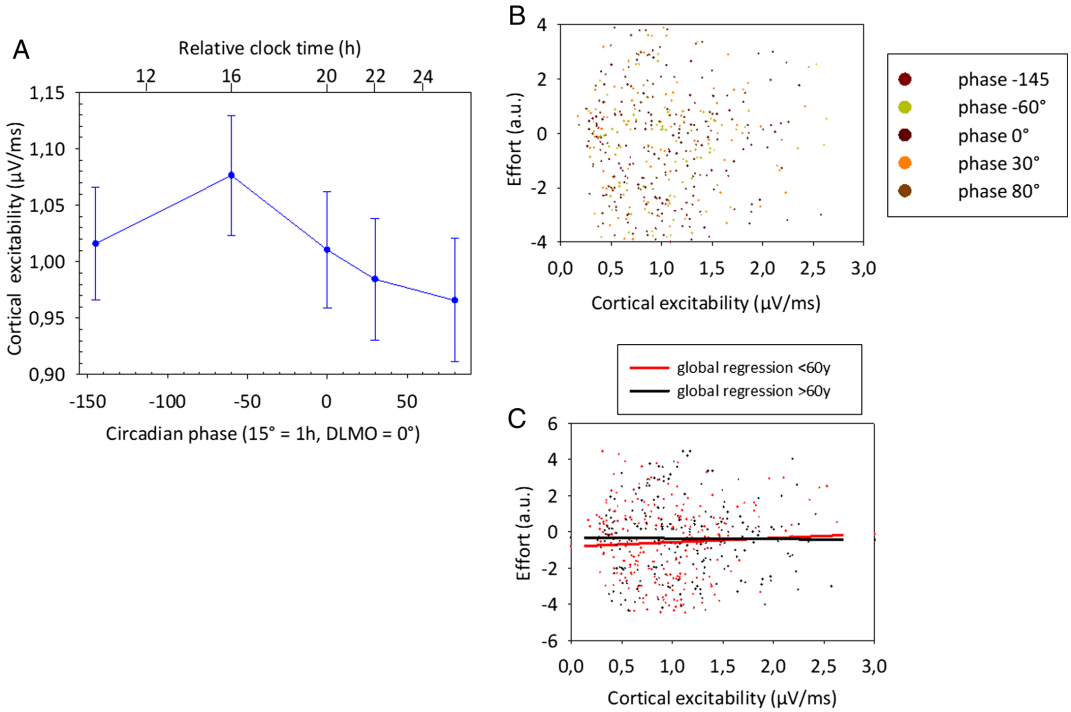
substantial portion of the sample prevented assessing the link between effort and the interaction between the circadian phase and 3-back performance. The absence of performance decrement for the 3-back task during the night could be related to the reduced acute impact of lack of sleep during a night of sleep deprivation for more demanding tasks (Lo et al., 2012). For the SART, we can only speculate that even though performance has been reported to suffer more from sleep loss/circadian misalignment than the 2-back task (Sagaspe et al., 2012), the protocol may not be challenging enough to trigger variation in the task. The metric we used for quantification of performance to the SART (d') may also not be as sensitive as the reaction times we used for the PVT. In the framework of theories on the management of cognitive fatigue (Hockey, 1997, 2011, 2013), the absence of links between effort and performance at the 3-back and SART tasks may also result from a voluntary decision to withdraw effort and try to maintain performance by exploiting low-cost processes, as the motivation may decrease according to the strain that one experience.

Contrary to our hypothesis, we found that more effort is associated with poorer performance to the PVT and 2-back task, at least when instructions are to perform as well as possible in all cases and without particular reward. Our finding could support, as previously described for motivation (Dinges & Kribbs, 1991), that, although it may help to maintain in part performance (Engle-Friedman, 2014; Massar, Lim, Sasmita, et al., 2019; Sanders, 1983; Wilkinson, 1961), more effort expended to perform cognitive task is not sufficient to overcome the performance decline caused by the underlying physiological changes brought by high need for sleep (Pilcher & Walters, 1997). Alternatively, based on our results, one could posit that poorer reduced attentional capacity during sleep loss leads to lower cognitive performance and more effort as wakefulness is extended without direct causal link between effort and performance. Given the high correlation between sleepiness, fatigue, and motivation, other subjective dimensions were associated to cognitive performance during prolonged wakefulness so that we are not in a position to isolate the specific contribution of effort to performance. Reward motivation was for instance reported to partially alleviate sleep deprivation-related performance decline, particularly during the biological night. Interestingly, we also observed that the link between effort and cognitive performance at PVT (mRTs) and 2-back working memory task changes in our older participants (60–69 years), with more effort associated with worse performance change than in younger individuals (50–59 years). As increasing age is also associated with a reduction in effort fluctuation during the wakefulness extension period, it could be proposed that advancing age leaves little opportunity to intentionally recruit additional resources when facing cognitive challenge. Whether the lack of resources has a biological; for example, blood glucose depletion (Gailliot et al., 2007); cognitive; for example, control processes (Shenhav et al., 2017); or motivational; for example, a cost–benefit analysis (Anderson, 1990); origin remains to be determined. Few evidence supports that inefficient effort management is related to a risk of cognitive decline (see however Oren et al., 2019). One could consider that reduction in effort variation and more effort associated with the worst performance in our older participants provides support to this assumption. This hypothesis remains to be tested in longitudinal studies of population at risk for Alzheimer's disease.

In a final step, we explored potential brain bases of effort variations during wakefulness extension. We considered cortical

Figure 5

Association Between Effort and Variations in Cortical Excitability Dynamic



Note. Time course of cortical excitability (A) and its associations with effort (B) and according to age groups (C) during wake extension protocol. Colors of the dots correspond to the circadian phases of data collection during the 20 h wake extension protocol as indicated in the inset legend. Regressions lines are displayed for illustration purposes each age group and do not substitute GLMM outputs. All values are reported relative to individual melatonin onset, which was used as reference time point for internal circadian phase (i.e., 0°, 15° = 1 hr). All values are reported relative to individual melatonin onset (DLMO = 0°; 15° = 1 hr). GLMM = generalized linear mixed model; DLMO = dim light melatonin onset. See the online article for the color version of this figure.

excitability which consists in the reactivity of cortical neurons to a stimulation. It is in direct link with membrane potential and action potential threshold and drives neuronal response selectivity. We previously showed that it was jointly influenced by sleep homeostasis and the circadian signal in healthy young adults so that it showed nonlinear variations during wakefulness extension (Ly et al., 2016). These variations were reduced in individuals aged > 50 years with associations with performance to executive tasks, namely 2-back, 3-back, and SART (Gaggioni et al., 2019). As previously reported in a subset of the present sample (Van Egroo et al., 2019), we found an overall decrease of cortical excitability from the evening to the end of the protocol. Here, we report no association between effort variations and cortical excitability. The latter may be more strongly related to executive functions, undergoing limited changes in aging during wakefulness extension, rather than to attention and subjective dimensions such as effort. Another possibility may be the choice of the target location for TMS stimulation. We selected the superior frontal gyrus due to its sensibility to changes in sleep pressure and circadian phase (Huber et al., 2013; Ly et al., 2016). However, brain areas the most frequently associated to effort signal are the medial prefrontal regions and anterior cingulate cortex (Chong et al., 2017; Holroyd & Yeung, 2012; Massar, Lim, & Huettel, 2019; Shenhav et al., 2017; Verguts et al., 2015). More studies focusing on cortical excitability and other aspects of brain function are needed to establish the brain bases of effort variations as one remains awake during the day and beyond habitual sleep time.

Finally, higher education was associated to better performance on accuracy measures (d') at the 2-back and SART tasks. These results are in the continuity of previous studies discussing education as the main protective factor against dementia (Stern et al., 2020). We also observed an effect of sex on PVT and SART, with a better performance in woman. Previous studies reported an advantage in women, particularly for verbal tasks (for reviews, see Deckers et al., 2019; Lee et al., 2022). Proposed mechanisms to explain sex effect might involve hormonal differences, genetic factors, differences in brain networks, socioeconomic roles, and health choices.

Conclusion

We report that effort is remarkably sensitive to wakefulness extension in late-middle-aged adults (50–70 years), as previously

described for younger individuals and for other subjective dimensions such as sleepiness, fatigue, and motivation (Odle-Dusseau et al., 2010; Pilcher & Walters, 1997). In addition, effort variations dampen as one gets older in line with the global decrease in the sleep–wake regulation signals with age and the acute reduction of performance decline during sleep loss. Effort increment with time awake appears to be insufficient to overcome the marked cognitive performance decline brought by high sleep need, and the association between effort and cognitive performance changes in our older participants. This study suggests that the association between subjective perception of effort and cognitive performance in a challenging condition is sensitive to age. One perspective for future studies should be to assess effort variation during total sleep deprivation (or other challenging conditions) in population at risk for Alzheimer's disease and to assess whether it could be useful as an easy first assessment tool for the prodromal and preclinical diagnosis of the disease.

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