

1 **Effort during prolonged wakefulness is associated with performance to attentional and**
2 **executive tasks but not with cortical excitability in late middle-aged healthy individuals**

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18 **Conflict of interest statement:** the authors have declared that no conflict of interest exists.

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20 **Citation:** Mouraux C., Van Egroo M., Chylinski D., Narbutas J., Phillips C., Salmon E., Maquet P., Bastin C.,

21 **Collette F. ‡, Vandewalle G. ‡ (2022).** Effort during prolonged wakefulness is associated with performance to
22 attentional and executive tasks but not with cortical excitability in late-middle-aged healthy individuals.

23 *Neuropsychology*. 2022 Epub ahead of print. PMID: 36355646.

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26 **Author contributions:** Dr Vandewalle and Dr Collette had full access to all of the data in the study and
27 take responsibility for the integrity of the data and the accuracy of the data analyses.

28 Conceptualization: Drs Collette, Maquet and Vandewalle.

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30 Formal analysis: Mrs. Moureaux and Dr Vandewalle.

31 Funding acquisition: Drs, Phillips, Bastin, Salmon, Maquet, Collette and Vandewalle.

32 Investigation: Drs Van Egroo, Chylinski, Narbutas

33 Methodology: Drs Phillips, Maquet, Collette and Vandewalle

34 Project administration: Drs. Salmon, Maquet, Bastin, Collette and Vandewalle

35 Resources: Drs. Salmon & Maquet

36 Acquisition, analysis, or interpretation of data: all authors.

37 Drafting of the manuscript: Mrs. Moureaux, Dr Collette and Vandewalle.

38 Critical revision of the manuscript for important intellectual content: all authors.

39 Supervision: Dr Vandewalle is the supervisor of Mrs. C. Moureaux.

40

41 **5Funding/Support:** This work was supported by WELBIO/Walloon Excellence in Life Sciences and
42 Biotechnology Grant (WELBIOCR-2010-06E), FNRS-Belgium (FRS-FNRS, F.4513.17 & T.0242.19 &
43 3.4516.11), Fondation Recherche Alzheimer (SAO-FRA 2019/0025, 2020/0026), University of Liège
44 (ULiège), Fondation Simone et Pierre Clerdent, European Regional Development Fund (Radiomed
45 project), Actions de Recherche Concertées (ARC SLEEPDEM 17/27-09) of the Fédération Wallonie-
46 Bruxelles. Mrs Koshmanova, Drs Collette and Vandewalle are supported by the F.R.S.-FNRS Belgium.

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48

49 **Abstract**

50 **Objective.** Sleep-loss negatively affects brain function with repercussion not only on objective
51 measures of performance, but also on many subjective dimensions, including effort perceived for the
52 completion of cognitive processes. This may be particularly important in aging, which is accompanied
53 by important changes in sleep and wakefulness regulation. We aimed to determine whether
54 subjectively perceived effort covaried with cognitive performance in healthy late-middle-aged
55 individuals. **Method.** We assessed effort and performance to cognitive tasks in 99 healthy adults (66
56 women; 50-70y) during a 20-h wake extension protocol, following 7 days of regular sleep and wake
57 times and baseline night of sleep in the laboratory. We further explored links with cortical excitability
58 using transcranial magnetic stimulation coupled to electroencephalography (TMS-EEG). **Results.**
59 Perceived effort increased during wake extension and was highly correlated to subjective metrics of
60 sleepiness, fatigue and motivation, but not to variations in cortical excitability. Moreover, effort
61 increase was associated with decreased performance to some cognitive tasks (psychomotor vigilance
62 [PVT] and 2-back working memory task). Importantly, effort variations during wakefulness extension
63 decreased from age 50 to 70y, while more effort is associated with worse performance in the older
64 individuals. **Conclusion.** In healthy late middle-aged individuals, more effort is perceived to perform
65 cognitive tasks, but it is not sufficient to overcome the performance decline brought by lack of sleep.
66 Entry in the seventh decade may stand as a turning point in the daily variations of perceived effort and
67 its link with cognition.

68

69

70 **Keypoints.**

- 71 • Does perceived effort for completion of cognitive tasks vary with advancing age and how is
72 associated to performance?
- 73 • Increase in perceived effort is associated with cognitive performance, and more effort is
74 associated with worse performance in the older individuals.
- 75 • The daily variations of perceived effort and its link with cognition seems to vary according to
76 age in a healthy late middle-aged population.
- 77 • Changes in effort across the protocol were not associated with changes in cortical excitability
78 concomitantly assessed using TMS-EEG.

79

80 **Keywords:** Aging, effort, wake extension, cognitive performance

81

82 **INTRODUCTION**

83 Stable cognitive efficiency across the day-night cycle is regulated through interactions between sleep
84 homeostasis, keeping track of time awake, and the circadian system, organizing physiology over the
85 24h day/night cycle (Dijk and Czeisler, 1995; Schmidt et al., 2012). Under normal sleep condition, the
86 circadian signal counteracts the homeostatic build-up of sleep need during the day to maintain
87 relatively stable cognitive performance up to the next sleep episode. Any disruption of this fine-tuned
88 interplay is detrimental to performance (Lo et al., 2012; Schmidt et al., 2012). If wakefulness is
89 extended into the biological night, performance sharply decreases because the circadian signal turns
90 into a sleep promoting signal while sleep pressure is high (Dijk and Czeisler, 1995). Likewise, chronic
91 sleep loss leads to performance decrement over the course of a normal waking day (Lo et al., 2012;
92 Schmidt et al., 2012).

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

104 The negative effect of sleep loss on performance spans across multiple cognitive domains (Lim
105 and Dinges, 2010; Pilcher and Huffcutt, 1996) with larger deficits observed on alertness and sustained
106 attention and smaller and less consistent deficits on executive functions or other complex tasks
107 including memory tasks (Lim and Dinges, 2010; Lowe et al., 2017). When investigating the effect of

108 sleep deprivation on specific processes within a same task, (Tucker et al., 2010) observed that the
109 executive components of working memory scanning efficiency, resistance to proactive interference
110 and switching between phonemic clusters were not significantly degraded by sleep deprivation,
111 contrary to non-executive ones. These results suggests that the effect of prolonged wakefulness is
112 more detrimental for the automatic aspects of cognition. Critically, largest effects of insufficient sleep
113 during prolonged wakefulness are detected over subjective domains, such as motivation, fatigue or
114 effort perception (Lo et al., 2012; Odle-Dusseau et al., 2010; Pilcher and Huffcutt, 1996). This may be
115 particularly important because subjective dimensions, such as motivation, can mitigate or amplify the
116 negative effect of insufficient sleep on cognitive performance, particularly when wakefulness is
117 extended beyond habitual sleep time (Hull et al., 2003).

118 Effort is considered as a regulator of the cognitive workload level used to perform a task
119 depending on its specific characteristics (e.g., task difficulty, duration) and on individual processing
120 capacity (Kool and Botvinick, 2018; Shenhav et al., 2017). Effort is also tightly associated with
121 motivation and fatigue. For instance, cognitive fatigue may appear when motivation is impaired and
122 effort increases, leading to performance decrement and attentional impairment (Boksem and Tops,
123 2008; Hopstaken et al., 2015). Yet, whether effort varies during prolonged wakefulness and how it
124 relates to cognitive performance is not established. Based on theories on management of cognitive
125 fatigue (Hockey, 1997, 2011, 2013), Massar et al. (2019a) discussed an integrated framework in which
126 sleep-related performance decrement may result from a voluntary decision to withdraw effort.
127 Indeed, performance goals that may be readily attained by exploiting lower-level non-costly processes
128 under normal conditions need compensatory effort that may be experienced as a strain under sleep
129 deprivation. Active monitoring systems would control how much effort would be allocated to
130 performance maintenance, depending on the felt strain, and the goal value (i.e., motivation related to
131 the importance of task).

132 While brain mechanisms underlining subjective affect changes during prolonged wakefulness
133 have been partially elucidated (Minkel et al., 2012; Mullin et al., 2013; Venkatraman et al., 2007; Yoo

134 et al., 2007), the brain mechanisms underpinning the link between effort and cognitive performance
135 during prolonged wakefulness are not established (Massar et al., 2019b). Likewise, how the brain
136 creates the effort signal and manage effort involvement according to motivation and task goals is still
137 debated. Neuroimaging research has indicated a role of the ventral striatum and ventromedial
138 prefrontal cortex for valuation of effort and reward (see Massar et al., 2019a). The dorsal anterior
139 cingulate cortex (dACC) was ascribed a role in the implementation of a general signal that is necessary
140 to energize many effortful cognitive control actions (Holroyd and Yeung, 2012) and to integrate the
141 internal estimates of values and effort costs to determine whether or not to allocate effort to an action
142 (Shenhav et al., 2017; Verguts et al., 2015). In agreement with these proposals, Chong et al. (2017)
143 observed that making choices about different cognitive or physical tasks involving effort is associated
144 to brain activity in the dorsolateral prefrontal cortex, anterior insula, dorsal anterior cingulate and
145 dorsomedial prefrontal cortex.

146 There is few evidence in the literature on how aging is associated to changes in effort
147 perception and whether inefficient effort management is related to a risk of cognitive decline. Devine
148 et al. (2021) observed that older adults seem to modulate effort investment over time differently from
149 young adults and adolescents, with expended effort to accumulate reward as quickly as possible. Oren
150 et al. (2019) reported that the performance of demanding cognitive tasks led to subsequent changes
151 in functional connectivity between anterior and posterior parts of the hippocampus, and that these
152 changes predict cognitive decline at 2-years follow-up.

153 To address the issue of effort management in healthy aging, we investigated the variation of
154 perceived effort during 20h of continuous wakefulness under strictly controlled conditions in a large
155 sample (N = 99) of healthy late middle-aged adults (50 to 70 y), following 7 days of regular sleep and
156 wake times, and baseline night of sleep in the laboratory. We capitalized on baseline data from the
157 dataset COFITAGE, devoted to the identification of biological, sleep and lifestyle characteristic
158 influencing cognitive changes in healthy aging. We assessed subjective effort, together with sleepiness,
159 fatigue and motivation, and objective performance measures during tasks probing sustained attention,

160 inhibition and working memory. Because our results indicated that aging was not linearly associated
161 with effort and performance, we further explored how aging in the 6th and 7th decade would modulate
162 effort and its association with cognition. We hypothesized that effort would rise during wakefulness
163 extension, particularly in the younger individuals of our sample that are more sensitive to sleep
164 homeostasis and circadian signal. We further anticipated that effort would mitigate the effect of lack
165 of sleep and would therefore be associated with better performance during the night.

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

175

176 **METHODS**

177 **Participants**

178 101 healthy participants aged 50 to 70 y (68 women; mean \pm SD = 59.4 \pm 5.3 y) were enrolled between
179 June 15th 2016 and October 2nd 2019 for a multi-modal cross-sectional study taking place at the GIGA-
180 Cyclotron Research Centre/In Vivo Imaging of the University of Liège (Cognitive fitness in aging –
181 COFITAGE – study; EudraCT: 2016-001436-35. The current list of publications streaming from this
182 dataset is provided in Supplemental Material). They gave their written informed consent and received
183 a financial compensation. This research was approved by the Ethical Committee of the Faculty of
184 Medicine at the University of Liège, Belgium.

185 Exclusion criteria were as follows : Body Mass Index (BMI) < 18 and > 29; smoking; excessive

186 alcohol consumption (>15 units/week); excessive caffeine consumption (>6 cups/day, two subjects
187 were unintentionally included while drinking 6.5 and 9 cups/day respectively); clinical symptoms of
188 cognitive impairment [Dementia Rating Scale < 130 (Mattis, 1988) and Mini Mental State Examination
189 ≤ 27 (Folstein et al., 1975)]; recent severe brain trauma; shift work in the past 6 months ; trans-meridian
190 travel in the past two months; high levels of anxiety (21-item self-rated Beck Anxiety Inventory ≥ 17)
191 (Aaron T Beck et al., 1988) and depression (21-item self-rated Beck Depression Inventory ≥ 17) (Aaron
192 T. Beck et al., 1988); recent psychiatry history; chronic medication affecting the central nervous system
193 (stable treatment for more than 6 months for hypertension or hypothyroidism were included).
194 Participants with sleep apnea (apnea-hypopnea index ≥ 15 /h) were screened and excluded during an
195 in-lab screening night of polysomnography. One study participant was excluded due to missing
196 melatonin assay value at the time of completing the analyses and another for undosable melatonin in
197 saliva samples. Demographic characteristics of the final 99 participants are shown in **Table 1**.

Table 1: Sample characteristics (mean \pm SD [ranges]).

| | N = 99 |
|---|-----------------------------|
| Sex (female/male) | 66/33 |
| Age (y) | 59.4 \pm 5.3 [50-69] |
| Education (y) | 15.2 \pm 3.0 [9-25] |
| Right-handed | 86 |
| Ethnicity | Caucasian |
| Dementia Rating Scale | 142.1 \pm 2.3 [134-144] |
| Raven's Progressive Matrices | 51.1 \pm 5.0 [32-59] |
| Mill Hill Vocabulary Scale | 26.9 \pm 3.6 [12-32] |
| Body Mass Index (kg/m ²) | 24.7 \pm 2.9 [18-29] |
| Anxiety | 2.9 \pm 3.2 [0-17] |
| Mood (depression) | 5.3 \pm 4.4 [0-17] |
| Caffeine (cups/day) | 2.8 \pm 1.7 [0-9]* |
| Alcohol (doses/week) | 3.5 \pm 3.7 [0-15] |
| Treated for hypertension (stable >6 months) | 9 |
| Treated for hypothyroidism (stable >6 months) | 20 |
| Systolic blood pressure (mmHg) | 119.97 \pm 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] |

198
199 Anxiety was measured by the 21-item Beck Anxiety Inventory (Aaron T Beck et al., 1988); mood by
200 the 21-item Beck Depression Inventory II (Aaron T. Beck et al., 1988); caffeine and alcohol
201 consumption by self-reported questionnaires; sleep quality by the Pittsburgh Sleep Quality Index
202 (Buysse et al., 1989); daytime sleepiness by the Epworth Sleepiness Scale (Johns, 1993); chronotype
203 by the Horne-Östberg questionnaire (average value correspond to intermediate chronotype, no
204 participants were extreme chronotypes, *i.e.* scores < 30 or > 70) (Horne and Ostberg, 1976). Systolic
205 and diastolic blood pressures were measured in-bed after laying down for > 15 min and 1 to 2h prior
206 to bedtime. Dim light melatonin onset was computed as described in the next sections.
207 * two subjects were unintentionally included while drinking 6.5 and 9 cups/day respectively

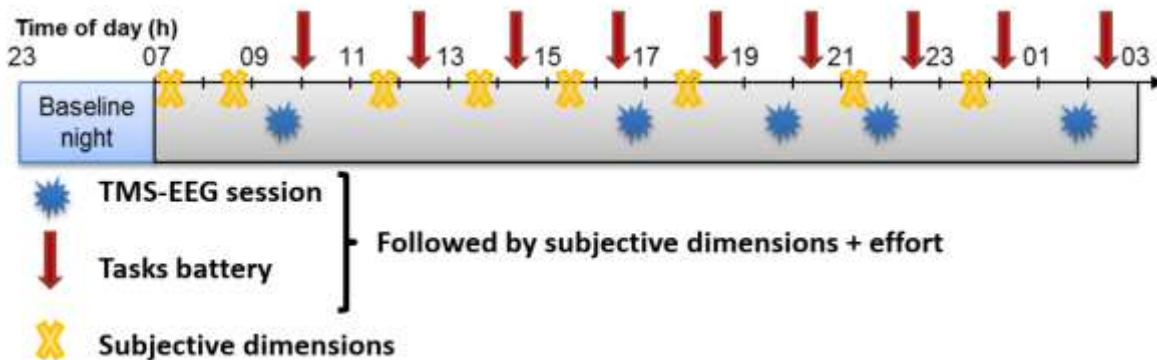
208

209 **Wake-extension protocol**

210 All procedures were previously reported (first in (Van Egroo et al., 2019)). After one week of regular
211 sleep-wake schedule verified by using wrist actigraphy (Actiwatch[®], Cambridge Neurotechnology, UK)
212 and sleep diaries, participants arrived at the lab 6h before usual bedtime. They were then placed in
213 dim light ~6.5h before bedtime, had a light meal in the evening before sleeping the night in the
214 laboratory under electroencephalogram (EEG). The 20-h wake extension protocol was initiated upon
215 awakening which represents a moderate wakefulness extension challenge. After a light standardized
216 breakfast and a shower, a transcranial magnetic stimulation (TMS) compatible EEG cap was placed and
217 participants were kept under strictly controlled constant conditions (dim light < 5 lux; temperature
218 around 19°; in-bed semi-recumbent position except for bathroom visits in scheduled time range;
219 sound-proofed rooms; no time information; regular isocaloric food intake) (Duffy and Dijk, 2002).

220 Saliva was collected hourly to assay melatonin concentration and detect the nocturnal

221 initiation of its secretion, which considered as a gold standard mean to assess circadian phase (Duffy
 222 and Dijk, 2002). Melatonin assays consisted in radioimmunoassay (Department of Clinical Chemistry,
 223 Liège, Belgium), as previously described (English et al., 1993) with limit of detection of the assay for
 224 melatonin at 0.8 ± 0.2 pg/ml using 500 μ L volumes. Every two hours, participants had to complete a
 225 test battery on a laptop. Nine test batteries and 5 TMS-EEG sessions were completed over the wake
 226 extension protocol. The timing of the TMS-EEG sessions was set to increase session frequency around
 227 the so-called evening wake-maintenance zone, which corresponds to the time at which the circadian
 228 system maximally promotes wakefulness and opposes sleep need (Strogatz et al., 1987). After each
 229 test battery and TMS-EEG sessions, they had to fill in visual analogue scales (VAS) about subjective
 230 metrics including effort. They also had to fill in these scales (excluding effort) 8 more times between
 231 batteries and TMS-EEG sessions so that subjective dimensions were assessed approximately every
 232 hour (**Figure 1**). Note that participants were not informed neither about the number of test battery,
 233 saliva samples, etc. nor about the exact duration of the wake-extension protocol to avoid interference
 234 from motivational biases on wake-dependent effects on measurements (Hull et al., 2003).



235

236 **Figure 1: Wake extension protocol.** Following baseline sleep under EEG, participants completed 9 tasks
 237 batteries approximately every 2h and 5 TMS-EEG sessions. Measures of effort and other subjective
 238 metrics were collected after each task battery and TMS-EEG session. Subjective dimensions excluding
 239 effort were also collected 8 times in between batteries and TMS-EEG sessions. The protocol was
 240 conducted under strictly controlled constant routine conditions (dim light < 5 lux; temperature ~19°; in-
 241 bed semi-recumbent position; sound-proofed rooms; no time information; regular isocaloric food
 242 intake).

243

244 **Cognitive test batteries and visual analogue scales**

245 A training session was completed upon arrival in the lab to ensure participants had correctly
246 understood all task instructions. Test batteries of the wake extension protocol included 4 tasks, always
247 in the same order. The first task was a visual Sustained Attention to Response Task (SART) where
248 participants had to press (the right keyboard arrow when the number “4” was pseudo-randomly
249 appearing on the screen and the left one for any other numbers from 0 to 9 (228 items; ~ 10% of hits;
250 item display duration: 250 ms; inter-stimulus interval ISI: 1000 ms, task duration: 4m45s). The task
251 evaluates motor inhibition and attention (Sagaspe et al., 2012). Participants then completed the 2-
252 back and the 3-back versions of a visual n-back task. Participants were instructed to state whether or
253 not the current letter was identical to the consonant presented 2 and 3 stimuli earlier, respectively for
254 the 2-back and 3-back tasks (60 items; 30% of hits; ISI: 2000 ms, task duration: 2m30s). Both focus on
255 continuous update of information in working memory with a higher memory load in the 3-back task
256 (Lo et al., 2012). Finally, a visual Psychomotor Vigilance Task (PVT), which probes sustained attention
257 (Basner and Dinges, 2011), was completed. It requires pressing a computer space bar as soon as a
258 chronometer pseudo-randomly starts on the screen (~50 items; random interval of 2-10 s, task
259 duration: 5m). Test batteries ended with subjective assessments.

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

268

269 **TMS-EEG sessions**

270 All TMS-EEG procedures are as described in (Van Egroo et al., 2019). A “pretest” TMS-EEG session was
271 performed prior to the wake-extension protocol to determine optimal stimulation parameters (*i.e.*
272 location, orientation and intensity) that allowed for EEG recordings free of muscular and magnetic
273 artefacts. As in previous experiments (Gaggioni et al., 2019; Huber et al., 2013; Ly et al., 2016), the
274 target location was in the superior frontal gyrus due to its sensibility to changes in sleep pressure and
275 circadian phase (Huber et al., 2013; Ly et al., 2016), the reduced probability to elicit involuntary
276 reaction such as muscular twitches or eye blinks when stimulated. For all TMS-EEG recordings, pulses
277 were generated by a Focal Bipulse 8-Coil (Nexstim, Helsinki, Finland). Interstimulus intervals were
278 randomized between 1900 and 2200 ms. TMS-evoked responses were recorded with a 60-channel
279 TMS-compatible EEG amplifier (Eximia, Helsinki, Finland), equipped with a proprietary sample-and-
280 hold circuit which provides TMS artefact-free data from 5 ms post stimulation. Electrooculogram was
281 recorded with two additional bipolar electrodes. EEG signal was band-pass filtered between 0.1 and
282 500 Hz and sampled at 1450 Hz. Before each recording session, electrodes impedance was set below
283 5 k Ω . Each TMS-EEG session included ~250 single pulse TMS (mean = 252 \pm 15) with the same
284 Interstimulus intervals as for pretests. Auditory EEG potentials evoked by the TMS clicks and bone
285 conductance were minimized by diffusing a continuous white noise through earphones and applying a
286 thin foam layer between the EEG cap and the TMS coil. A sham session, consisting in 30 TMS pulses
287 delivered parallel to the scalp with noise masking, was administered to verify the absence of auditory
288 EEG potentials after at least one TMS-EEG session. Absence of auditory responses was confirmed in all
289 participants.

290 TMS-EEG data were preprocessed as previously described (Van Egroo et al., 2019) in SPM12
291 implemented in MATLAB2013a (The Mathworks Inc., Natick, MA). In brief, TMS-EEG data underwent
292 semi-automatic artefacts rejection, low-pass filtering at 80 Hz, downsampling to 1000 Hz, high-pass
293 filtering at 1 Hz, splitting into epochs spanning -101 and 300 ms around TMS pulses, baseline correction
294 (from -101 to -1 ms pre-TMS), and robust averaging. As described in (Van Egroo et al., 2019), the actual

295 stimulation site and the position of the EEG cap varied from subject to subject (due to head size and
296 morphology, placement of the EEG cap, signal quality). In addition, electrode signal could be of low
297 quality at the closest location from the stimulation site. A full description of stimulation site variation
298 is provided in (Van Egroo et al., 2019). Cortical excitability was computed as the slope at the inflexion
299 point of the first component of the TMS-evoked EEG potential on the electrode closest to the
300 stimulation hotspot (in $\mu\text{V}/\text{ms}$). The electrode considered was constant across all sessions of the same
301 volunteer.

302

303 **Data analysis and statistics**

304 To express time according to internal circadian phase, which was meant to be the same for all aspects
305 of the project in all subjects, rather than clock time, which varied across subject depending to habitual
306 sleep-wake schedule, all data were realigned with respect to the onset of melatonin secretion - dim
307 light melatonin onset (DLMO) –, considered as a gold standard assessment of circadian phase (Duffy
308 and Dijk, 2002). DLMO was determined based on assays in saliva using the hockey-stick method, with
309 ascending level set to 2.3 pg/ml (Hockey-Stick software v1.5) (Danilenko et al., 2014). The circadian
310 phases of each test batteries, TMS-EEG sessions and KSS/VAS assessments were inferred from
311 individual DLMO time (i.e., phase 0° ; $15^\circ = 1\text{h}$). Results of cognitive tests and subjective assessments
312 (including effort) were then resampled following linear interpolation at the planned/theoretical phases
313 of test batteries (-140° , -110° , -80° , -50° , -20° , 10° , 40° , 70° , 100°). The same procedure was carried out
314 for cortical excitability and subjective assessments - including effort - for planned/theoretical phases
315 of TMS-EEG sessions (-145° , -60° , 0° , 30° , 80°). Hourly subjective assessments - excluding effort - were
316 resampled at the planned/theoretical hourly phases (-190° , -175° , -160° , -145° , -130° , -115° , -100° , $-$
317 85° , -70° , -55° , -40° , -25° , -10° , 5° , 20° , 35° , 50° , 65° , 80° , 95° , 110°). Importantly, a constant routine
318 approach is meant to unmask in part any circadian influence (Duffy and Dijk, 2002). One cannot,
319 however, separate the effect of time spent awake and circadian phase, as any change with time spent
320 awake will reflect their dual influences.

321 Performance to the PVT was inferred from the number of lapses (> 500 ms) and mean reaction
322 time (mRT) following removal of anticipation (< 100 ms), lapses and error (> 3000 ms). Fast and slow
323 RT were also computed for supplementary results as the 10% fastest and slowest RT, respectively,
324 following removal of anticipation and lapses. For the 2-back, 3-back and SART, we used the D-prime
325 (d') score to characterize performance to the task. d' takes into account hit and false alarm and thus
326 represents a response discriminability index [i.e., a measure of sensitivity, following the signal
327 detection theory (Ingleby, 1967)], with higher d' values meaning better performance.

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

335 Statistical analyses were performed using Generalized Linear Mixed Models (GLMMs) in SAS
336 9.4 (SAS Institute, Cary, NC, USA). Dependent variable distribution was first determined and GLMMs
337 were adjusted accordingly. All GLMMs were adjusted for demographic variables of age, sex and
338 education. Subject (intercept) was included as random factor. Circadian phase was included as a
339 repeated measure together with an autoregressive estimation of autocorrelation of order 1 [AR (1)].
340 Degrees of freedom were estimated using Kenward-Roger's correction. In the search for associations
341 between effort and other metrics, we included triple interactions between circadian phase, age and
342 the metric of interest. When non-significant, the triple interaction was removed from the model to
343 assess separate circadian phase and age by metric of interest interactions. When GLMM yielded a
344 significant interaction with age, the sample was split between subjects aged <60 and ≥60 y (median
345 split) to test for significant difference between the younger and older subsample. This was meant to
346 get a better understanding of the interaction effect. Statistical significance was set at $p < .05$. Semi-

347 partial R^2 ($R^2_{\theta^*}$) values were computed to estimate the effect sizes of significant fixed effects and
348 statistical trends in all GLMMs (Jaeger et al., 2017). Two types of post hoc analyses were used: LS
349 MEANS procedure for simple contrasts of phase and ESTIMATE procedure for comparison of phases
350 relative to each other. P -values in post-hoc contrasts (difference of least square means) were adjusted
351 for multiple testing with Tukey's procedure and t -values obtained by ESTIMATE assesment were
352 adjusted for multiple analyses with Sidak's procedure.

353 Optimal sensitivity and power analyses in GLMM remain under investigation (e.g. Kain et al.,
354 2015). We nevertheless computed an *a priori* sensitivity analysis to get an indication of the minimum
355 detectable effect size in our main analyses given our sample size. According to G*Power 3 (version
356 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
357 allowed us to detect small effect sizes $r > .29$ (2-sided; absolute values; 95% confidence interval: .1 –
358 .46; $R^2 > .08$, R^2 95% confidence interval: .01 – .21) within a linear multiple regression framework
359 including 5 covariates (effort, phase, age, sex, education).

360

361 **Transparency and openness**

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

369

370 **RESULTS**

371 **Age-related dampening of the variation of effort during wake extension protocol**

372 For all analyses, we expressed time with respect to internal circadian phase, taking the onset of

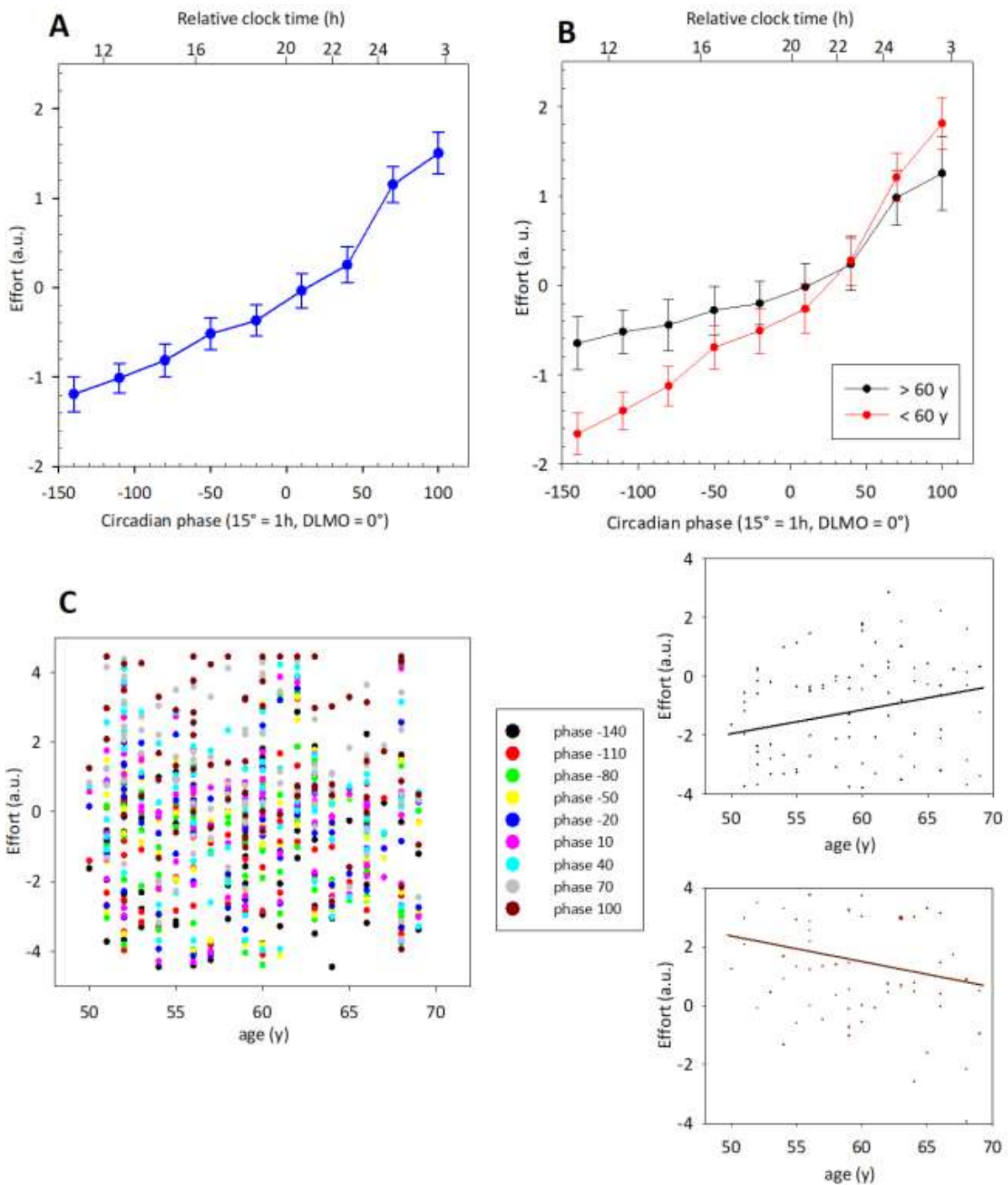
373 melatonin secretion as a gold standard mean to detect the anchor circadian phase 0° (Duffy and Dijk,
374 2002) (see methods). This procedure means that 15° represents 1h and that phase can be either
375 negative or positive, if an event of the protocol was occurring before or after circadian phase 0° ,
376 respectively. Importantly, although, constant routine protocol unmask in part any circadian influence,
377 any changes we report arise from the dual influence of the increase in sleep need and of the circadian
378 system.

379 We first investigated the variation of effort during wakefulness extension. To address this
380 issue, we used effort values resampled according to tasks battery theoretical phases (-140°, -110°, -
381 80°, -50°, -20°, 10°, 40°, 70° and 100°) (the same procedure was applied to all analyses, see methods).
382 A GLMM including age, sex and education as covariates revealed a main effect of circadian phase
383 (GLMM main effect of circadian phase: $F_{8, 723.4} = 13.25, p < 0.0001, R^2_{\theta^*} = 0.13$) (**Figure 2A**). Post-hoc
384 analyses revealed a global increase of effort from the beginning to the end of the protocol (effort: -
385 140° > -50° to 100°, - 110° > -50° to 100°, -80° > -20° to 100°, -50° > 10° to 100°, -20° > 40° to 100°, 10°
386 > 40° to 100°, 40° > 70° to 100°, 70° > 100°; $p < 0.05$; corrected for multiple tests). Consecutive phases
387 were significantly different starting at 70° denoting a more abrupt change in effort during the biological
388 night.

389 Interestingly, while the same GLMM did not yield a significant main effect of age ($F_{1, 93.75} <$
390 $0.0001, p = 0.98$), it revealed that effort variations with circadian phase changed with age, even in our
391 limited age range sample (circadian phase x age interaction; $F_{8, 725} = 9.08, p < 0.0001, R^2_{\theta^*} = 0.09$). Post
392 hoc analyses, at p-value threshold uncorrected for multiple comparisons, yielded a significant positive
393 association between effort and age at phase -140° ($t_{143.1} = 2.18, p = 0.03$) and a significant negative
394 correlation at phase 100° ($t_{179} = -2.15, p = 0.03$) (**Figure 2C**). Additional post hoc contrasts showed that
395 the relation between effort and age was significantly different from the beginning to the end of the
396 protocol (age x circadian phase interaction: -140° > 10° to 100°, -110° > 40° to 100°, -80° > 40° to 100°;
397 $p < 0.05$; corrected for multiple tests), depicting reduced variations in effort in the older individuals of
398 our sample. To visualise this, we split the sample between the younger (<60y; N= 50) and older (≥60y;

399 N= 49) individuals on **Figure 2B**.

400



401

402 **Figure 2: Variations of effort during the wake extension protocol and link with age.** Effort time course

403 during 20h of prolonged wakefulness of the whole sample N=99 (A) and according to age groups (<60y

404 or ≥60y) (B). Regressions display of the association between effort and age at phase -140° (top, black)

405 and 100° (bottom, marron) (C). Scatter plot of effort as a function of age over the different circadian

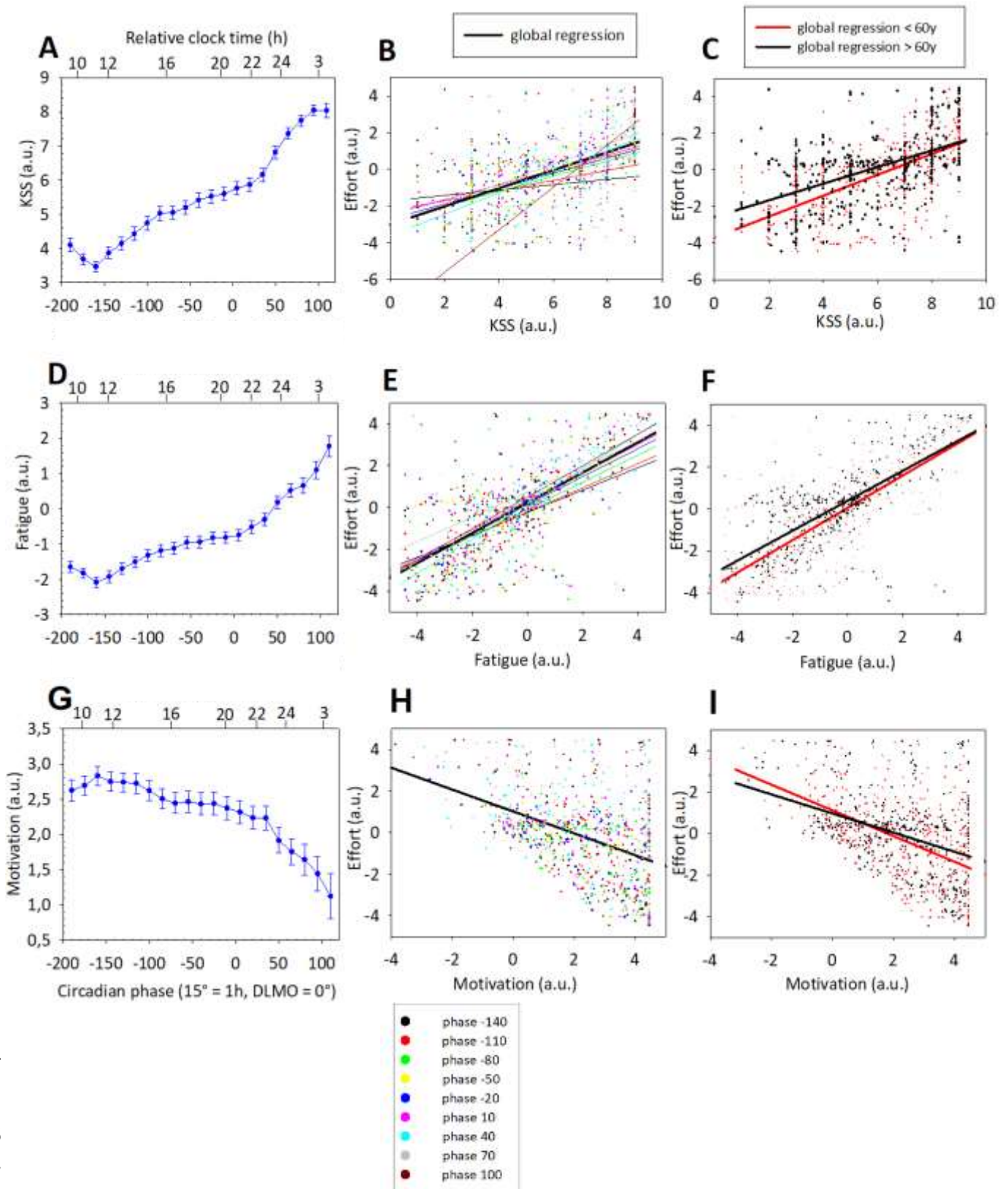
406 phases of the protocol (colour according to legend inset). Right insets show significant associations at

407 phase -140° (top) and 100° (bottom). Regressions lines are displayed for illustration purposes of the
408 significant associations yielded by the GLMM and do not substitute GLMM outputs. Effort is reported
409 relative to individual melatonin onset which was used as reference time point for internal circadian
410 phase (i.e. 0°; 15° = 1h) and effort assessment is expressed in arbitrary unit (a. u.).

411 **Effort correlates with variations in other subjective measures**

412 We then wanted to compare the time-course of effort with other subjective metrics. We focused on
413 subjective sleepiness, fatigue and motivation as they are most related to effort [exploratory results for
414 the other subjective dimensions can be found as supplementary information (**Supplementary Figure**
415 **S1**)] (Boksem and Tops, 2008; Hopstaken et al., 2015). All three subjective measures underwent
416 expected significant changes with circadian phase (GLMM main effect of circadian phase; sleepiness:
417 $F_{20, 1876} = 133.07, p < 0.0001, R^2_{\theta^*} = 0.59$; fatigue: $F_{20, 1877} = 90.23, p < 0.0001, R^2_{\theta^*} = 0.49$; motivation: $F_{20,$
418 $1854} = 20.63, p < 0.0001, R^2_{\theta^*} = 0.18$) (**Figure 3A, D, G**). Further analyses revealed that effort was
419 significantly associated with all three measures (**Table 2; Figure 3B, E, H**) with effort positively
420 associated with sleepiness and fatigue and negatively associated with motivation. A significant
421 interaction between subjective metric and circadian phase was detected for sleepiness and fatigue but
422 not for motivation (**Table 2; Figure 3B, E, H**). The associations between sleepiness/fatigue and effort
423 are present at almost each circadian phase ($p < .05$ corrected for multiple post hoc tests; except
424 sleepiness at phase -140°, $p < 0.2$ uncorrected, and fatigue at phase 10° and 40°, $p > .2$), but sleepiness
425 and fatigue were more related to effort with variable magnitude during prolonged wakefulness (many
426 post-hoc comparisons between phases are significantly different – not shown).

427 Importantly, beyond a potential main effect of age, effort was significantly associated with
428 the interaction between subjective metric and age for all three metrics (**Table 2**). To gain insight in
429 these interaction, we again split the sample between the younger (<60y; N= 50) and older (≥60y; N=
430 49) individuals (**Figure 3C, F, I**) of the sample and find that the link between effort and subjective
431 metrics decrease in the older compared to the younger group (subjective metric x group; sleepiness:
432 $F_{1, 765.4} = 28.40, p < .0001$; fatigue: $F_{1, 799.8} = 19.34, p < .0001$; motivation: $F_{1, 807.7} = 11.43, p = .0008$).



433

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438 **Figure 3: Association between effort and variation in other subjective measures.** Time course of

439 subjective metrics (left panels), relationships with effort in all individuals (middle panels), and in

440 younger (< 60y) and older ($\geq 60y$) individuals of our sample (right panels): sleepiness (A-C), fatigue (D-

441 motivation (G-I). Colours of the dots correspond to the circadian phases of data collection during

442 the 20h wake extension protocol as indicated in the inset legend. Regressions in middle panels display
 443 the associations between effort and cognitive metrics across all measurements, i.e. irrespective of
 444 circadian phase (thick black line), when significant, and for each circadian phase (according to legend
 445 inset colour code), when significant at least for one specific phase. Regressions lines are displayed for
 446 illustration purposes of the significant associations yielded by the GLMM and do not substitute GLMM
 447 outputs. A significant interaction between subjective metric and circadian phase was also detected for
 448 sleepiness and motivation but not for fatigue. All values are reported relative to individual melatonin
 449 onset which was used as reference time point for internal circadian phase (i.e., 0°, 15° = 1h) and
 450 subjective metrics, including effort, are expressed in arbitrary unit (a. u.).
 451

452 **Table 2. Associations between perceived effort and other subjective measures.**

| | <i>SM</i> | <i>SM x age</i> | <i>phase</i> | <i>SM x phase</i> | <i>age</i> | <i>sex</i> | <i>education</i> |
|--------------------------------------|---|--|---|--|--|-------------------------------|--------------------------------|
| <i>Sleepiness</i> (<i>N</i> =99) | $F_{(1,804.7)}= 135.36$ $p<.0001$ $R^2_{\beta^*}=.08$ | $F_{(1,792.2)}= 35.39$ $p<.0001$ $R^2_{\beta^*}=.04$ | $F_{(8,731.9)}= 14.61$ $p<.0001$ $R^2_{\beta^*}=.025$ | $F_{(8,724.3)}=7.87$ $p<.0001$ $R^2_{\beta^*}=.08$ | $F_{(8,180.9)}=18.00$ $p<.0001$ $R^2_{\beta^*}=0.09$ | $F_{(1,93.2)}=.06$ $P=.81$ | $F_{(1,92.1)}=1.61$ $P=.21$ |
| <i>Fatigue</i> (<i>N</i> =99) | $F_{(1,790.4)}= 65.08$ $p<.0001$ $R^2_{\beta^*}=.14$ | $F_{(1,724.3)}= 46.06$ $p<.0001$ $R^2_{\beta^*}=.06$ | $F_{(8,765.4)}= 2.3$ $p<.02$ $R^2_{\beta^*}=.14$ | $F_{(8,723.8)}=0.96$ $p=.47$ | $F_{(1,92.2)}=.01$ $P=.93$ | $F_{(1,90.7)}=.07$ $P=.8$ | $F_{(1,90.5)}=1.11$ $P=.3$ |
| <i>Motivation</i> (<i>N</i> =99) | $F_{(1,804.6)}= 14.81$ $p<.0001$ $R^2_{\beta^*}=.02$ | $F_{(1,805.6)}= 7.44$ $P=.006$ $R^2_{\beta^*}=.01$ | $F_{(8,721.6)}= 16.32$ $p<.0001$ $R^2_{\beta^*}=.15$ | $F_{(8,718.4)}=2.19$ $p<.03$ $R^2_{\beta^*}=.02$ | $F_{(1,134)}=1.93$ $P=.17$ | $F_{(1,94.2)}=.04$ $P=.85$ | $F_{(1,92.9)}=.8$ $P=.37$ |

453 Outputs of GLMM using effort measure as dependent variable and SM as independent variable.
 454 SM: subjective dimension (i.e. sleepiness, fatigue or motivation)
 455

456 **Effort correlates with some but not all cognitive performance metrics**

457 For the PVT we focused on mean reaction time (mRT). Analyses showed that PVT mRT (*N*=99)
 458 significantly varied throughout the wakefulness extension (GLMM main effect of circadian phase; $F_{8,732.9} = 64.88, p < 0.0001, R^2_{\beta^*} = 0.42$) (**Figure 4A**). Post hoc analysis showed that performance worsens
 459 during wakefulness extension protocol with biological night measures slower than those collected
 460 during biological day (-140° < 10° to 100°, -110° < 40° to 100°, -80° < 40° to 100°, -50° < 40° to 100°, -
 461 20° < 40° to 100°, 10° < 40° to 100°, 40° < 70°, 70° < 100°, $p < 0.05$; corrected for multiple tests). PVT
 462 mRT showed a significant triple interaction between circadian phase, age and effort (circadian phase x
 463 age x effort; mRT: $F_{8,696.1} = 2.47, p = 0.012, R^2_{\beta^*} = 0.03$) which we further decomposed in simple
 464 interactions and main effects to get a full sense of it (**Table 3**). PVT mRT were significantly positively
 465

466 associated with effort, i.e. more effort associated with slower RT, while the interaction between effort
 467 and circadian phase was also significant (**Figure 4B; Table 3**). Post-hoc statistics revealed significant
 468 positive associations between effort and PVT mRT at phase 70° and phase 100° (70°: $t_{755.8} = 3.41$, $p =$
 469 0.0062 ; 100°: $t_{50.94} = 3.32$, $p = 0.0085$) and differences between phases (effort x mRT: $-140^\circ < 100^\circ$,
 470 $p < .05$ corrected; $140^\circ < -80^\circ$ and 10° to 100° , $-110^\circ < 70^\circ$ to 100° , $-20^\circ < 70^\circ$ to 100° , $p < 0.05$
 471 uncorrected) (**Figure 4B**). These findings denote that more effort was associated with faster mRT,
 472 particularly towards the beginning of the protocol. Statistical analyses for other PVT metrics (slow/fast
 473 reaction times) can be found as supplementary information (**Supplementary Figure S2**) and lead to
 474 similar outputs. Interestingly, PVT lapses (RT > 500ms) were not associated to effort (**Table 3**,
 475 **Supplementary Figure S2**).

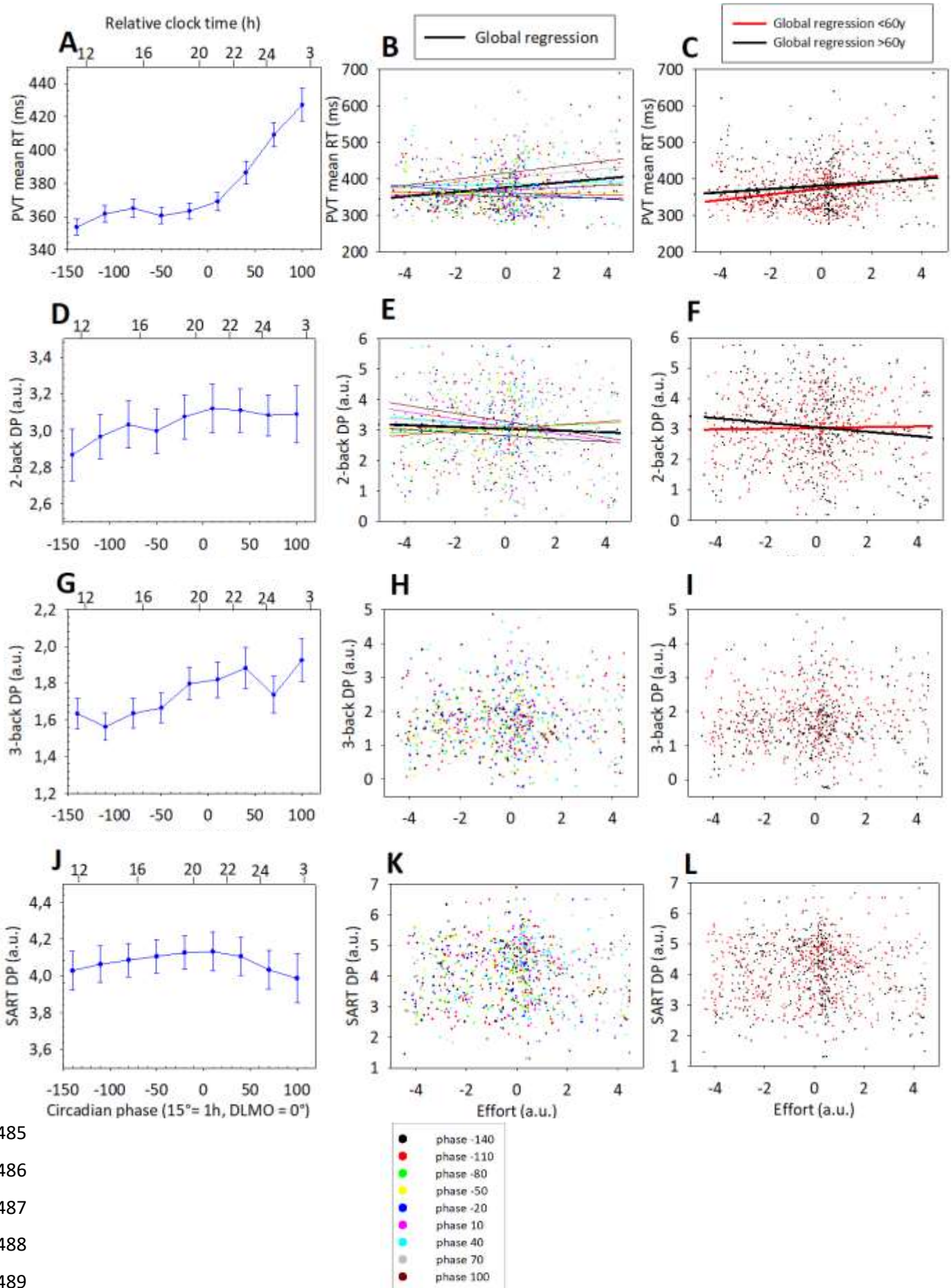
476 Critically, while mRT were not significantly associated to age, the analysis yielded a significant
 477 interaction between effort and age group (**Table 3**). When decomposing our sample into the younger
 478 (<60y; N= 50) and older (≥ 60 y; N= 49) individuals, we find that that more effort is associated with worse
 479 performance (i.e. slower mRT) in the older compared the younger group (mRT x group; $F_{1, 765.4} = 28.40$,
 480 $p < 0.0001$) (**Figure 4C**).

481

482 **Table 3. Associations between perceived effort and cognitive performance metrics.**

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

483 Performance was set as the dependent variable and effort as independent variable. * When
 484 significant, main effect of sex correspond to women having better performance than men.



485
 486
 487
 488
 489

490 **Figure 4: Association between effort and cognitive performance during the wake extension protocol.**
491 *Time course of cognitive metrics (left panels) and their relationship with effort according to circadian*
492 *phase (middle panels) and according to age groups (<60y or ≥60y; right panels). PVT mean reaction*
493 *time –mRT- (A-C), 2-back d' (D-F), 3-back d' (G-I), and SART d' (J-L). Regression in middle panels display*
494 *the associations between effort and cognitive metrics across all measurements, i.e. irrespective of*
495 *circadian phase (thick black line), when significant, and for each circadian phase (according to legend*
496 *inset colour code), when significant at least for one specific phase. Regressions lines are displayed for*
497 *illustration purposes of the significant associations yielded by the GLMM and do not substitute GLMM*
498 *outputs. All values are reported relative to individual melatonin onset, which was used as reference*
499 *time point for internal circadian phase (i.e., 0°, 15° = 1h). Due to insufficient valid data point, circadian*
500 *100° for d' of 3 back task was not included in the statistical analyses reported in the main text*

501
502 Performance to the 2-back task, as indexed by d' values, did not vary significantly during
503 protocol (N=99; GLMM main effect of circadian phase; $F_{8, 686.5} = 1.74, p = 0.09$) (**Figure 4D**). d' was both
504 significantly related to effort as a main effect and in interaction with circadian phase (**Figure 4E, Table**
505 **3**). Post hoc analyses demonstrated that effort was significantly negatively associated with 2-back d'
506 at all phases (-140° to -20° & 70°, $p < .05$, corrected for multiple post hoc tests; 10°, 40°, 100° $p < .05$
507 uncorrected) and the association at phase 100° was significantly different from the beginning of the
508 protocol (d' : 100° > -140° to -50° and 70°, $p < 0.05$, corrected for multiple tests) (**Figure 4E insets**). This
509 finding indicates that, except during the last session of the protocol, greater effort was associated with
510 better performance to the 2-back task. As for the PVT metric, 2-back d' was not significantly associated
511 to age as a main effect, but significantly varied in association with the interaction between effort and
512 age (**Table 3**). When decomposing our sample into younger (<60y; N= 50) and older (≥60y; N= 49)
513 individuals, we observe that more effort is associated with worse performance (i.e. lower d') in the
514 older group and with better performance (i.e. higher d') in the younger group without reaching
515 statistical significance ($d' \times$ group interaction; $F_{1, 698.1} = 2.35, p = 0.12$) (**Figure 4F**).

516 When considering performance to the 3-back task (excluding the last circadian phase of the
517 protocol, see methods) we find that d' did not significantly change during the protocol (N=99; GLMM
518 main effect of circadian phase; $F_{7, 617.4} = 4.38, p = .63$) (**Figure 4G**). 3-back d' performance was however

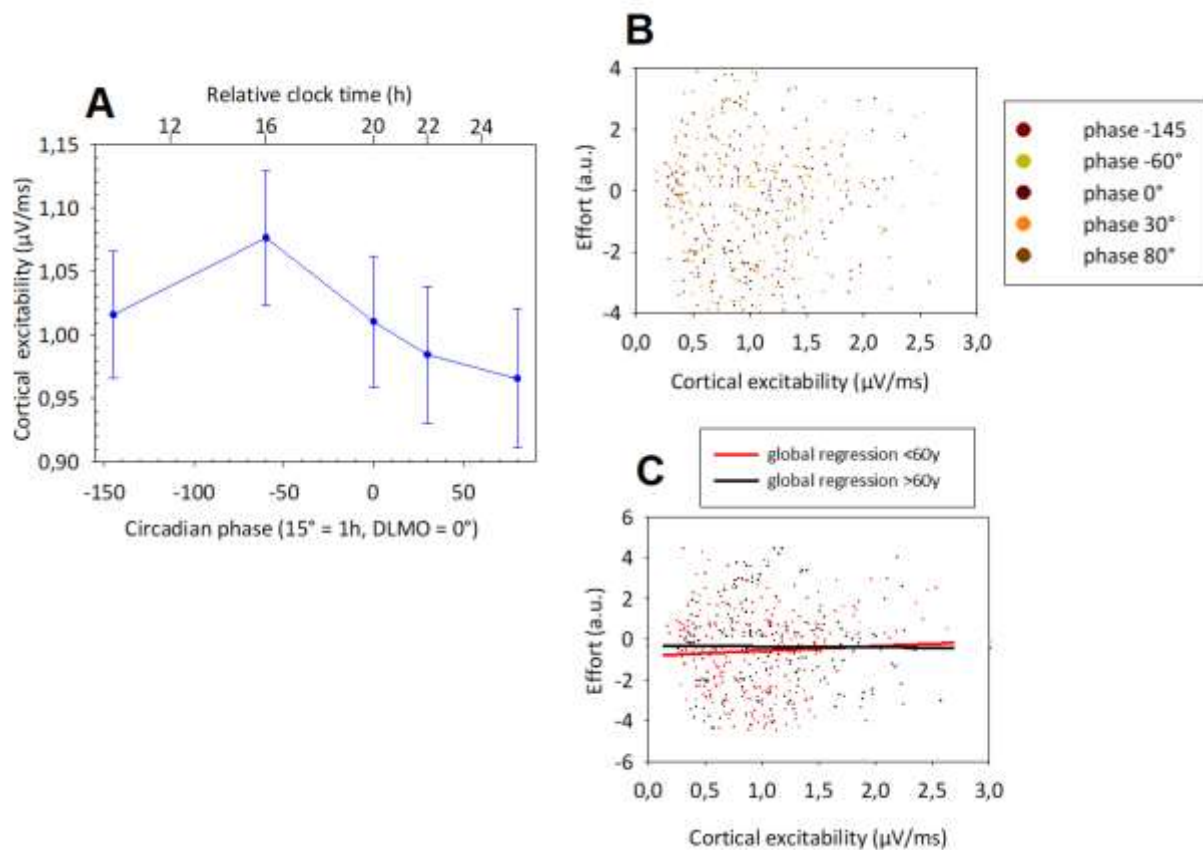
519 not associated with effort, both as a main effect of effort or in interaction with circadian phase or age
520 (**Table 3; Figure 4H, I**). Similarly, performance on the SART, also indexed through d' , did not significantly
521 vary throughout the wake extension protocol (N = 99; GLMM main effect of circadian phase; $F_{8, 739.6} =$
522 $.55, p = 0.82$) (**Figure 4J**). SART performance was however not associated with effort both as a main
523 effect of effort or in interaction with circadian phase or age (**Table 3, Figure 4K, L**).

524

525 **No significant associations between effort and cortical excitability**

526 Our final analyses focused on cortical excitability, as indexed by the slope of the first
527 component of the early EEG response to a TMS pulse, as a potential correlate of effort. As previously
528 reported based on part of the current sample (Van Egroo et al., 2019), cortical excitability significantly
529 changed during the protocol (GLMM main effect of circadian phase; $F_{4, 372.1} = 6.29, p < 0.0001, R^2_{\theta^*} =$
530 0.06) (**Figure 5A**). Post-hoc analyses revealed a cortical excitability decrease between the second and
531 the fourth and last fifth sessions (slope: $-60^\circ > 30^\circ, -60^\circ > 80^\circ, p < 0.05$, corrected for multiple tests).
532 We then sought for associations between effort and cortical excitability. No association was detected
533 with cortical excitability (GLMM main effect of cortical excitability; $F_{1, 391.2} = 0.04, p = 0.84$) neither with
534 the interaction between cortical excitability and phase (GLMM cortical excitability x phase; $F_{4, 362.5} =$
535 $0.62, p = 0.65$) nor with the interaction between cortical excitability and age (GLMM cortical excitability
536 x age; $F_{4, 391.8} = 0.03, p = 0.85$) (**Figure 5B, C**).

537



538

539 **Figure 5: Association between effort and variations in cortical excitability dynamic.** Time course of
 540 cortical excitability (A) and its associations with effort (B) and according to age groups (C) during wake
 541 extension protocol. Colours of the dots correspond to the circadian phases of data collection during the
 542 20h wake extension protocol as indicated in the inset legend. Regressions lines are displayed for
 543 illustration purposes each age group and do not substitute GLMM outputs. All values are reported
 544 relative to individual melatonin onset, which was used as reference time point for internal circadian
 545 phase (i.e., 0° , $15^\circ = 1\text{h}$). All values are reported relative to individual melatonin onset (DLMO = 0° ; 15°
 546 = 1h).

547

548 DISCUSSION

549 In this study, we first aimed to characterize variations of cognitive effort during 20h of wakefulness
 550 extension in a sample of 99 healthy late middle-aged individuals aged 50 to 69 y. Prior reports found
 551 an increase in effort with time awake (Ode-Dusseau et al., 2010; Pilcher and Walters, 1997) while

552 others did not find significant changes (Drummond et al., 2005b). Our results are in line with the
553 former, as we observe a significant increase in effort, potentially sharper during the biological night.
554 Interestingly, this increase was reduced in the older participants of our sample. Effort increase was
555 also directly correlated with other subjective metrics such as sleepiness and fatigue while it was
556 opposite to motivation, which decreased with time awake in our study sample. Hence, similar to other
557 subjective feelings (Ode-Dusseau et al., 2010), effort is sensitive to wakefulness extension in
558 individuals aged 50 to 70y, particularly for individuals aged < 60y. We further show that effort increase
559 with time awake is significantly associated with decreased performance to a PVT task and a 2-back
560 task, particularly during the biological night for the latter, while no significant links were detected when
561 considering the 3-back task and SART. Importantly, we observe that the link between PVT and 2-back
562 performance vary according to age, with more effort associated with worse performance in the older
563 vs. younger individuals of our sample. Finally, in an exploratory analysis, we find no significant
564 association between effort and cortical excitability.

565 The sharpness of the increase in effort may appear surprising given the moderate challenge
566 that 20h wakefulness extension represents. Together with the relatively large size of our sample, the
567 fact that we conducted our study under strictly controlled constant routine condition may have
568 unmasked effort variations that could be otherwise hindered by physical activity, posture changes or
569 ambient light (Duffy and Dijk, 2002). This type of protocol is meant to unmask the influence of the
570 circadian system on physiology and behaviour so that circadian changes become more prominent. Any
571 changes in the measures of interest remains, however, the reflection of the dual influence of the build-
572 up of the need for sleep and of the influence of the circadian system. Interestingly, we observe a
573 reduction in effort fluctuation with increasing age despite the limited age range of our sample.
574 Qualitative inspection of the data indicates that effort may be higher at the beginning of the protocol
575 as one gets older while its rise is shallower as wakefulness is extended. This pattern is in line firstly
576 with higher cognitive effort in elderly under normal well-rested conditions to support optimal level of
577 performance compared to younger (Hess and Ennis, 2012). In addition, the reduced effort rise during

578 wakefulness extension is compatible with the previously reported decreases in homeostatic build-up
579 of sleep need and circadian signal variation over the sleep-wake cycle (Landolt et al., 2012; Schmidt et
580 al., 2012). In other words, because older people are less sensitive to the adverse effect of sleep loss,
581 they are likely to exert less effort in an attempt to maintain performance during sleep deprivation.
582 Alternatively, the lower effort could be explained by a potential ceiling effect for further effort
583 enhancement (for example, due to lower brain reserve; (Cabeza et al., 2018). Further studies are
584 needed to test these two interpretations.

585 Effort, as well as the other subjective dimensions we assessed, is among the first signs of the
586 detrimental effects of wakefulness extension as it decreased early during the protocol. Therefore the
587 increase in the perceived amount of effort required to perform a certain task would be an alarm signal
588 of the beginning of the effect of sleep deprivation with the impending arrival of performance decline
589 (Ode-Dusseau et al., 2010). We find a direct link between effort and performance to the PVT, which is
590 the only task showing a global decrease in performance during our moderate wake extension
591 challenge, in agreement with a greater impact of sleep loss on attentional processes (Drummond et
592 al., 2005a; Lo et al., 2012). Also in line with a reduced impact of sleep need on executive tasks (Lo et
593 al., 2012), performance to the 2-back task remains stable during the protocol. Yet, it was also
594 associated with effort. It is only for the SART and 3-back task which did not show performance decline
595 during the protocol, that no significant link with effort was detected. Performance to the 3-back was,
596 as expected (De Beni and Palladino, 2004; Gaggioni et al., 2019), much poorer than for the 2-back, and
597 that 3-back performance increased with time likely because of a learning bias in those that could
598 overcome the initial difficulty of the task. The low performance at the 3-back in a substantial portion
599 of the sample prevented assessing the link between effort and the interaction between circadian phase
600 and 3-back performance. The absence of performance decrement for the 3-back task during the night
601 could be related to the reduced acute impact of lack of sleep during a night of sleep deprivation for
602 more demanding task (Lo et al., 2012). For the SART, we can only speculate that even though
603 performance has been reported to suffer more from sleep-loss/circadian misalignment than the 2-

604 back task (Sagasse et al., 2012), the protocol may not be challenging enough to trigger variation in the
605 task. The metric we used for quantification of performance to the SART (d') may also not be as sensitive
606 as the reaction times we used for the PVT. In the framework of theories on management of cognitive
607 fatigue (Hockey, 1997, 2011, 2013), the absence of links between effort and performance at the 3-back
608 and SART tasks may also results from a voluntary decision to withdraw effort and try to maintain
609 performance by exploiting low-cost processes, as the motivation may decrease according to the strain
610 that one experience.

611 Contrary to our hypothesis, we found that more effort is associated with poorer performance
612 to the PVT and 2-back task, at least when instructions are to perform as well as possible in all cases
613 and without particular reward. Our finding could support, as previously described for motivation
614 (Dinges and Kribbs, 1991), that, although it may help to maintain in part performance (Engle-Friedman,
615 2014; Massar et al., 2019b; Sanders, 1983; Wilkinson, 1961), more effort expended to perform
616 cognitive task is not sufficient to overcome the performance decline caused by the underlying
617 physiological changes brought by high need for sleep (Pilcher and Walters, 1997). Alternatively, based
618 on our results, one could posit that poorer reduced attentional capacity during sleep loss leads to lower
619 cognitive performance and more effort as wakefulness is extended without direct causal link between
620 effort and performance. Given the high correlation between sleepiness, fatigue and motivation, other
621 subjective dimensions were associated to cognitive performance during prolonged wakefulness so that
622 we are not in a position to isolate the specific contribution of effort to performance. Reward
623 motivation was for instance reported to partially alleviate sleep deprivation related performance
624 decline, particularly during the biological night. Interestingly, we also observe that the link between
625 effort and cognitive performance at PVT (mRTs) and 2-back working memory task changes in our older
626 participants (60-69 y), with more effort associated with worse performance change than in younger
627 individuals (50-59y). As increasing age is also associated with a reduction in effort fluctuation during
628 the wakefulness extension period, it could be proposed that advancing age leaves little opportunity to
629 intentionally recruit additional resources when facing cognitive challenge. Whether the lack of

630 resources has a biological (e.g blood glucose depletion (Gailliot et al., 2007)), cognitive (e.g. control
631 processes (Shenhav et al., 2017)) or motivational (e.g., a cost-benefit analysis (Anderson, 1990)) origin
632 remains to be determined. Few evidence supports that inefficient effort management is related to a
633 risk of cognitive decline (see however Oren et al., 2019). One could consider that reduction in effort
634 variation and more effort associated with worst performance in our older participants provides
635 support to this assumption. This hypothesis remains to be tested in longitudinal studies of population
636 at risk for Alzheimer's disease.

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

656 Finally, higher education was associated to better performance on accuracy measures (d')
657 at the 2-back and SART tasks. These results are in the continuity of previous studies discussing
658 education as the main protective factor against dementia (Stern et al., 2020). We also observed an
659 effect of sex on PVT and SART, with a better performance in woman. Previous studies reported an
660 advantage in women, particularly for verbal tasks (for reviews, see Deckers et al., 2019; Lee et al.,
661 2022). Proposed mechanisms to explain sex effect might involve hormonal differences, genetic factors,
662 differences in brain networks, socioeconomic roles, and health choices.

663

664 **CONCLUSION**

665 We report that effort is remarkably sensitive to wakefulness extension in late middle-aged adults (50
666 to 70y), as previously described for younger individuals and for other subjective dimensions such as
667 sleepiness, fatigue and motivation (Ode-Dusseau et al., 2010; Pilcher and Walters, 1997). In addition,
668 effort variations dampen as one gets older in line with the global decrease in the sleep-wake regulation
669 signals with age and the acute reduction of performance decline during sleep loss. Effort increment
670 with time awake appears to be insufficient to overcome the marked cognitive performance decline
671 brought by high sleep need, and the association between effort and cognitive performance changes in
672 our older participants. This study suggests that association between subjective perception of effort
673 and cognitive performance in a challenging condition is sensitive to age. One perspective for future
674 studies should be to assess effort variation during total sleep deprivation (or other challenging
675 conditions) in population at risk for Alzheimer's disease and to assess whether it could be useful as an
676 easy first assessment tool for the prodromal and pre-clinical diagnosis of the disease.

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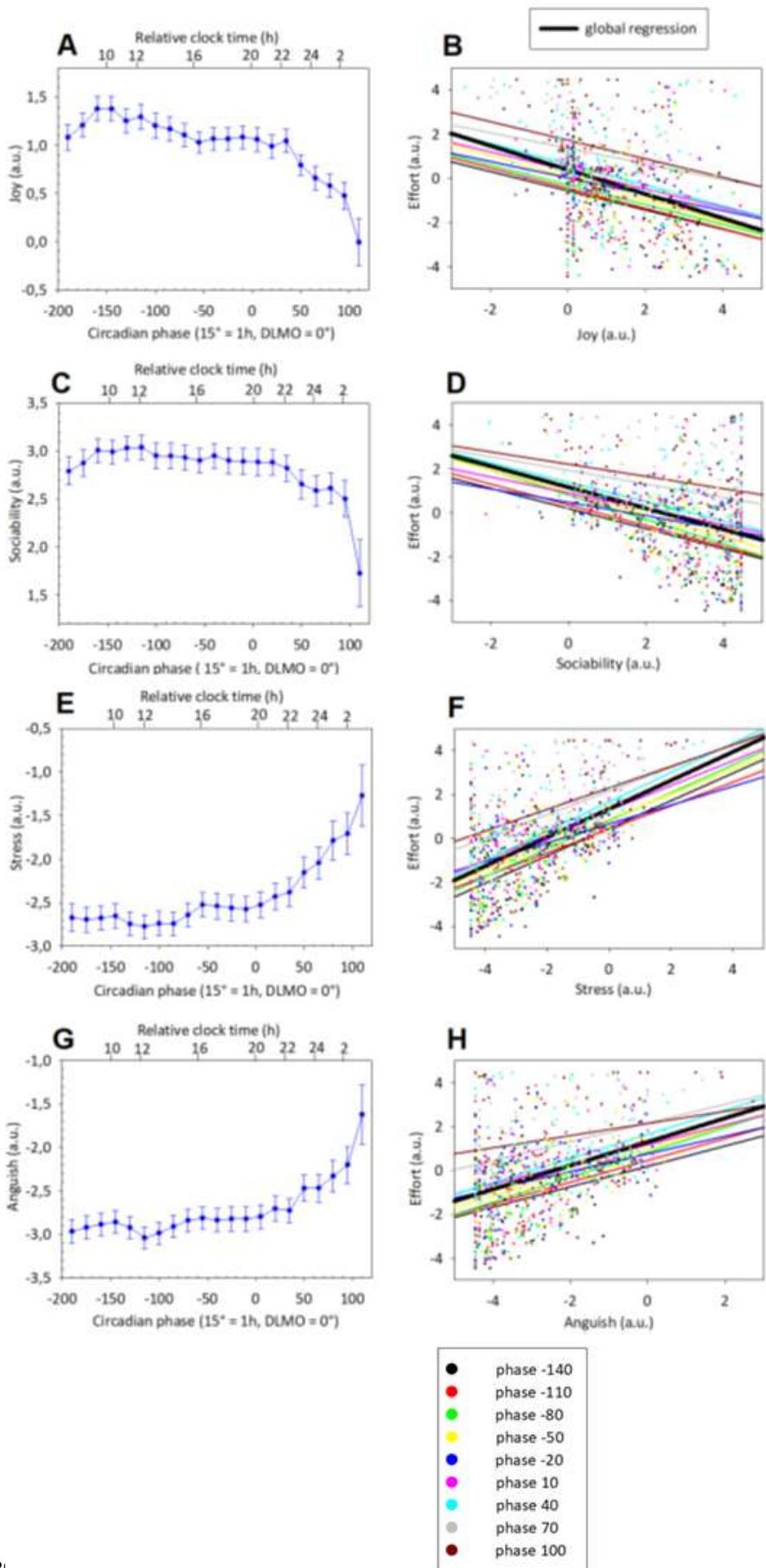
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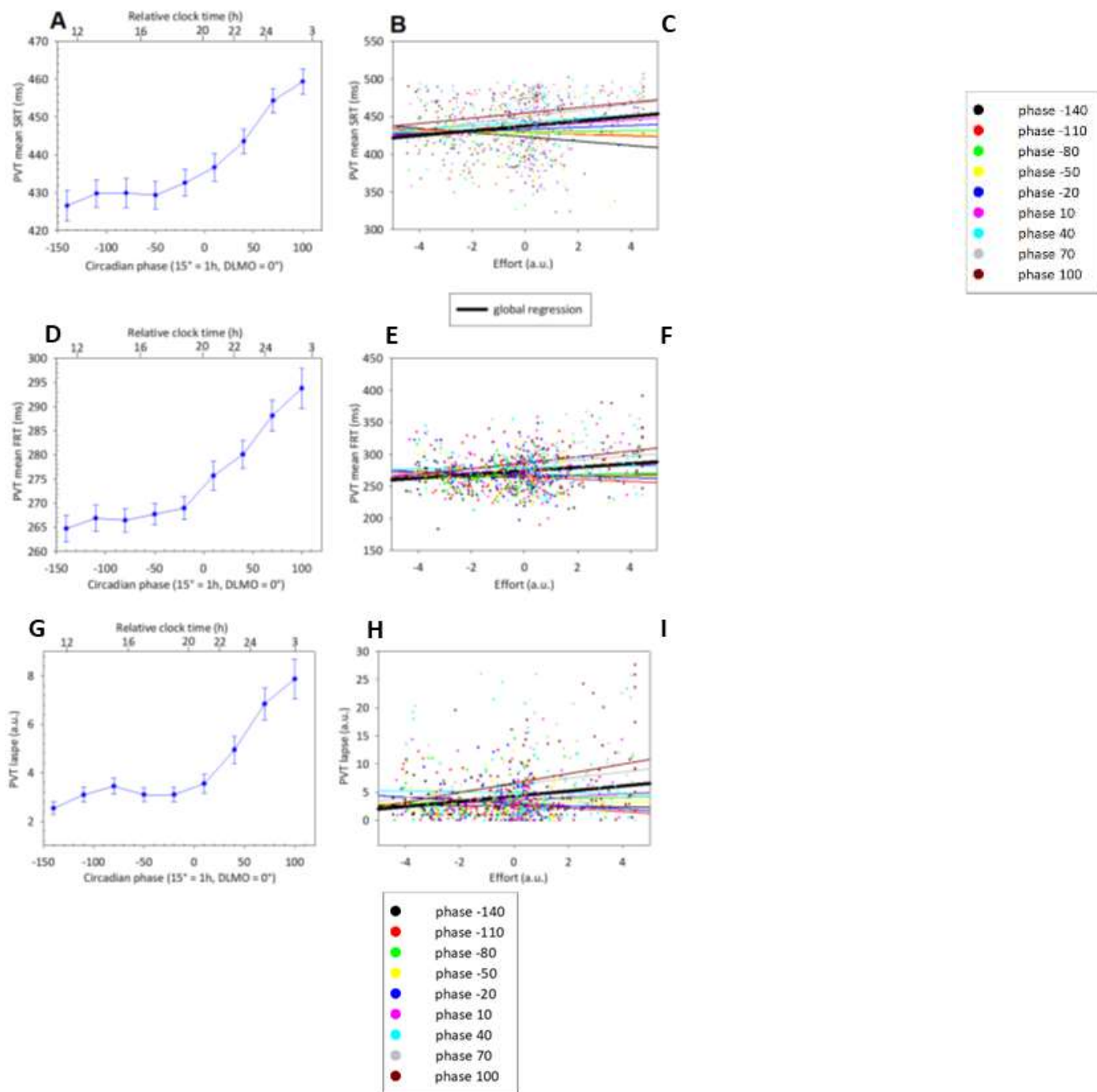
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894 **Supplementary Figure S1: Association between effort and variation in additional subjective**
895 **measures.** Time course of subjective metrics (left panels), relationships with effort in all individuals
896 (middle panels), and in younger (< 60y) and older (\geq 60y) individuals of our sample (right panels): joy
897 (A-C), sociability (D-F) stress (G-I) and anguish (J-L). Colours of the dots correspond to the circadian
898 phases of data collection during the 20h wake extension protocol as indicated in the inset legend.
899 Regression in middle panels display the associations between effort and cognitive metrics across all
900 measurements, i.e. irrespective of circadian phase (thick black line), when significant, and for each
901 circadian phase (according to legend inset colour code), when significant at least for one specific phase.
902 Regressions lines are displayed for illustration purposes of the significant associations yielded by the
903 GLMM and do not substitute GLMM outputs. Refer to Table S1 for output of GLMMs. All values are
904 reported relative to individual melatonin onset which was used as reference time point for internal
905 circadian phase (i.e., 0° , $15^\circ = 1h$) and subjective metrics, including effort, are expressed in arbitrary
906 unit (a. u.).
907



908

909 **Supplementary figure S2: Association between effort and additional PVT performance measures**
 910 **during the wake extension protocol.** Time course of cognitive metrics (left panels) and their
 911 relationship with effort according to circadian phase (middle panels) and according age groups (<60y
 912 or ≥ 60y; right panels). PVT mean slower reaction time –SRT- (A-C), PVT mean faster reaction time –
 913 FRT- (D-F), PVT lapse (G-I). Regression in middle panels display the associations between effort and
 914 cognitive metrics across all measurements, i.e. irrespective of circadian phase (thick black line), when
 915 significant, and for each circadian phase (according to legend inset colour code), when significant at
 916 least for one specific phase. Regressions lines are displayed for illustration purposes of the significant

917 *associations yielded by the GLMM and do not substitute GLMM outputs. Refer to Table S2 for output*
918 *of GLMMs. All values are reported relative to individual melatonin onset, which was used as reference*
919 *time point for internal circadian phase (i.e., 0°, 15° = 1h). Due to insufficient valid data point, circadian*
920 *100° for d-prime of 3 back task was not included in the statistical analyses reported in the main text*

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923 **SUPPLEMENTARY TABLES**

924

925 **Supplementary Table S1. Associations between perceived effort and additional subjective measures.**

| | <i>SM</i> | <i>SM x age</i> | <i>phase</i> | <i>SM x phase</i> | <i>age</i> | <i>sex</i> | <i>education</i> |
|---------------------------------------|--|--|--|---|---------------------------------------|-------------------------------------|--------------------------------------|
| <i>Joy</i> (<i>N</i> =99) | F_(1,815.6)= 22.33 p<.0001 | F_(1,815.8)= 15.36 p<.0001 | F_(8,725.8)= 47.66 p<.0001 | F _(8,724.4) = .36 P=.94 | F _(1,109) =1.26 P=.26 | F _(1,93.8) =.65 P=.42 | F _(1,95.7) =.7 P=.15 |
| <i>Sociability</i> (<i>N</i> =99) | F_(1,793.1)= 6.68 P=.009 | F_(1,791.2)= 3.75 P=.05 | F_(8,713.5)= 9.08 p<.001 | F_(8,712.4)=3.41 p=.0007 | F _(1,206) =1.76 P=.19 | F _(1,92.9) =.07 P=.8 | F _(1,92) =1.41 P=.24 |
| <i>Stress</i> (<i>N</i> =99) | F_(1,710)= 5.87 P=.015 | F _(1,692.1) = 2.28 P=.13 | F_(8,717.7)= 19.77 p<.0001 | F_(8,715.5)=2.17 P=.03 | F _(1,151.1) =1.05 P=.31 | F _(1,89.9) =.08 P=.78 | F _(1,89.2) =2.84 P=.09 |
| <i>Anguish</i> (<i>N</i> =99) | F _(1,788.2) = 2.23 P=.13 | F _(1,778.9) = .68 P=.41 | F_(8,722.2)= 14.11 p<.0001 | F _(8,720.6) =1.75 P=.08 | F _(1,190.3) =.32 P=.57 | F _(1,92.6) =.1 P=.75 | F _(1,91.8) =2.49 P=.12 |

926 Outputs of GLMM using effort measure as dependent variable and SM as independent variable.

927 SM: subjective dimension (i.e. sleepiness, fatigue or motivation). Complementary to Figure S1.

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929

930 **Supplementary Table S2. Associations between perceived effort and additional PVT performance**

931 **metrics.**

| | <i>Effort</i> | <i>Effort x age</i> | <i>phase</i> | <i>Effort x phase</i> | <i>age</i> | <i>sex</i> | <i>education</i> |
|--|--|--|--|---------------------------------------|--------------------------------------|---|--------------------------------------|
| <i>mean slow RT</i> (<i>PVT</i>) (<i>N</i> =99) | F _(1,809.9) = .83 P=.36 | F _(1,717.2) = .00 P= 1 | F_(8,724.5)=22.64 p<.0001 | F _(8,739) =1.8 P=.073 | F _(1,92) = .24 P=.62 | F_(1,92.2)= 10.09 P=.002 | F _(1,92) = .24 P=.62 |
| <i>mean fast RT</i> (<i>PVT</i>) (<i>N</i> =99) | F _(1,396.6) = 3.94 P=.17 | F _(1,327.6) = 2.72 P=.10 | F_(8,710.6)=14.04 p<.0001 | F _(8,674.7) =.96 P=.47 | F _(1,92,2) =1.82 P=.18 | F_(1,92,3)= 7.14 P=.008 | F _(1,92,2) = .7 P=.4 |
| <i>Lapses</i> (<i>PVT</i>) (<i>N</i> =99) | F _(1,670.3) = .39 P=.53 | F _(1,665.5) = 0.00 P=1 | F_(8,678.4)= 11.89 p<.0001 | F _(8,699.6) =1.79 P=.07 | F _(1,90.8) =1.15 P=.29 | F_(1,91.3)=9.3 P=.003 | F _(1,91.6) =1.17 P=.28 |

932 Performance was set as the dependent variable and effort as independent variable. Complementary
933 to Figure S2.

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937 **Publications from the dataset COFITAGE – June 2022**

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