Increased cortical excitability but stable effective connectivity index during attentional lapses

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Abstract

Modern lifestyle curtails sleep and increases night-time work and leisure activities. This has a deleterious impact on vigilance and attention, exacerbating chances of committing attentional lapses, with potential dramatic outcomes. Here, we investigated the brain signature of attentional lapses and assessed whether cortical excitability and brain response propagation were modified during lapses and whether these modifications changed with aging. We compared electroencephalogram (EEG) responses to transcranial magnetic stimulation (TMS) during lapse and no-lapse periods while performing a continuous attentional/vigilance task at night, after usual bedtime. Data were collected in healthy younger (N=12; 18-30 y) and older individuals (N=12; 50-70 y) of both sexes. The amplitude and slope of the first component of the TMS-Evoked Potential (TEP) were larger during lapses. In contrast, TMS response scattering over the cortical surface, as well as EEG response complexity, did not significantly vary between lapse and no-lapse periods. Importantly, despite qualitative differences, age did not significantly affect any of the TMS-EEG measures. These results demonstrate that attentional lapses are associated with a transient increase of cortical excitability. This initial change is not associated with detectable changes in subsequent effective connectivity - as indexed by response propagation - and are not markedly different between younger and older adults. These findings could contribute to develop models aimed to predicting and preventing lapses in real life situations.

Keywords: Vigilance, lapses, Transcranial Magnetic Stimulation, Electroencephalogram, Errors, Aging, Sleep

Statement of Significance

We show that attentional lapses as detected during a visuomotor attentional task are characterized by a transient increase of cortical excitability, measured using EEG responses to TMS pulses, without affecting brain effective connectivity as indexed by response propagation over the cortical surface. Importantly cortical excitability changes were not markedly different in younger and older adults. These results shed new light on the brain signature of attentional lapses and could contribute to better predict and prevent lapses in real-life situations.

1. Introduction

Attention is a cognitive process that is required for the normal functioning of other cognitive domains. When attention is not focused on the environment, we can experience a detachment that may lead to lapses of attention. Lapses are more prevalent when vigilance decreases, and can contribute to errors[1]. Their full electrophysiological characterization could therefore contribute to error detection, anticipation, and prediction, which is of foremost importance in many disciplines in which they can have catastrophic consequences (e.g. driving, medicine, military, industry, etc.).

The prevalence of attentional lapses is tightly related to the regulation of sleep and wakefulness. During the day, while well-rested, they are relatively rare, because sleep need is low and the circadian system helps to maintain wakefulness[2]. If one extends wakefulness during the night beyond habitual sleep time, sleep need further increases while the circadian system promotes sleep, such that lapses become more frequent[1,3]. Invasive recordings in animals have associated lapses with local and transient periods of neuronal silence (OFF-periods), which resemble what happens during sleep[4,5]. Intracranial recordings in a few epileptic patients showed that neuronal spiking in response to stimulations is attenuated, delayed, and lengthened before cognitive lapses[6]. In addition, slower EEG activity of local field potentials remains relatively high prior to and during lapses[6]. A similar phenomenon may therefore take place in animals and humans during lapses of attention. Yet, the neural bases of attentional lapses have not been fully characterized in healthy human beings, likely in part because isolating an attention lapse is not straightforward. Boundaries of lapses are difficult to define since a lapse often consists in the absence of response to stimulus[7]. In addition, lapses may alter sensory perception or higher cognitive functions[8]. In this context, transcranial magnetic stimulation coupled to electroencephalography (TMS-EEG) represents an ideal mean to probe the neural mechanisms underlying lapses. TMS triggers brain responses over a relatively small area of the cortex and mimics normal brain functioning,

while bypassing sensory inputs and processing[9]. Once EEG is recorded, one can characterize brain responses in terms of shape, propagation, and complexity[9].

Cortical excitability reflects the responsiveness and response selectivity of cortical neurons to stimulations and can be probed with TMS-EEG[9]. Its sensitivity to both sleep need and the circadian system has been demonstrated[10,11], as well as its changes during sleep[12]. Cortical excitability progressively increases with wakefulness extension, with local influences of the circadian system exacerbating the night-time increament[11]. TMS response propagation varies during prolonged wakefulness. When focusing on the night-time period, when one would be normally asleep, participants with lower response propagation perform worse on a vigilance task, suggesting that a reduction in response spreading at night is associated with worse performance and a potentially higher number of lapses[13]. During slow wave sleep, a further increase of cortical excitability and a limited response propagation is observed[12] concomitantly to a reduction in response complexity[14]. Whether similar changes happen during attentional lapses is unknown.

Modifications in sleep and wakefulness regulation are hallmarks of the aging process[15,16]. Sleep becomes “shallower”, more fragmented, and more sensitive to challenges over the adult lifespan[17,18], while the circadian system advances sleep timing and seems to send a weaker sleep and wakefulness promoting signal[19,20]. However, one suffers less from acute sleep loss in aging, such that lapses are less common in older individuals during sleep deprivation[21]. Cortical excitability dynamics during wakefulness extension is also dampened in aging, reflecting both a reduction in strength of both sleep homeostasis and circadian signals[22]. Whether age-related changes in sleep-wake regulation are reflected in modifications in cortical excitability and brain response propagation during lapses of attention has not been investigated.

Here, we performed a retrospective analysis of TMS-EEG studies to compare TMS-evoked potentials (TEP), as a probe for cortical excitability, and TMS response spatial

propagation over the cortex, as a proxy for effective connectivity, during lapses of attention versus normal periods with no-lapse. We collected data recorded at night in healthy younger and older adults, and assessed whether lapses of attention were associated with detectable alteration in cortical excitability and TMS response propagation. Our hypothesis was that cortical excitability and response propagation would, respectively, increase and decrease during lapses, and to a greater extent in younger compared to older individuals.

2. Methods

Data included in this analysis were retrospectively selected among three different studies, including repeated assessment of cortical excitability using TMS-EEG over the superior frontal gyrus during wakefulness extension protocols[11,15,22]. All studies were approved by the Ethics Committee of the Faculty of Medicine at the University of Liège, Belgium. Participants gave their written informed consent prior to entering the study and received financial compensation.

2.1. PARTICIPANTS

Participants' exclusion criteria were as follows: Body Mass Index (BMI) ≤ 18 and ≥ 29; recent psychiatric history or severe brain trauma; addictions, chronic medication affecting the central nervous system; hypertension; smoking, excessive alcohol (> 14 units/week) or caffeine (> 9 cups/day) consumption; shift work in the past 6 months; transmeridian travel in the past two months; anxiety, as measured by the 21-item self-rated Beck Anxiety Inventory (score ≥ 10)[23]; depression, as assessed by the 21-item self-rated Beck Depression Inventory (score ≥ 14)[24]. Participants with stable treatment (for > 6 months) for hypertension and/or hypothyroidism were included in the study. Participants with sleep apnea (apnea-hypopnea index ≥ 15/hour) were excluded based on in-lab adaptation and screening night of polysomnography. Older participants with clinical symptoms of cognitive impairment were excluded [Dementia rating scale < 130[25] or Mini mental state examination (MMSE) < 27[26]].

Twelve individuals aged between 18 and 30 years old and 12 individuals aged between 50 and 70 were included in the current analyses (**Table 1**).

[Table 1 here]

2.2. EXPERIMENTAL PROTOCOLS

Structural MRI was performed on a 3-Tesla MR scanner (MAGNETOM Prisma, Siemens, Germany) through a T1-weighted MPRAGE sequence (*TR = 7.92 ms, TE = 2.4 ms, TI = 910 ms, FA = 15°, FoV = 256 x 224 x 176 mm³, 1 mm isotropic spatial resolution)*. Structural data were used for TMS-neuronavigation and EEG source reconstruction. All participants completed a "pre-test" TMS-EEG session to select the optimal stimulation point over the superior frontal gyrus to avoid muscular or electromagnetic artefacts. Participants were then asked to maintain regular sleep-wake schedules during the 7 days preceding the experiments (+/- 30 min). Compliance was verified using sleep diaries and wrist actigraphy (Actiwatch©, Cambridge Neurotechnology, UK) which was analysed with pyActigraphy (DOI: http://doi.org/10.5281/zenodo.2537921) to assess sleep and wake times. If a participant deviated from her/his schedule > 30 min more than once over the 7 days preceding the experiment, s/he was either excluded or rescheduled to a later date. On the day preceding the experiment, participants arrived at the laboratory 6 to 8 hours before their habitual bedtime and were kept in dim light (< 5 lux) for 5 to 6.5 hours preceding bedtime. They then slept in the laboratory at their habitual sleep and wake times under EEG recording (in darkness, 0 lux). A TMS-compatible EEG cap was placed upon awakening and remained for the whole duration of the protocol. Participants remained awake in dim-light (5 lux) for the 20[15], 29[11], or 35 hours[22] following wake time, including repeated TMS-EEG assessments. To increase the likelihood of lapses, only night-time TMS-EEG recordings were considered in the analyses in each study, following ~19h[15] and ~24h[11,22] of continuous wakefulness, corresponding to 2AM and 7AM for a subject waking up at 7AM (**Table 1; Figure 1A; Supplementary Table S1**). To be included in the analyses, the session had to include at least 20 lapses as defined below.

2.3. TMS-EEG DATA ACQUISITION

Stimulation and neuronavigation were achieved with a Navigated Brain Stimulation (NBS) system (Nexstim, Helsinki, Finland) which uses a focal bipulse 8-shape coil equipped with infrared position sensors and a head tracker allowing for coregistration of T1-weighted structural MR images. Recording was done with a 60-channel TMS-compatible EEG amplifier (Eximia, Helsinki, Finland), equipped with a sample-and-hold circuit to provide TMS-artefact-free data from 5 ms post-stimulation[27]. Electrooculogram (EOG) was recorded with two additional bipolar electrodes. EEG signal was band-pass filtered between 0.1 and 500 Hz and sampled at 1450 Hz. Prior to each recording session, electrodes impedance was maintained < 5 kΩ. Auditory EEG potentials evoked by the TMS clicks and sensory stimulation were minimized by playing a continuous pink noise through earphones and applying a thin foam layer between the EEG cap and the TMS coil[9]. Stimulation point was set on the superior frontal gyrus, contralateral hemisphere to subject's handedness, due to its sensibility to sleep pressure[10], the reduced probability to elicit involuntary reaction such as muscular twitches or eye blinks when stimulated, and its direct involvement in the attentive task used[28,29]. Each session included around 250 pulses, with interstimulus intervals that were randomly set to 1900 to 2200 ms. Participants were continuously monitored by a research staff member during TMS/EEG recording to ensure they would not fall asleep.

2.4. COMPENSATORY TRACKING TASK

During each TMS/EEG recording, participants were instructed to perform a Compensatory Tracking Task (CTT), a visuomotor vigilance task[30]. The task consists in keeping a constantly moving cursor on a central circular target, using a trackball device. Performance is measured as the distance, in pixels, between the cursor and the target. Transitory lapses of attention immediately result in temporary increases of the target-cursor distance. A lapse was defined as a time when the cursor was located outside of a central 200 by 200 pixels box surrounding the target (distance from the screen: 60 cm; size of square: 6.2 cm; visual angle: 6.10°) and >500 ms from the last trackball movement. TMS-

evoked responses occurring during and <1s around a lapse were considered as acquired during a lapse. CTT was preferred to other classic lapse measures, such as the psychomotor vigilance task (PVT)[7], because it does not need the burst-like muscular activity time-locked to the TEP but rather requires continuous smooth and limited movement of a single finger.

2.5. TMS-EEG DATA PROCESSING – CORTICAL EXCITABILITY MEASURES

Data were visualized and processed in MATLAB 2015 (The Mathworks Inc, Natick, MA). Data were visually inspected to reject trials with magnetic artefacts and eye movements. Noisy and artifacted channels were rejected. Data were highpass-filtered at 1 Hz, then downsampled to 1000 Hz and finally lowpass-filtered at 80 Hz. Individual trials were then epoched between -100 and 300 ms post TMS. Baseline correction between -100 and -1.5 ms was applied before averaging across trials, using robust averaging method[31], a method which estimates the data distribution of each time bin and downweights strong deviants (> 5 standard deviations). The electrode closest to the TMS-EEG target in the stimulation hemisphere was chosen to extract excitability. Excitability of the cortex was inferred based on the first component of the averaged TEP (0-30 ms; **Figure 1E**). Amplitude (in µV) and maximal slope (referred to as slope, µV/ms) were the main parameters extracted to define cortical excitability, together with the latencies to the first negative and positive peaks of the TEP.

2.5. TMS-EEG DATA PROCESSING – RESPONSE SCATTERING AND COMPLEXITY

We computed brain response scattering (ReSc) – i.e. propagation -, at the cortical surface following EEG source reconstruction, as well as complexity (ReC) for exploratory purposes. The solutions for EEG source reconstruction depend on the signal-to-noise ratio. Therefore, the fact that lapses are inherently less frequent than no-lapse periods was likely to bias comparison across conditions. We therefore recomputed the EEG response average and variance matching TMS pulse number across lapses and no-lapses period at the

individual level (**Figure 2B-C**). Included no-lapse TMS pulses consisted of those at were least 2 pulses apart from lapses and immediately following of preceding them. If a lapse included several TMS pulses, we considered as many surrounding pulses as no-lapse pulses.

Source reconstruction followed the procedure previously described[13]. Briefly, the averaged TMS-evoked EEG response from 0 to 300 ms post-TMS pulse on all available channels was used to obtain a spatio-temporal matrix of significant cortical sources. Sensor and fiducial positions were used for a realistic head model with Boundary Element Method (BEM) constructed based on individual MRI, sensor and fiducial positions, to perform all the analyses within the individual subject space. The inverse solution was based on the "Multiple Sparse Prior" (MSP) method with 5124 dipoles to model the propagation of significant current in the brain induced by the stimulation. ReSc consists of the sum of the geodesic distance between significant sources and the TMS target, averaged over the entire 5–300 ms period post-TMS **Figure 1F**).

ReC was computed at the sensor level using balanced number of trials across lapses and no-lapse periods by applying the algorithm for estimating perturbational complexity to an evoked response[32]. The algorithm aims to estimate the spatio-temporal complexity with on a transition matrix which quantifies the complexity of the trajectories of an evoked brain signal (i.e., a TEP) over the reduced dimensionality space of its principal components. A lower ReC means that the brain response is more stereotypical, less variable over time and space. Importantly, in the current study, the processing of the data is different from the original paper TEP[32] so that a comparison of absolute values between studies is not pertinent, while it provides relevant insights about complexity relative changes.

[Figure 1 Here]

2.6. STATISTICAL ANALYSIS

Statistical analyses were performed with SAS version 9.4 (SAS, Institute, Cary, NC, USA). The outlier threshold was set at 3 standard deviations from the mean, but no outlier values were detected. TEP amplitude, slope, and latencies, as well as ReSc, constituted dependent variables of separate Generalized Linear Mixed Models (GLMM; PROC GLIMMIX SAS procedure), considering subject as random factor and response type (lapse, no-lapse) as repeated measures with autoregressive correlation type 1 (ar(1)). Dependent variable distributions were estimated using the allfitdist function in MATLAB (developed by Mike Sheppard, part of the MvCAT package[33]) and set accordingly in each GLMM. Models included the following covariates: age group, sex, BMI, and TMS parameters (mean generated electric field at the hotspot and electrode of interest distance from hotspot). A factor "study", together with response-type-by-study and response-type-by-age-group interactions were included to take into account that each study session of interest was acquired at different times-of-day/circadian phases, leading to differences between age-groups in elapsed time awake and in circadian phase. Partial effect sizes of the significant effects were calculated based on semi-partial R-squared ($R^2_{\beta*}$) computation for GLMM according to the literature[34]. We set the significance threshold to p-value = 0.01, accounting for Bonferroni correction for testing five models.

For all frequentist GLMMs were also computed complementary Bayesian repeated measure ANOVAs (linear mixed model) using JASP software (version 0.13.1.0[35]) to assess further whether a factor was contributing or not to a given model. Similar to the frequentist analyses, Bayesian rm-ANOVAs were computed with subject as random factor and response-type (lapse, no-lapse) as repeated measure and including age group, study, and TMS parameters as covariates. Including more covariates results in a model too complex for JASP software to converge. Separate models including sex and BMI as covariates showed not effect of these covariates (data not shown) and do not change the conclusions drawn

from Bayesian estimations. Inclusion Bayes factor ≤ 0.3 and ≥ 3 respectively indicate an absence of contribution or a non-negligible contribution[35].

3. Results

As indicated in **Table 1**, except for BMI and caffeine consumption where older individuals had higher values, age groups did not differ for any demographic factor such as sex of the participants and the number of lapses per session.

When assessing differences between electrophysiological measures between lapses and no-lapse periods, we first considered slope of TEP as the most typical assessment of cortical excitability[10,11]. GLMM including sex, age, BMI, study and TMS parameters as covariates indicated that response type (lapse vs no-lapse) significantly affected TEP slope, with higher slope for lapse compared to no-lapse periods (p = .009) representing a large effect size ($R^2_{\beta^*}$ = .29) (**Figure 2A,E; Table 2**). Similarly, TEP amplitude showed an effect of response type (p = .0003) with higher amplitude for lapses vs. no lapse periods, representing a large effect size ($R^2_{\beta^*}$ = .48) (**Figure 2B,E; Table 2**). We further found that latencies of the first TEP negative and positive peaks were, respectively, shorter and longer for lapses vs. no lapse periods (negative peak: p = .0007; large effect size, $R^2_{\beta^*}$ = 0.45; positive peak: p = .008, large effect size: $R^2_{\beta^*}$ = 0.30) (**Figure 2C-E; Table 2**). Bayesian statistical analysis confirmed the strong main effect of response-type (lapses vs no-lapses) for amplitude ($BF_{inclusion}$ = 34.229) as well as positive latency ($BF_{inclusion}$ = 4.113). In contrast, it did not allow to draw conclusion (0.3 ≤ $BF_{inclusion}$ ≤ 3) on the main effect of response-type effect for neither slope ($BF_{inclusion}$ = 0.961), nor negative latency ($BF_{inclusion}$ = 0.423) (**Table 3**). Given the unbalanced number of trials across response type (lapse < no-lapse period), we recomputed statistical included equal individual numbers of trials for both response types, considering only the no-lapse periods near lapses. Except for a noticeable change in noise level, average response over the no-lapse period appears similar when including all or the reduced set of TMS pulses (**Figure 2B-C**), particularly over the early component of the TEP.

Accordingly, statistical outcomes of the analyses of TEP cortical excitability measures remain the same with the reduced set of TMS pulses for the no-lapse period (data not shown).

[Figure 2 Here]

[Table 2 here]

Importantly, age group and the interaction between age and response-type were not significantly associated with any of the 4 TEP parameters, suggesting that differences between lapses vs. no-lapse periods did not differ across age groups (**Table 2**). Inclusion Bayesian factor associated with age or the interaction between age and response type provided no evidence for an effect of age ($BF_{inclusion}$ < 3) on TEP slope and both latencies (age: $BF_{inclusion}$ < 2, P(incl|data) < 0.85; age x response type: $BF_{inclusion}$ < 0.84, P(incl|data) < 0.28). In contrast, Inclusion Bayesian factor indicates an main effect of age for TEP amplitude ($BF_{inclusion}$ = 4.734, P (incl|data) = 0.93), but no evidence of an interaction between age and response-type ($BF_{inclusion}$ = 2.935, P(incl|data) < 0.575). In other words, Bayesian approach indicates that amplitude is lower in older compared to younger participants, but it does not provide evidence in favour nor against a contribution of age in the differences detected between lapses and no-lapse periods.

We then turned to TMS Response Scattering (ReSc) to assess whether TMS response propagation would differ between lapses and no-lapse periods. GLMM yielded no significant difference in ReSc during lapses as compared to no-lapse periods (p = .73) (**Figure 3; Table 2**). A significant effect of age was detected (p = .02, $R^2_{\beta^*}$ = 0.29), with older individuals showing reduced ReSc, as well as a significant interaction between age and response-type (p = .05, $R^2_{\beta^*}$ = 0.18), with a reduced difference between lapses and no-lapse periods in older individuals but these effects did not reach corrected statistical significance. Bayesian analyses provided no evidence in favour or against of an effect of response-type ($BF_{inclusion}$ = 0.430, P (incl|data) = 0.546) and age group difference ($BF_{inclusion}$ = 0.424, P

(incl|data) = 0.543) but yielded evidence against an interaction between age and response-type ($BF_{inclusion}$ = .24, P (incl|data) = 0.1). Finally, to assess whether the local cortical excitability differences between lapses and no-lapse reported above could have contributed to differences in ReSc, we added TEP amplitude in the model. TEP amplitude was not associated to ReSc ($F_{(1,\ 27.71)}$ = 0.11, p = .75) and the main effect of age group was only marginally affected (p = .037) while the interaction between age and response type becomes non-significant (p = .06), suggesting that the uncorrected-for-multiple-comparison interaction initially detected may arise from the initial difference in cortical excitability.

[Figure 3 here]

4. Discussion

We used TMS-EEG to measure cortical excitability and brain response propagation during lapses and no-lapse periods while performing a continuous vigilance/sustained attention task. We report that, during attentional lapses, the first component of TEP shows a significant increase in slope, amplitude, and latency to its positive peak together with a shorter negative peak latency. In line with our hypothesis, these results demonstrate that cortical excitability is increased during lapses of attention. Yet, in contrast with our original hypothesis, these changes in cortical excitability were not associated with changes in TMS response propagation, as indexed by ReSc. This indicates that, once initiated, the dispersion of the TMS response does not depend on the occurrence of attentional lapses. Finally, and again contrary to our expectation, we find no clear evidence that age might affect cortical excitability and ReSc during lapses.

Increased cortical excitability is observed when wakefulness is extended into the biological night and during healthy human sleep[12]. Recent findings indicate that cortical excitability, inferred based on the amplitude of an early TMS-evoked EEG response, varies according to concomitant variations in alertness, indexed based on theta/alpha EEG rhythm

ratio and Hori scoring system[36]. Extending these findings, we show that night-time cortical excitability increases during lapses as compared to normal attention periods. All these changes are arguable part of the same continuum, but the underlying mechanism is unclear. Animal data showed that local neuronal silent periods are more prevalent with increasing wakefulness duration and sleep deprivation, similarly to neuronal off-periods, or down-states, during sleep[5]. During sleep, these off-periods contribute to neuronal firing synchrony to generate the typical EEG slow waves, while during wakefulness off-periods are associated with slower local field potential variations, slower scalp EEG oscillations and reduced performance. Similarly, investigation in epileptic human patients indicates that attentional lapses during normal wakefulness are preceded and concomitant to attenuated, delayed, and lengthened spiking of individual neurons in the medial temporal lobe[6]. These effects appeared exacerbated following sleep deprivation, although based on a few patients only. We are not in a position to truly assess whether off-periods during lapses indirectly contributed to the observed increase in excitability as it would require invasive recordings and/or phase assessment of the EEG oscillation at which TMS pulses were delivered (and therefore more trials). A parsimonious explanation for a larger initial EEG response to TMS pulses is that neurons are more hyperpolarized during lapses and/or have a higher input resistance potentially because of temporary fluctuations in neuromodulator levels, such as acetylcholine[37] or norepinephrine[38]. Excitatory Post Synaptic Potentials (EPSP) would therefore trigger action potentials more easily so that more neurons would contribute to the response, leading to a strong change in TEP amplitude. In other words, some neurons would be responding to the TMS pulse, which mimics normal stimulus brain processing, when they would not outside a lapse, resulting in altered cortical neuron response selectivity. The fact that we find no Bayesian evidence in favour of a main effect of response-type (lapses – no lapse periods) on slope suggest that, in comparison to the recruitment of neuron numbers during lapses, neuron synchrony is not deeply modified during lapses. Finally, increased cortical excitability during lapses could also be related to cortical and/or thalamic neurons responding more prominently with a burst during lapses[39,40].

To explore long-range response to TMS, we assessed whether TMS response complexity (ReC)[32] differed between lapses and no-lapse period, bearing in mind that optimal ReC computation requires more trials (> 100; i.e. better signal-to-noise ratio). Analyses suggest that ReC does not change during lapses, reinforcing the idea of an intact brain processing following initial response (**Supplementary Figure S1)**. The assumption remains to be properly tested however, using for instance functional magnetic resonance imaging and/or other behavioural tests. Yet, the fact that response propagation does not seem to significantly change during night-time lapses suggests that, despite an overall reduction of long-range signal propagation and integration during sleep deprivation[4], long-range cortical processing remains mostly unchanged during lapses. Our result could mean therefore that impaired brain processing, slower behavioural responses, reduced performance, and/or absence of response during lapses are mostly triggered by an alteration of the initial cortical responses rather than by altered functioning of higher cortical areas.

Contrary to frequentist statistics, Bayesian statistics indicate a main effect of age group on TEP amplitude, irrespective of the occurrence of a lapse. This apparent difference between age-groups is most likely derived from the selection of night-time sessions for the present analyses. Aside from important inter-individual variability[15], cortical excitability indices of older individuals remain overall relatively stable during prolonged wakefulness[22], when younger individual show important increases in these indices at night. This means that while cortical excitability is similar between younger and older adults during the day, younger individuals present significantly higher values at night. In other word, the most parsimonious explanation for the non-negligible effect of age detected for TEP amplitude is that the effect of being awake at night, when one should normally be sleeping, on cortical excitability is more important in younger than in older individuals.

Similarly, using frequentist statistics, we find that ReSc, and therefore effective connectivity, may be lower in older individuals irrespective of lapse occurrence at a significant threshold uncorrected for multiple comparisons. Using Bayesian statistics we find

evidence against an age-group difference. In a separate analyses (data not shown, unpublished analyses by GG) we find that ReSc associated with TMS response during no-lapse period is lower in older individuals at all circadian phases, i.e. during the day and overnight. Lower ReSc may be related to the changes in spontaneous EEG activity in aging reported both during wakefulness and sleep[18,41]. It may also be underlined by a degradation of the brain white and grey matter[42] which could, respectively, result in a higher dispersion of the electrical response, to a reduced number of neurons responding to TMS, or to difference excitation/inhibition balance[43,44]. Despite this overall difference in ReSc and contrary to our expectations, our results suggest that, age was not associated with modifications in the electrophysiological changes associated to lapses. In fact, Bayesian analyses support it is not the case for ReSc. Therefore, the large impact of aging on sleep and wakefulness regulation[19,20], with a reduced prevalence of lapses during acute sleep deprivation in older individuals, and the more stable sleepiness and EEG spectral composition[45,46], is not reflected in significant changes in the phenomenology of lapses *per se,* both when considering cortical excitability and response propagation. We stress that we only included individuals with at least 20 lapses in the session considered to ensure good signal-to-noise ratio of the average electrophysiological response. Whether the reduced number of trials and the exclusion of participant with less lapses contributed to the absence of age group difference is not known.

EEG recordings of TMS responses can be used to study cortico-cortical interactions from a causal perspective. In that respect, ReSc constitutes an index of effective connectivity. The reduction in TMS response propagation during sleep was interpreted as reduced effective connectivity that is essential to loss of consciousness[12]. Our participants did not sleep during the TMS-EEG recordings – even micro-sleep –, as they were closely monitored, and they were conscious. In that respect, it is not surprising that ReSc remains stable during lapses when compared to normal attention. One can however arguably postulate that their consciousness was altered during lapses vs. no-lapse periods.

Interestingly previous observation[12] suggests that, as compared to normal wakefulness, cortical excitability increases while response propagation remains wake-like during REM sleep[47], which is a conscious experience while behaviourally detached from the environment. Future research will tell whether other awake detached behaviour, such as mind-wandering or mind blanking[48] resemble lapses and/or REM sleep in terms of cortical excitability and effective connectivity.

In addition, whether cortical excitability and brain response propagation (and effective connectivity) are qualitatively or quantitatively similarly affected by attentional lapses after sleep deprivation or by those, more sporadic, detected during normal rested wakefulness, remains to be assessed. Night-time/sleep deprivation lapses are likely to favour sleep onset, while daytime lapses are less likely to do so, such that one can expect brain activity differences. Moreover, since we only stimulated the frontal cortex, which shows the largest increase in sleep slow wave prevalence following sleep loss[49], we expect regional differences in cortical excitability changes associated with lapses. On the other hand, given that sleep slow wave power shows a relative increase over the entire brain following sleep loss, we expect also a relative increase in excitability during lapses whatever the stimulated brain region[50]. Quantifying local vs. global variations will require further investigations. Likewise, since ReSc is a global brain measure, we consider that our findings reflect the stability of whole-brain effective connectivity during a lapse. This does not preclude, however, the origin of the initial brain response to affect its propagation.

In conclusion, we report that during night-time attentional lapses, cortex excitability is higher while brain responses propagation remains unchanged, both in younger (18-30 years old) and older (50-70 years old) individuals. The relevance of these findings is not limited to the theoretical understanding of sleep and wakefulness regulation but may help online detection of lapses and interventions to prevent errors (e.g. through closed-loop electrophysiological stimulation[51,52]).

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Authors Contribution

PC, MVE, JN, DC, GG and GV collected and preprocessed the data. Data reanalysis: PC. Manuscript drafting: PC, GV. Manuscript editing: All.

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Figures captions:

Figure 1: Overview of protocol and analysis. A. Overview of the studies retrospectively analyzed and selected TMS/EEG sessions (Study 1[22], 2[11] and 3[15]; see method for more details). **B-D.** Butterfly plot of the average TMS responses over all 60 channels in a representative subject, when considering all no lapse periods (**B**) and all lapses (**D**), and when considering an equal (lower) number of no-lapse period TMS pulses to include the same number of pulses as during lapses (**C;** see method). **E.** Average TMS response of the electrode closest to the stimulation point, from which the following are extracted *a)* Latency of the negative peak *b)* Latency of the positive peak *c)* Peak to peak amplitude *d)* Steepest slope, i.e. the tangent at the inflection point. **F.** Response scattering (ReSc) was computed following EEG source reconstruction and binarization of the significant and non-significant sources in time and space. ReSc is computed from this spatiotemporal binary matrix (ST) from 5 ms post-TMS to 300 ms post-TMS (t) as the sum of geodesic distance (d) between significant sources (x) and the TMS target.

Figure 2: Early TMS-evoked response during lapse and no-lapse periods. Amplitude (**A**), slope (**B**), negative (**C**) and positive (**D**) peak latencies during lapse and no-lapse periods in both age groups (Red = Older, Blue = Young). Individual lines represent single-subject values. Dots are the group means and the vertical bars represent the standard error. (**E**) TEP during lapse and no-lapse in a representative subject.

Figure 3: Response Scattering (ReSc) during lapse and no-lapse periods. ReSc during lapses and no-lapses in both age groups (Red = Older, Blue = Young). Individual lines represent single-subject values. Dots are the group means and the bars represent the standard error.

Table 1: Demographics of the young and older groups

	Young	Older	Comparison
Number of subjects	12	12	
Age (y)	22 ± 2.76	59.58 ± 6.46	
Sex: Female (Male)	2 (10)	6 (6)	p = .19
Body Mass Index (kg/m²)	22.05 ± 2.59	25.08 ± 1.68	**p = .003**[&]
Number of lapses (mean ± s.d.)	46.08 ± 30.91 Median: 31.5 Range: 25-116	41.25 ± 21.35 Median: 35 Range: 21-100	p = .66
Right-handed	11	10	p = 1
Mill Hill vocabulary scale*	22.17 ± 3.65	25.5 ± 3.2	p = .07
Anxiety	2.50 ± 2.54	2.92 ± 2.64	p = .7
Mood	2.7 ± 2.59	4.00 ± 4.30	p = .28
Caffeine (cups/day)	1.33 ± 1.97	3.96 ± 2.68	**p = .01**
Alcohol (doses/week)	3.92 ± 3.58	5.17 ± 4.79	p = .48
Subjective sleep quality	4.17 ± 1.19	6.67 ± 4.25	p = .07
Daytime sleepiness	4.67 ± 2.84	4.67 ± 3.85	p = 0.99
Chronotype	53.75 ± 5.07	52.67 ± 8.90	p = .72
Elapse time awake at TMS assessment (hrs)	23.65 ± 1.72	20.38 ± 2.49	**p = .001**[&]
Degrees relative to dim-light melatonin onset (15° = 1h) at TMS assessment (hrs)	149.03 ± 25.66	95.63 ± 38.06	**p = .0006**[&]

All values correspond to mean ± SD. Cognitive performance was measure by the Mill Hill Vocabulary Scale [26]; Anxiety by the 21-item Beck Anxiety Inventory[22]; depression by the 21-item Beck Depression Inventory II[23]; caffeine and alcohol consumption by self-reported questionnaires; subjective sleep quality by the Pittsburgh Sleep Quality Index[27]; daytime sleepiness by the Epworth Sleepiness Scale[28]; chronotype by the Horne-Östberg questionnaire (no participants were extreme chronotypes, i.e. scores <30 or >70)[29].

*Mill Hill scale was administered to 6 young participants.

[&] these factors are included in the statistical model reported here-after. Differences in elapse time awake and circadian phase are taken into account by including a "study" factor.

Table 2: GLMM outcomes for the four excitability measurements and response scattering (ReSc). Significant results (following multiple testing correction; p = 0.01) are in bold. When a variable reaches uncorrected-for-multiple-comparison significance level (p < 0.05), the partial effect size is reported.

Dependent Variables	Independent variables								
	Response Type	Study	Age Group	Response Type * Study	Response Type * Age Group	Sex	BMI	Induced Electric Field	Electrode distance
Slope	**$F_{(1,20)}$ = 8.30 p = .009 $R^2_{\beta^*}$ = 0.29**	$F_{(2,16)}$ = 0.07 p = .93	$F_{(1,16)}$ = 1.27 p = .93	$F_{(2,20)}$ = 0.21 p = .81	$F_{(1,20)}$ = 2.90 p = .10	$F_{(1,16)}$ = 0.16 p = .70	$F_{(1,16)}$ = 0.02 p = .90	$F_{(1,16)}$ = 0.02 p = .90	$F_{(1,16)}$ = 0.76 p = .40
Amplitude	**$F_{(1,20)}$ = 18.75 p = .0003 $R^2_{\beta^*}$ = 0.48**	$F_{(2,16)}$ = 0.06 p = .95	$F_{(1,16)}$ = 1.26 p = .28	$F_{(2,20)}$ = 0.18 p = .84	$F_{(1,20)}$ = 2.97 p = .10	$F_{(1,16)}$ = 0.09 p = .77	$F_{(1,16)}$ = 0.00 p = .99	$F_{(1,16)}$ = 0.04 p = .85	$F_{(1,16)}$ = 0.17 p = .69
Negative Latency	**$F_{(1,20)}$ = 16.11 p = .0007 $R^2_{\beta^*}$ = 0.45**	$F_{(2,16)}$ = 0.09 p = .92	$F_{(1,16)}$ = 0.94 p = .35	**$F_{(2,20)}$ = 6.19 p = .008 $R^2_{\beta^*}$ = 0.38**	$F_{(1,20)}$ = 1.54 p = .23	$F_{(1,16)}$ = 1.06 p = .32	$F_{(1,16)}$ = 0.21 p = .65	$F_{(1,16)}$ = 0.00 p = .96	$F_{(1,16)}$ = 0.63 p = .44
Positive Latency	**$F_{(1,20)}$ = 8.61 p = .008 $R^2_{\beta^*}$ = 0.30**	$F_{(2,16)}$ = 1.77 p = .20	$F_{(1,16)}$ = 1.74 p = .21	$F_{(2,20)}$ = 0.11 p = .90	$F_{(1,20)}$ = 1.07 p = .31	$F_{(1,16)}$ = 0.51 p = .49	$F_{(1,16)}$ = 0.30 p = .59	$F_{(1,16)}$ = 3.90 p = .07	$F_{(1,16)}$ = 0.03 p = .87
ReSc	$F_{(1,20)}$ = 0.12 p = .73	$F_{(2,17)}$ = 3.06 p = .07	$F_{(1,17)}$ = 6.29 p = .02 $R^2_{\beta^*}$ = 0.27	$F_{(2,20)}$ = 2.29 p = .13	$F_{(1,20)}$ = 4.36 p = .05 $R^2_{\beta^*}$ = 0.18	$F_{(1,17)}$ = 0.01 p = .93	$F_{(1,17)}$ = 0.53 p = .48	$F_{(1,17)}$ = 0.42 p = .52	NA

Table 3: Results of Bayesian repeated-measured ANOVA. Only age group, study and TMS parameters were included as covariates as the inclusion of more covariates did not allow model to converge using JASP software. Separate models including sex and BMI as covariates show not effect of these covariates and does not change the conclusions drawn from the Bayesian estimations reported in the table. Evidence indicating absence of contribution ($BF_{inclusion} < 0.3$) or non-negligible contribution ($BF_{inclusion} > 3$) of a given factor are in bold.

Dependent Variables	Independent variables								
	Response Type	Study	Age group	Induced Electric Field	Electrode distance	Response Type * Study	Response Type * Age Group	Study * Age Group	Response Type * Age Group * Study
Slope	P(incl|data) = 0.729 $BF_{Inclusion}$ = 0.961	P(incl|data) = 0.471 $BF_{Inclusion}$ = 0.318	P(incl|data) = 0.845 $BF_{Inclusion}$ = 1.942	P(incl|data) = 0.340 $BF_{Inclusion}$ = 0.516	P(incl|data) = 0.437 $BF_{Inclusion}$ = 0.775	**P(incl|data) = 0.086 $BF_{Inclusion}$ = 0.203**	P(incl|data) = 0.245 $BF_{Inclusion}$ = 0.704	P(incl|data) = 0.152 $BF_{Inclusion}$ = 0.387	**P(incl|data) = 0.005 $BF_{Inclusion}$ = 0.092**
Amplitude	**P(incl|data) = 0.990 $BF_{inclusion}$ = 34.229**	P(incl|data) = 0.544 $BF_{Inclusion}$ = 0.425	**P(incl|data) = 0.930 $BF_{Inclusion}$ = 4.734**	P(incl|data) = 0.360 $BF_{Inclusion}$ = 0.563	P(incl|data) = 0.398 $BF_{Inclusion}$ = 0.662	P(incl|data) = 0.163 $BF_{Inclusion}$ = 0.422	P(incl|data) = 0.575 $BF_{Inclusion}$ = 2.935	P(incl|data) = 0.212 $BF_{Inclusion}$ = 0.584	**P(incl|data) = 0.016 $BF_{Inclusion}$ = 0.300**
Negative Latency	P(incl|data) = 0.542 $BF_{Inclusion}$ = 0.423	**P(incl|data) = 0.450 $BF_{Inclusion}$ = 0.292**	P(incl|data) = 0.823 $BF_{Inclusion}$ = 1.659	P(incl|data) = 0.457 $BF_{Inclusion}$ = 0.841	P(incl|data) = 0.327 $BF_{Inclusion}$ = 0.486	**P(incl|data) = 0.064 $BF_{Inclusion}$ = 0.149**	**P(incl|data) = 0.089 $BF_{Inclusion}$ = 0.212**	P(incl|data) = 0.147 $BF_{Inclusion}$ = 0.373	**P(incl|data) = 0.005 $BF_{Inclusion}$ = 0.090**
Positive Latency	**P(incl|data) = 0.920 $BF_{Inclusion}$ = 4.113**	P(incl|data) = 0.520 $BF_{Inclusion}$ = 0.387	P(incl|data) = 0.586 $BF_{Inclusion}$ = 0.506	P(incl|data) = 0.386 $BF_{Inclusion}$ = 0.628	P(incl|data) = 0.319 $BF_{Inclusion}$ = 0.468	P(incl|data) = 0.152 $BF_{Inclusion}$ = 0.389	P(incl|data) = 0.279 $BF_{Inclusion}$ = 0.838	P(incl|data) = 0.155 $BF_{Inclusion}$ = 0.397	**P(incl|data) = 0.011 $BF_{Inclusion}$ = 0.196**
ReSc	P(incl|data) = 0.546 $BF_{Inclusion}$ = 0.430	**P(incl|data) = 0.441 $BF_{Inclusion}$ = 0.281**	P(incl|data) = 0.543 $BF_{Inclusion}$ = 0.424	P(incl|data) = 0.320 $BF_{Inclusion}$ = 0.470	P(incl|data) = 0.431 $BF_{Inclusion}$ = 0.759	**P(incl|data) = 0.114 $BF_{Inclusion}$ = 0.280**	**P(incl|data) = 0.119 $BF_{Inclusion}$ = 0.292**	P(incl|data) = 0.187 $BF_{Inclusion}$ = 0.498	**P(incl|data) = 0.016 $BF_{Inclusion}$ = 0.297**

Figure_1

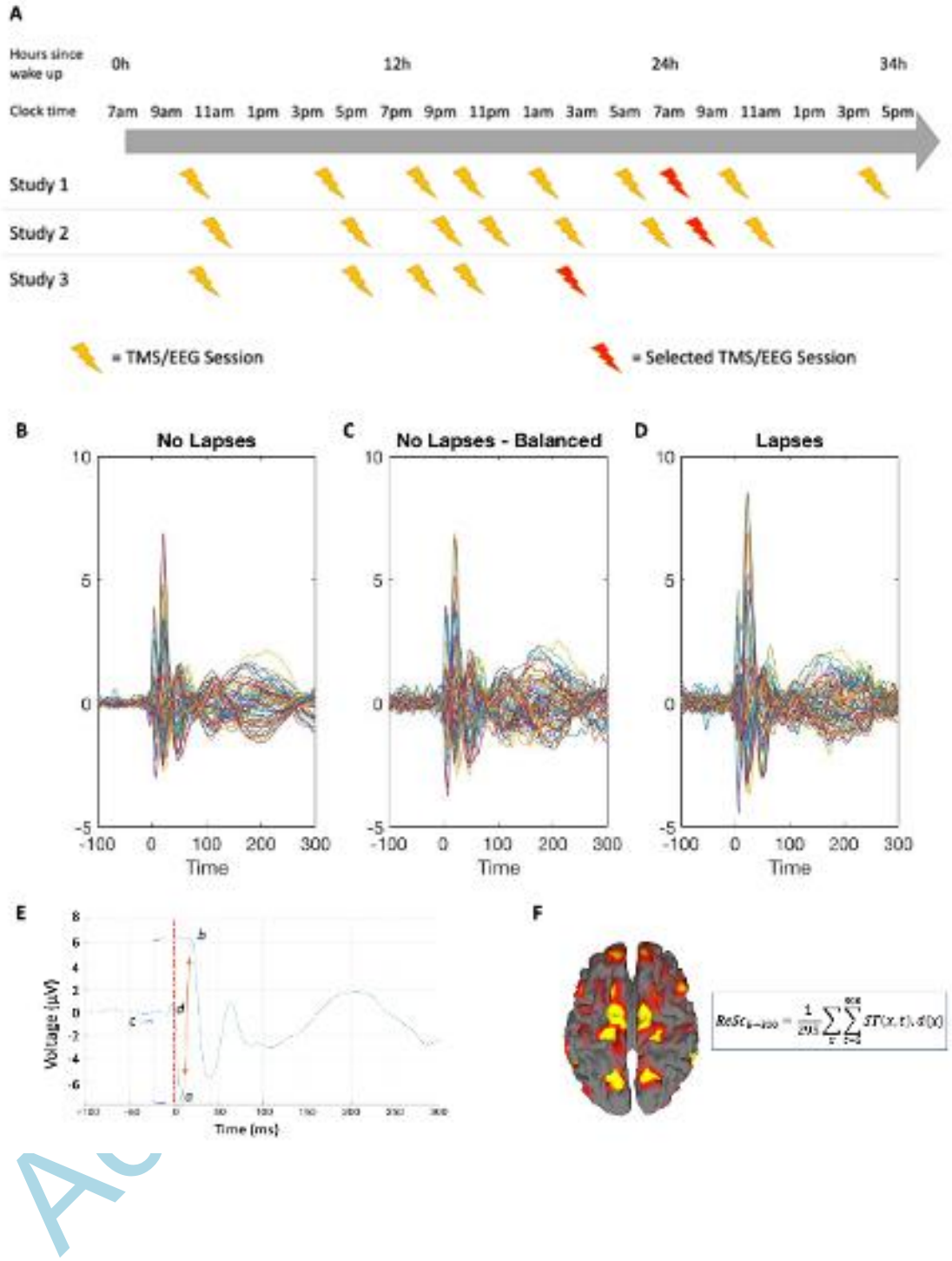

Figure_2

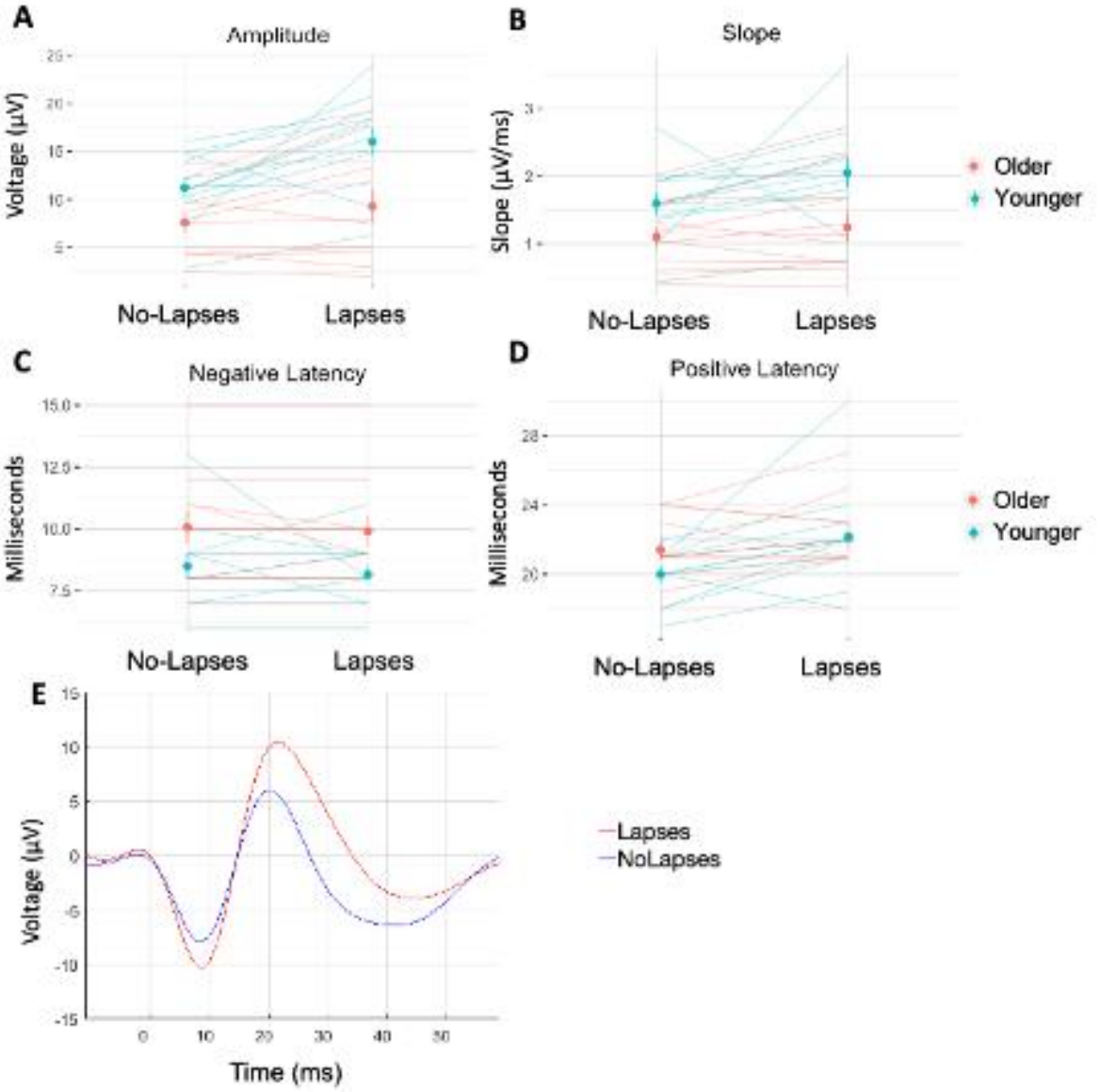

Figure_3