Daily dynamics of resting-state EEG theta and gamma fluctuations are associated with cognitive performance in healthy aging

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Abstract

Objectives: Healthy age-related cognitive changes are highly heterogeneous across individuals. This variability is increasingly explained through the lens of spontaneous fluctuations of brain activity, now considered as powerful index of age-related changes. However, brain activity is a biological process modulated by circadian rhythms, and how these fluctuations evolve throughout the day is under investigated.

Methods: We analyzed data from one hundred and one healthy late middle-aged participants from the Cognitive Fitness in Aging study (68 women and 33 men; aged 50-69 years). Participants completed five EEG recordings of spontaneous resting-state activity on the same day. We used weighted phase-lag index (wPLI) analyses as an index of the functional synchrony between brain regions couplings and we computed daily global PLI fluctuation rates of the five recordings to assess the association with cognitive performance and β-amyloid and tau/neuroinflammation pathological markers.

Results: We found that theta and gamma daily fluctuations in the salience-control executive inter-network (SN-CEN) are associated with distinct mechanisms underlying cognitive heterogeneity in aging. Higher levels of SN-CEN theta daily fluctuations appear to be deleterious for memory performance and were associated with higher tau/neuroinflammation rates. In contrast, higher levels of gamma daily fluctuations are positively associated with executive performance, and were associated with lower rate of β-amyloid deposition.

Discussion: Thus, accounting for daily EEG fluctuations of brain activity contributes to better understand subtle brain changes underlying individuals' cognitive performance in healthy aging. Results also provide arguments for considering time-of-day when assessing cognition for old adults in a clinical context.

Keywords: Brain oscillations, Cognition, Inter-networks connectivity, Ultradian rhythms, late middle-aged individuals

1. Introduction

There is large interindividual variability in human cognitive performance, and performance also fluctuate across the lifespan at the individual level. Evidence exists suggesting that cognitive heterogeneity through human development follows a U-shaped trajectory, with young children showing the greatest heterogeneity, followed by least heterogeneity in young adulthood, and again larger heterogeneity when people grow old (Williams et al., 2005). During aging, some healthy individuals can show slight cognitive decline and are considered as potentially at risk of neurodegenerative pathologies, while others show similar cognitive performance to that of younger individuals. The brain bases of inter-individual variability in cognitive aging remain, however, only partly elucidated.

Fluctuation of brain activity follows an inverted U-shaped curve, such that, compared to young adults, young children and older adults show lower fluctuations in blood-oxygen-level-dependent (BOLD) signal detected in functional magnetic resonance imaging (fMRI) (Garrett et al., 2011) and electroencephalographic (EEG) signal (Sleiman-Malkoun et al., 2015). These spontaneous fluctuations of brain activity were first considered to consist of noise, but are now known to critically contribute to brain function for optimal brain responsivity to changes in the environment (Uddin et al., 2020). Thus, recent imaging studies aim to better understand individual cognitive trajectories in aging through the lens of brain fluctuations (for review, see Waschke et al., 2021). Part of these works documented brain activity fluctuations in resting-state conditions, as it was assumed that brain activity at rest in so-called Resting-State Networks (Uddin et al., 2019) reflect the stable and intrinsic functional connectivity of the brain that is linked with cognitive abilities (Miraglia et al., 2017). Among the six Resting-State Networks (i.e. Central Executive Network (CEN), Salience Network (SN), Default Mode Network (DMN), Dorsal Attention Network

(DAN), Visual System (VS), and Sensorimotor Network (SMN)), reduced fluctuations of brain functional connectivity in older adults were especially measured within the DMN involved in the integration of information across the cortex, and the CEN that interact with the DMN during mind-wandering-state. These reductions of brain fluctuations at rest in older adults were associated to lower cognitive performance relative to young adults, while higher fluctuations of brain functional connectivity were interpreted as reflecting preserved brain communication efficiency and flexibility in aging (Kumral et al., 2020; but see Jauny et al.,2022 regarding delta band activity). These findings provide arguments for further investigating networks' fluctuations at rest to shed new lights on the cognitive heterogeneity in healthy aging.

Brain functional connectivity at rest in aging has increasingly been investigated through the lens of EEG, whose high temporal resolution enables capturing subtle changes in spontaneous neural dynamics over time, and therefore detecting early signs of age-related cognitive decline (Courtney & Hinault, 2021). Time-frequency methods enable to decompose the EEG signal in five frequency bands, namely from the slowest to the fastest rhythm: delta (1-4Hz), theta (4-8Hz), alpha (8-12Hz), beta (13-30Hz) and gamma (30, up to 100Hz). Measures of brain dynamics, such as phase synchrony analyses are used to assess the synchronization of a given rhythm across two distant brain regions, which has been associated with neural communications, and can provide information about cognitive functioning in aging (see Babiloni et al., 2020 for a review). Relative to young adults, a global slowing of brain activity was observed with aging, reflected by an increase of theta and delta phase synchrony and a decrease of beta and gamma phase synchrony, which has been associated with lower cognitive performance (Lopez et al., 2014). Interestingly, older adults with cognitive performance similar to younger individuals exhibit an increase in brain synchrony between distant brain regions, interpreted as a compensatory mechanism (Frutos Lucas

et al., 2020). Noteworthy, normal aging is associated with structural changes and/or the presence of tau and β-amyloid proteins. The abnormal accumulation of these proteins can lead to pathological cognitive decline (Courtney & Hinault., 2021). Impairments in phase synchrony between distant regions underlying specific cognitive processes, occur long before age-related structural alterations or β-amyloid and tau proteins abnormal deposition (Babiloni et al., 2020, 2021). Therefore, EEG signal is a direct marker of brain activity that allows better detection of acute age-related brain changes and their interpretation in regard to individuals' cognitive performance.

In addition, to vary with aging and across individuals, cognition is not stable across the day (Valdez, 2019). Cognitive performance depends on the interplay between prior sleep-wake history, which sets the need for sleep, and the circadian system which promotes wakefulness and cognition during the day, and favors sleep at night (Gaggioni et al., 2019). This interplay also results in daily fluctuations in brain response characterized as cortical excitability, that were linked to cognitive changes in aging, with large fluctuation between the beginning and the end of the day associated with preserved cognitive abilities in healthy older adults (Van Egroo et al. 2019, Gaggioni et al. 2019). However, resting-state connectivity assessed by EEG time-frequency studies have mostly investigated phase synchrony of brain rhythms fluctuations through short single recordings of approximately 5 minutes. Thus, how fluctuation in phase synchrony of brain rhythms evolve throughout the day at resting in healthy aging and how they are associated with cognitive performance remain insufficiently characterized. We reasoned that the fluctuation of phase synchrony should be related to cognitive performance as well as tau and β-amyloids burdens, and could provide novel markers of age-related cognitive decline.

We therefore investigated the variability of brain activity synchrony within resting-state networks across the day in healthy late middle-aged participants aged 50 to 69 years old. Our goals were threefold: i) investigate brain activity synchrony fluctuations across the day at rest in healthy aging: we expected more synchrony fluctuations among networks at the beginning compared to the end of the day, thus reflecting the daily dynamics of brain rhythms fluctuations; ii) study the relationships between global daily networks' rhythms synchrony fluctuations and cognitive performance: we hypothesized that high level of fluctuations during the day would be associated with better cognitive performance, thus reflecting preserved brain efficiency to maintain cognitive abilities; iii) assess the association between global networks' rhythms synchrony fluctuations across the day and pathological markers: we expected that high amount of tau/neuroinflammation would be associated with lower global daily networks' synchrony fluctuations, as it would reflect a deleterious influence on brain functioning and communication.

2. Methods

2.1. Participants

We analyzed data from one hundred and one healthy late middle-aged participants (68 women and 33 men; aged 50-69 years). Based on previous work investigating aging effects on oscillatory activity, a sample size of one hundred and one participants would provide 90% power to detect an effect size of Cohen's f = 0.14, with an alpha = 0.05 (Hinault et al., 2021). No participants reported any recent history of neurological or psychiatric disease or were taking medication affecting the central nervous system. No participant was excluded based on MRI grey or white matter abnormality. Extended information about protocol, exclusion criteria, recruitment, consent and financial reward can be found in previous publications (first in Van Egroo et al., 2019, 2021;

Narbutas et al., 2021; Chylinski et al., 2021, 2022; Rizzolo et al., 2021). A subsample of 64 participants who had data for tau/neuroinflammation-PET imaging was also considered for additional analyses. Demographic characteristics of the final samples are described in Table 1. The study was approved by the Ethics Committee of Medicine Faculty of Medicine of the University of Liège, Belgium.

2.2. Wake-extension protocol

Participants were enrolled in a multimodal longitudinal study designed to identify cerebral biomarkers of normal cognitive aging (the Cognitive Fitness in Aging – COFITAGE – study; Van Egroo et al., 2019). Five EEG recordings of spontaneous resting-state activity were performed on the same day, between 10a.m. and 1a.m. in the context of a wake-extension protocol. The day before, participants arrived to the laboratory 8 hours before their habitual bedtime and were kept in dim light (<5 lux) for 6.5 h preceding bedtime. Following this baseline night, the wake-extension protocol consisted of 20 hours of continuous wakefulness under strictly controlled constant routine conditions, (i.e., in-bed semi-recumbent position, dim light <5 lux, temperature ~19°C, regular isocaloric food intake, no time-of-day information and sound-proofed rooms) to counteract the effect of external influences on endogenous circadian rhythms, assessed with salivary melatonin. Neuropsychological assessment, β-amyloid-PET and Tau/neuroinflammation-PET imaging together with T1-weighted MRI were also acquired on separate visits. All procedures were previously reported (first in Van Egroo et al., 2019, 2021; Narbutas et al., 2021; Chylinski et al., 2021, 2022; Rizzolo et al., 2021) (Figure 1A).

2.3. Neuropsychological assessment

Neuropsychological assessment was administered in two 1.5h sessions and consisted of a battery of cognitive tests assessing three specific domains: memory, attention and executive functions (Table 1; see also Supplementary Table 1 in Supplementary Material for the entire set of neuropsychological assessment). The raw scores were converted to z-scores and three domain-specific composite scores were computed as the standardized sum of z-scores of the domain-specific scores, where higher values indicate better performance. We focused our analyses on the four composite scores (Table 1) and we also included the recognition memory score of the Mnemonic Similarity task (MST), which consists in visually recognizing images of objects incidentally encoded. Previous published work on the COFITAGE database (Rizzolo et al., 2021), in line with the literature (Pishdadian et al., 2020), showed that this score might be an early cognitive marker of memory decline among the group.

2.4. Salivary melatonin assessment

Salivary melatonin was measured by radioimmunoassay (Stockgrand Ltd, Guildford, UK). The detection limit of the assay for melatonin was 0.8 ± 0.2 pg/l using 500 µl volumes. To account for the fact that each participant's circadian phase is variable, and that the course of the protocol might vary slightly between individuals, we considered the Dim-light melatonin onset time (DLMO). DLMO were computed for each participant using the hockey-stick method, with ascending level set to 2.3 pg/ml (Hockey-Stick software v1.5). Saliva samples were collected every hour in order to specify individuals' endogenous circadian rhythmicity during time awake by computing the phase between individuals' wake-up time and individuals' DLMO time (DLMO = phase 0°; 15° = 1h), since we were interested in fluctuations over the course of the day.

2.5. PET imaging

β-Amyloid-PET and Tau/neuroinflammation-PET imaging were performed on an ECAT EXACT+ HR scanner (Siemens, Erlangen, Germany). β-Amyloid-PET imaging was performed with radiotracers [18F]Flutemetamol except for three subjects for which [18F]Florbetapir was used. Tau/neuroinflammation-PET imaging was performed with [18F]THK5351 for all subjects. For both β-Amyloid and tau/neuroinflammation PET imaging, a standardized uptake value ratio (SUVR) was calculated (Table 1). As β-Amyloid-PET imaging were acquired using different radioligands, their SUVR values were converted into Centiloid units (in line with previous works of this cohort, see Van Egroo et al., 2019 and Narbutas et al., 2021). Volumes of interest were determined using the automated anatomical labeling atlas (AAL). β-Amyloid burden was averaged over composite masks covering neocortical regions reported to undergo the earliest aggregation sites for β-Amyloid pathology (frontal medial cortex, fusiform gyrus and temporal gyrus), while Tau/neuroinflammation burden was averaged over regions corresponding to Braak stages of early regional tau pathology (entorhinal cortex and hippocampus). The detailed PET imaging procedure was previously published in Narbutas et al., 2021.

2.6. Anatomical data

Participants' T1-weighted MRI acquisition was performed on a 3-Tesla MR scanner (MAGNETOM Prisma, Siemens) to assess brain grey matter integrity (Table 1). The following parameters were used: repetition time (TR) = 18.7ms; flip angle (FA) = 20 degrees; 3D multiecho fast low angle shot (FLASH) sequence (TR/FA) = 136166; voxel size = 1 mm3 isotropic; acquisition time = 19minutes (see Van Egroo and al., 2019 for detailed parameters). The FreeSurfer (Fischl, 2012) software was used to generate cortical surfaces and automatically

segment cortical structures from each participant's T1-weighted anatomical MRI, to account for individual brain anatomy during source reconstruction.

2.7. EEG recording and analyses

2.7.1. Data acquisition

For each participant, two minutes of resting-state EEG (sampling rate: 1450 Hz, bandpass filter: 0.1-500 Hz) were recorded five times throughout the wake-extension protocol (at 10:00 a.m., 4:00 p.m., 8:00 p.m., 10:00 p.m. and 1:00 a.m.) with a 60-channel EEG system (Eximia, Nexstim, Helsinki, Finland) covering the whole scalp. Participants were instructed to relax and avoid blinking while staring at a black dot.

2.7.2. Pre-processing

Artifact and channel rejection (on continuous data), filtering (0.5-40Hz bandpass, on unepoched data), re-referencing (i.e., using the algebraic average of the left TP9 and right TP10 mastoid electrodes) and source estimation were performed using Brainstorm (Tadel et al., 2011). Physiological artefacts (blinks, saccades) were identified and manually removed through Independent Component Analyses (ICA) using Infomax algorithm (EEGLAB, runica.m). Independent Component Analyses approach consists in removing artifacts from the recording without removing the affected data portions, by identifying spatial components that are independent in time and uncorrelated with each other (Tadel et al., 2011).

2.7.3. Sources reconstruction

FreeSurfer (Fischl, 2012) segmentation of individuals T1-weighted anatomical MRI was used to improve the accuracy of the source reconstruction, and to account for anatomical changes with age. The EEG forward model was obtained from a symmetric boundary element method (BEM

model; OpenMEEG, Gramfort et al., 2010), fitted to the spatial positions of each electrode. A cortically constrained sLORETA procedure (Pascual-Marqui and Lehmann, 1994) was applied to estimate the cortical origin of scalp EEG signals. The estimated sources were then projected into a standard space (i.e., ICBM152 template) for comparisons between groups and individuals, while accounting for differences in native anatomy.

2.7.4. Analyses

The individual alpha-peak frequency (IAF) observed at occipital sites was used to estimate the range of each frequency band. Based on previous works (Toppi et al., 2018) the following frequency bands were considered: Delta (IAF-8/IAF-6), Theta (IAF-6/IAF-2), Alpha (IAF-2/IAF+2), Beta (IAF+2/IAF+14) and Gamma1 (IAF+15/IAF+30). Phase-lag index (weighted PLI analyses; Stam et al., 2007) was used to assess the phase synchrony between 68 regions of interest (ROI; 68 ROIs = 34 contralateral homologous ROIs) defined by using the Desikan-Kiliany atlas brain parcellation (Desikan et al., 2006). PLI analyses estimate the variability of phase differences between two regions over time. Similar phase difference across time is indicated by a PLI value close to 1 (i.e., high synchrony between regions), while large variability in the phase difference is indicated by a PLI value close to zero. PLI measure has been shown to be less sensitive to the influence of common sources and amplitude effects relative to phase-locking value, as it disregards zero phase lag that could reflect volume conduction artefacts (Stam et al., 2007).

2.8. Statistical tests

Analyses were first conducted on the fluctuation rate (standard deviation across a resting-state session) of the wPLI calculated within each coupling (68x68 ROIs matrix, 4624 couplings) in each frequency band. Data were analyzed through permutation t-tests (with false discovery rate correction for multiple comparisons (FDR) performed in Brainstorm (Tadel et al., 2011), using a

method originally implemented in Fieldtrip (Oostenveld et al., 2011). In each frequency band, we selected couplings for which the fluctuation rate of the wPLI differed significantly between the first and the fifth recordings, as it has been shown that the difference between these two sessions capture the fluctuations dynamic of brain activity across the day (Van Egroo et al., 2019). For each of those couplings, we calculated global wPLI fluctuation rates across the five sessions (standard deviation of the global mean wPLI of the five sessions). Couplings' global wPLI fluctuation rates were averaged within same intra- or inter-networks, according to their ROIs' membership of the six Resting State Networks (Uddin et al., 2019): Central Executive Network (CEN), Salience Network (SN), Default Mode Network (DMN), Dorsal Attention Network (DAN), Visual System (VS) and Sensorimotor Network (SMN) (Figure 1B). To note, pairs of contralateral homologous ROIs were always affiliated to the same Resting State Networks (see Supplementary Table 1 in Supplementary Material for detailed Desikan-Killany ROIs' attribution to the six Resting State Networks).

Regressions analyses were conducted to assess the association between networks' global wPLI fluctuation rates, cognitive performance scores (the three domain-specific composite scores and the recognition memory score of the MST), β-amyloid rates and tau/neuroinflammation rates (the latter only available for 64 participants), using JASP (https://jasp-stats.org/; version 0.18.1). Finally, Post-hoc sub-group analyses based on participants' age group, namely under 60 (m=54.8 years, std=2.88; N=46) vs. over 60 years (m=64.5 years, std=2.65; N=43) were performed to further investigate age-related effects and also control for medial split biases. Participants' age, sex and mean gray matter volume and individuals' wake-up/DLMO phase value were included as covariates in the analyses. Results were FDR corrected for multiple comparisons (see Supplementary Table 3 for detailed results concerning FDR correction).

3. Results

3.1. Theta and gamma inter-network connectivity fluctuate across the day

We first considered the changes in connectivity between the first and last session of the protocol (Figure 1B). Permutation t-test performed on couplings' wPLI fluctuation rates showed a significant difference between the first and the fifth recordings only in theta and gamma band. For the same inter-network couplings of the SN-CEN, results showed an increase of wPLI fluctuation rates in theta band ($t = -2.7999$, $p = 0.005$) (Figure 2A, top) and a significant decrease of wPLI fluctuation rates in gamma band ($t = 2.8671$, $p = 0.005$) (Figure 2A, bottom), between the first and the fifth recordings. Results also showed an increase of wPLI fluctuation rates between the first and the fifth recordings for inter-network couplings of the DMN-CEN ($t = -2.5178$, $p = 0.005$) in the theta band, and a significant decrease for wPLI fluctuation rates for inter-network couplings of the DMN-SN ($t = 2.5653$, $p = 0.005$), of the CEN-VS ($t = 2.8974$, $p = 0.005$) and of the CEN-DAN ($t = 2.6007$, $p = 0.005$) in the gamma band (see Supplementary Figure 1 in Supplementary Material). Visual inspection of the fluctuation shows that theta fluctuations increase while they progressively decrease in the gamma band, especially in inter-network couplings. For both theta and gamma, we observed qualitatively a peak of fluctuation rates at the third recording (8p.m.).

3.2. Distinct association of theta and gamma SN-CEN inter-network daily fluctuations and cognitive performance

As an index of inter-networks' global synchrony fluctuation rates in a day, we averaged the global wPLI fluctuation rates across the five sessions, computed for each of their respective couplings (Figure 1B). To test the hypothesis that daily neural fluctuations could help explaining the heterogeneity of cognitive performance across older individuals, we then assessed the associations

between global wPLI fluctuation rates of these identified inter-networks and the cognitive performance measured by the three-domain-specific composite scores and the recognition memory score (MST). Results were therefore focused on SN-CEN inter-network which was the only one associated with cognitive performance in both theta and gamma bands in the sections to follow. For all the results below, no effect of age, sex and mean gray matter volume and individuals' wake-up/DLMO phase value were found.

3.2.1. Negative association between Theta SN-CEN daily fluctuations and memory performance

Regression analyses showed that the global theta daily fluctuation rate across the five sessions in SN-CEN inter-network was negatively correlated with the recognition memory score of the MST (β = -10.138, t = -3.019, Benjamini-Hochberg adjusted p-value = 0.012) (Figure 2B, top). These results indicated that higher global fluctuation rates across the day in theta band, within the SN-CEN inter-network, might be related to lower memory performance.

3.2.2. Positive association between Gamma SN-CEN daily fluctuations and executive performance

Within the same SN-CEN inter-network as global theta daily fluctuations, global gamma daily fluctuation rates were positively correlated with the executive composite score (β = 19.201, t = 2.667, Benjamini-Hochberg adjusted p-value = 0.036) (Figure 2B, bottom). Higher global daily fluctuation rate in gamma band within the SN-CEN inter-network, appears to be related to higher executive performance.

3.3. Distinct association of theta and gamma SN-CEN inter-network daily fluctuations and early pathological markers

As results revealed associations with cognitive performance only for the SN-CEN internetworks' daily fluctuations both in theta and gamma band, further analyses were lead exclusively on this inter-network's activity to characterize the implication of early pathological markers burden in the associations found. Thus, we performed regressions analyses to investigate the association between global theta SN-CEN inter-network daily fluctuation rates and tau/neuroinflammation (for N = 64) and β-amyloid burden rates.

3.3.1. Positive association between Theta SN-CEN daily fluctuations and tau/neuroinflammation burden

Results showed that global theta SN-CEN daily fluctuation rate was positively correlated with tau/neuroinflammation burden rate ($\beta = 1.824$, $t = 2.536$, Benjamini-Hochberg adjusted p-value = 0.028) (Figure 2C, top). These results indicate that higher tau/neuroinflammation burden rate is associated with lower global theta SN-CEN inter-network daily fluctuation rate.

3.3.2. Negative association between Gamma SN-CEN daily fluctuations and early β-amyloid burden

Regression analyses showed a negative regression between gamma SN-CEN inter-network daily fluctuation rate and Amyloid-β burden rate ($\beta = -1.024$, $t = -2.449$, Benjamini-Hochberg adjusted p-value = 0.032) (Figure 2C, bottom). Once again, these results suggest that higher β-amyloid burden rate are associated with lower global gamma SN-CEN internetwork daily fluctuation rates.

Post-hoc sub-group analyses, based on participants' age group (over 60 vs. under 60 years) were performed to further investigate age-related effects and also control for medial split biases. Results showed a negative association between global daily theta fluctuations rate and Rm score (β = -15.411, t = -3.922, p < .001) and a positive association between global daily gamma fluctuations rate and composite executive score (β = 38.553, t = 2.510, p = 0.016) only for over 60 years participants. We also observed a positive association between global daily theta fluctuations rate and tau/neuroinflammation burden (β = 2.149, t = 2.145, p = 0.040) and a negative association between global daily gamma fluctuations rate and β-amyloid burden (β = -3.245, t = -2.865, p = 0.007) only in over 60 years participants again (see Supplementary Figure 2 in Supplementary Material).

4. Discussion

Our main goal was to characterize the daily dynamics of brain activity fluctuations at rest in aging and their associations with cognitive performance and biological markers related to the neuropathology of Alzheimer Disease (AD). For this, we investigated EEG resting-state rhythms fluctuations recorded five times across the day in a wake-extension protocol, completed in late middle-aged healthy participants. Brain fluctuations were considered instead of the mean activity, as recent studies on BOLD-signal highlighted that brain signal fluctuations were predictive of cognitive performance in a way that mean signal cannot capture (Garrett et al., 2011). Moreover, previous M/EEG works showed an association between the increase of resting-state neural fluctuations with aging and cognitive performance (Courtney & Hinault, 2021; Jauny et al., 2022; Hinault et al., 2021, 2023; Uddin et al., 2020; Kumral et al., 2020).

4.1. Increased theta and decreased gamma fluctuation rates across the day

We first showed an increase of theta fluctuations and a decrease of gamma fluctuations over the day (i.e., between 10a.m. and 1a.m) at rest. These results can be understood as the reflection of the interplay between sleep homeostasis which buildup sleep pressure non-linearly during the day, and the circadian system which promote sleep onset in the evening. Previous works on healthy young adults showed that theta and gamma are shaped by such circadian timescale, which results in a linear increase of slow theta rhythms synchrony and a decrease of fast rhythms with time awake (Munn et al., 2017). This pattern is stronger following sleep deprivation, which was interpreted as reflecting an accumulated sleep pressure and drowsiness (Snipes et al., 2022). However, we showed no effect of individual circadian rhythmicity (measured using individuals' wake-up/DLMO phase value) on the associations found, which might suggest limited variations of the protocol between individuals. The fluctuation peak qualitatively observed at 8:00p.m. might reflect the maximal strength of the circadian signal opposing sleep need over the so-called wake-maintenance zone. Increased slow-theta fluctuations and decreased fast-gamma fluctuations induced by the circadian processes could reflect a global slowing of brain fluctuations, which might be interpreted as a global decrease of resting-state functional connectivity during the day. This interpretation is in line with previous studies on BOLD-signal diurnal variations (Orban et al., 2020). Taken together, these results seem to highlight that healthy older people exhibit a similar daily temporal organization of brain rhythms fluctuations involved in resting-state functional connectivity as young individuals.

4.2. Daily organization of brain rhythms fluctuations involve inter-network couplings

The daily temporal organization of brain rhythms fluctuations was exclusively observed in the functional connectivity of inter-network couplings. Such result is in line with previous works on

healthy aging, which showed stronger inter-network functional connectivity and weaker within-network functional connectivity, also termed as functional dedifferentiation, suggesting a less specialized patterns of functional connections (Malagurski et al., 2020). Identified couplings were part of the salience – control executive (SN-CEN) and default mode – control executive (DMN-CEN) inter-networks for the theta band. In the gamma band, couplings from the SN-CEN, default mode – salience (DMN-SN), control executive – visual system (CEN-VS) and control executive – dorsal attention (CEN-DAN) inter-networks were observed. The SN, CEN and DMN networks are all three involved in both theta and gamma fluctuations over the day, suggesting that theta and gamma diurnal functional connectivity fluctuations commonly involve interactions between SN, CEN and DMN. These networks include crucial brain regions for whole brain network connectivity and cognitive functioning efficiency. Several studies showed an increased functional connectivity between these networks in older adults (Ng et al., 2016).

Interactions between these three resting-state networks were reported in a triple network model aimed at understanding differences in functional connectivity patterns at rest between healthy and cognitively impaired young adults (Uddin, 2015), then replicated to investigate these differences among older individuals (Chand et al., 2017). This model proposes the SN to play a role in switching between the DMN associated with internally directed cognitive activities and the CEN involved in externally directed cognitive functions. This inter-network reorganization of the SN with other networks, including the DMN and the CEN has been proposed as the hallmark of aging (LaCorte et al., 2016). It was proposed that the SN drives the DMN and the CEN during resting-state in healthy old participants showing a normal cognitive functioning while the disruption of the control of SN over the DMN and the CEN was associated with cognitive impairment in patients with mild cognitive impairment (MCI) (Chand et al., 2017). Our results showed that daily

fluctuations over the SN-CEN inter-network only, in both theta and gamma band were correlated with cognitive performance, namely the recognition memory score (MST) for theta and the executive composite score for gamma daily fluctuations. Thus, our results might provide further details on how this three-part interaction featuring the SN, the CEN and the DMN, fluctuates across the day in aging. Our results importantly reveal that daily fluctuations between SN and CEN networks seems to play a key role in the heterogeneity of cognitive changes associated with healthy aging.

4.3. High global daily theta SN-CEN fluctuations are associated with low memory performance

We observed that higher global theta daily fluctuations within the SN-CEN inter-network showed lower memory composite scores. This concerns the recognition memory score of the MST, which has been shown to be a sensitive measure to detect subtle general cognitive decline in aging (Rizzolo et al., 2021). Theta rhythm is widely associated with memory (Fell and Axmacher, 2011). In aging, theta widespread resting-state synchrony has been linked to individuals' cognitive and memory decline (Spinelli et al., 2022). Theta synchrony is predictive of the conversion from healthy aging to MCI in a group with subjective cognitive decline, and of decline from MCI to AD (Babiloni et al., 2021 for a review). Thus, considering global daily fluctuations provide further information about theta mechanisms in cognitive aging, such as higher amount of global theta fluctuations during the day seem to be deleterious for memory abilities.

4.4. High global daily gamma SN-CEN fluctuations are associated with high executive performance

On the other hand, within the same SN-CEN inter-network, we observed that participants with higher global gamma daily fluctuations also showed higher executive composite scores. In a state of resting-state wakefulness, previous work showed that gamma rhythm reflects neural bottom-up processing and integration of perceptual information between and within different cortical and subcortical brain regions (Jensen et al., 2014). A positive correlation between high global gamma fluctuation rates over the day at rest and executive functioning suggests a more efficient regulation of information processing and maintenance of wakefulness in individuals with preserved gamma dynamics. Our results are also in line with the literature on resting-state synchrony in healthy aging, which showed a higher synchrony of gamma activity in healthy controls relative to patients with MCI, interpreted in those studies as a compensatory mechanism (Pusil et al., 2019; Vecchio et al., 2016). These results are also in line with previous studies led on the same COFITAGE cohort, which have shown that less fluctuations of brain responsiveness across the day, measured as cortical excitability, where associated with lower cognitive performance (Gaggioni et al., 2019; Van Egroo et al., 2019). Thus, our results clarify the dynamics of gamma synchronization especially within the SN-CEN inter-network that is associated with preserved executive performance in terms of fluctuations over the day.

4.5. Distinct theta and gamma association with AD pathological markers

Our results also provide new information about the association of EEG markers with early tau/neuroinflammation and β-amyloid burden. In fact, the field of clinical neuroscience of ageing is increasingly focused on targeting the earliest signs of neuropathological markers (i.e. β-amyloid

and tau/neuroinflammation) in the absence of AD cognitive symptoms, in order to predict the progression of AD in very early stages (Spinelli et al., 2022). Importantly, distinct association of theta and gamma were observed with tau and with β-amyloid. Indeed, global theta daily fluctuations were positively correlated with tau/neuroinflammation burden in regions corresponding to Braak stages of early regional tau pathology, while global gamma daily fluctuations were negatively associated with β-amyloid burden in earliest aggregation sites for β-amyloid pathology. The positive association between global daily theta fluctuations and tau/neuroinflammation, is consistent with previous works conducted by Gaubert et al. (2019) investigating EEG resting-state activity between groups of patients with positive or negative tau/neurodegeneration. Their results revealed that theta activity in fronto-central regions was higher in tau/neuroinflammation-positive patients. Consistent findings across studies also highlight that both β-amyloid and tau/neuroinflammation were associated with slowing of brain rhythm activity in aging (Tanabe et al., 2020). Here we replicated the association for theta daily fluctuations only with tau/neuroinflammation, which would indicate that tau is associated with different features of theta brain rhythms.

The link between the global daily fluctuations in gamma band and β-amyloid burden could be in line with results in AD's mice models studies that have reported an association between gamma band activity and β-amyloid, showing a decreased gamma synchrony within the parietal cortex occurring before β-amyloid deposition (Verret et al., 2012) and a reduced β-amyloid burden induced by multi-sensory gamma stimulation (Martorell et al., 2019). Studies in human aging have only found positive associations between local gamma power and β-amyloid burden in AD patients rather than gamma widespread synchrony (see Babiloni et al., 2021 for a review). Studies in human aging are increasingly carried out to clarify the association between gamma-band and β-amyloid

burden as gamma sensory stimulation is considered as a potential therapeutic strategy in AD (see Ko et al., 2022 for a review). We here provide arguments to consider gamma fluctuations as a marker of the progression of β-amyloid deposition.

Furthermore, theta and gamma fluctuations, respectively associated with tau/neuroinflammation and β-amyloid burdens, were mainly measured within the SN-CEN inter-network. This finding echoes recent studies showing that the presence of these pathological markers in their early deposition sites, might disrupt the functional connectivity between large-scale networks, in particular the inter-connectivity of SN with other regions, in addition to the DMN, before the spread of the pathology that occurs later (Guzman-Vélèz et al., 2022).

Finally, assuming that a previous study led on the same cohort showed no association between tau/neuroinflammation and β-amyloid burdens and cognitive performance (Narbutas et al., 2021; Rizzolo et al., 2021), our results suggest that theta and gamma daily fluctuations might constitute early markers of age-related changes, both for cognition and for the progression pathological burdens.

4.6. Limits and perspectives

These findings are constrained by methodological limitations. First, our results were obtained from healthy middle-aged to older participants, with a lower mean age that other cohorts of aging individuals, and whose global cognitive performance is in the upper average range. Therefore, the present results could differ in individuals aged 70 and above. Furthermore, the study did not include a group of young adults, so we were not able to assess group differences relative to younger participants to determine the age-specificity of our results. Further studies will aim at investigating the individuals' cognitive trajectories by assessing the predictive value of daily theta and gamma

EEG fluctuations on longer longitudinal protocols, and the evolution of these daily brain fluctuations with advancing age. Finally, two-minutes of EEG resting-state recording might not be considered to be enough to optimally characterize the ongoing brain state, considering the loss of information due to signal preprocessing. However, recent studies showed that resting-state brain activity enable the differentiation of individuals from brain recordings as short as 30 seconds robustly in different recordings performed over time, ushering the notion of neural fingerprint (Castanheira and al., 2021). Notwithstanding, our study is the first to investigate daily dynamics of brain rhythms fluctuations using EEG time-frequency analyses methods in aging. Our results might indicate the involvement of a same functional inter-network, namely the SN–CEN inter-network, in two neural mechanisms (theta and gamma daily fluctuations) which appeared to be associated with distinct cognitive functions. Noteworthy, we assessed functional brain connectivity through the lens of the phase lag index (PLI) which is a bivariate connectivity measure that quantify the activity between couplings of brain regions in a data-driven approach. In addition, the initial selection of the couplings that were used to compute the cumulated fluctuations detected in each of the five sessions was based on the difference of fluctuations rates between the first and last recordings. This choice was based on the fact that this method led to similar statistical outcomes than linear regression fit approach (Van Egroo et al., 2019). Forthcoming research using multivariate analyses might be necessary to replicate our findings taking into account the complexity of functional network interactions as well as the five recordings in a chronological order for the initial section of couplings (Pusil et al., 2019).

5. Conclusion

Brain activity fluctuations, long considered as noise, are now considered as a key marker of age-related cognitive variability in several BOLD signal MRI studies (Garrett et al., 2011) contrasting to the small number of EEG studies in this field. Moreover, no study accounted for the daily dynamics of brain fluctuations in aging, while it is acknowledged that cognition varies during the day. Here, we showed that a higher level of theta fluctuations at rest is associated with lower memory performance and higher tau/neuroinflammation burden rates, while higher level of gamma fluctuations is associated with a better executive functioning and lower β-amyloid burden, suggesting that these two rhythm fluctuations have specific and opposite roles in cognitive functioning and AD markers progression. Moreover, daily fluctuations in both theta and gamma bands were observed over SN–CEN inter-network, which is in line with the dedifferentiation of network functional connectivity assumed to be a hallmark pattern of aging (Malagurski et al., 2020). Noteworthy, as our analyses were all adjusted for individuals' cortical thickness, our results suggest theta and gamma daily activity might be an electrophysiological marker of cognitive aging and early β-amyloid and tau deposition, that is independent or precede age-related changes of structural network integrity. Thus, investigating daily EEG fluctuations at rest contributes to better understand subtle brain changes underlying cognitive functioning in healthy aging, in the drive to precise neural fingerprints derived from wake resting-state EEG associated with cognition traits (Castanheira et al., 2021). Future research on age-related cognitive and brain changes might consider controlling and balancing for time of the day in their analyses, as we showed that brain network activity underlying cognitive functioning fluctuate across the day, that suggests also

fluctuations of cognitive performance during the day, in line with literature (Valdez, 2019). Using recent EEG frequency analysis techniques enables the identification of early markers of cognitive decline, even with a limited number of electrodes (Gaubert et al., 2020), thereby showing promising potential application for clinical use.

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Conflict of Interest

The authors have no actual or potential conflicts of interest.

Data Availability

This study was not preregistered. Data collection and sharing for this project were provided by the GIGA-CRC in vivo Imaging. Data access can be provided upon reasonable request.

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Table 1. Demographics, cognitive scores, tau and BA burden, structural and functional measures for the entire sample.

Variable	N (%)	Mean (SD)
Neuropsychological assessment		
Number of participants	101	
Female	68 (67.3%)	
Age		59.4 (5.3)
Years of education		15.2 (3.0)
Memory		
Composite score		0.014 (0.925)
FCSRT (sum of all free recalls)		34.228 (5.159)
MST (recognition memory score)		0.792 (0.153)
Executive		
Composite score		-0.038 (0.908)
2-min verbal literal fluency		24.660 (7.076)
2-min verbal categorial fluency		33.820 (7.032)
Digit-Span (inverse order)		6.614 (2.182)
TMT (RT for Part B)		68.673 (20.331)
N-back (3-back variant)		0.673 (0.145)
Stroop (number of errors for interfering items)		0.103 (0.060)
Attention		
Composite score		0.039 (0.981)
DSST (2-min score)		72.560 (12.629)
TMT (RT for Part A)		31.703 (8.671)
N-back (1-back variant)		0.976 (0.041)
D2 (GZ-F score)		401.730 (72.233)
CRT (reaction time to dissimilar items)		687.803 (137.516)
Aβ and tau/neuroinflamation – PET imaging		
Tau/neuroinflammation burden		
Number of participants	64	
Female	42 (65.6%)	
THK-PET in Braak I/II regions of interest		2.289 (0.247)
β-amyloid burden		
Number of participants	101	
Female	68 (67.3%)	
β-amyloid early stage		0.855 (0.052)
MRI		
Cortical gray matter volume (mm^3)		458,647.230 (39,834.230)
Phase synchrony		
Global std wPLI theta – SN-CEN		0.046 (0.021)
Global std wPLI gamma – SN-CEN		0.029 (0.013)

Notes. FCSRT = Free and Cued Selective Reminding Test; MST = Mnemonic Similarity task; TMT = Trail Making Test; DSST Digit symbol substitution test; GZ-F = Global score-faults; CRT = Choice Reaction Task; PET = positron emission tomography; std wPLI = standard deviation of the weighted phase lag index; SN-CEN = salience-control executive inter-network.

Figures

Figure 1. Experimental protocol, adapted from Van Egroo et al. (2019) (A); and schematic representation of statistical analyses on EEG signal (B).

Notes. MRI = magnetic resonance imaging; PET= positron emission tomography; COG = cognitive assessment; BN = Baseline-Night; EEG = electroencephalogram; Std wPLI = standard deviation of the weighted phase lag index. We first computed the fluctuation rate (standard deviation across a resting-state session) of the wPLI calculated within each coupling (68x68 ROIs matrix, 4624 couplings) in each frequency band. Through permutation test, we selected couplings for which the fluctuation rate of the wPLI differed significantly between the first and the fifth recordings. For each of those couplings, we calculated global wPLI fluctuation rates across the five sessions (standard deviation of the global mean wPLI of the five sessions). Couplings' global wPLI fluctuation rates were averaged within same intra- or inter-networks, according to their ROIs' membership of the six Resting State Networks (CEN, SN, DMN, DAN, VS, SMN).

Alt Text: Diagram of the temporal organization of the MRI, PET imaging, cognitive and EEG assessments, zooming in on the five EEG sessions and the statistical analyses computed on EEG signal.

Figure 2. Distinct associations of theta and gamma SN-CEN inter-network daily fluctuations with cognitive performance.

Notes. SN-CEN = salience-control executive inter-network; EEG = electroencephalogram; Std wPLI = standard deviation of the weighted phase lag index. **A)** Increased Theta and decreased gamma synchrony fluctuations in the SN-CEN inter-network between 10 a.m. and 1 a.m. ; **B)** Negative association between global daily theta fluctuations rate and Rm score (β = -10.138, t = -

3.019, p = 0.012; top) and positive association between global daily gamma fluctuations rate and composite executive score (β = 19.201, t = 2.667, p = 0.036; bottom); **C)** Positive association between global daily theta fluctuations rate and tau/neuroinflammation burden (β = 1.824, t = 2.536, p = 0.028; top) and negative association between global daily gamma fluctuations rate and β-amyloid burden (β = -1.024, t = -2.449, p = 0.032; bottom).

Alt Text: Graphs comparing the associations of theta and gamma SN-CEN inter-network daily fluctuations with cognitive performance, showing bar charts and regression plots, with detailed statistical values.

Figure 1

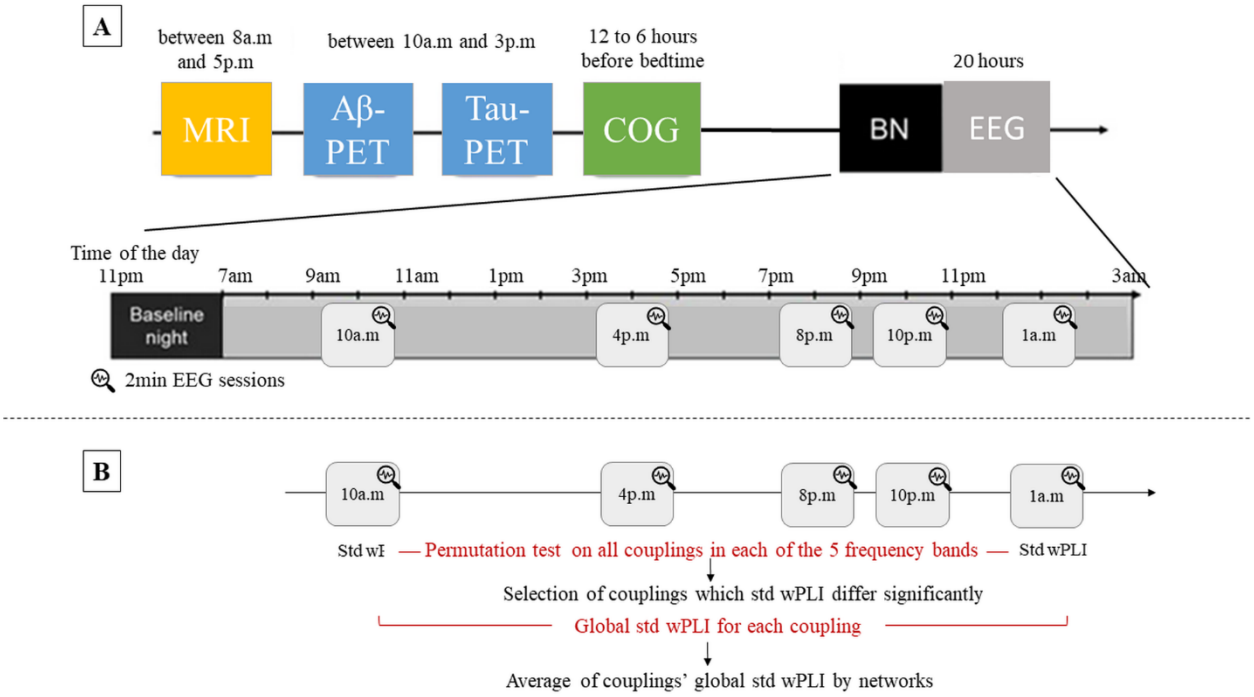

Figure 2