Sleep slow waves' negative-to-positive-phase transition: a marker of cognitive and apneic status in aging

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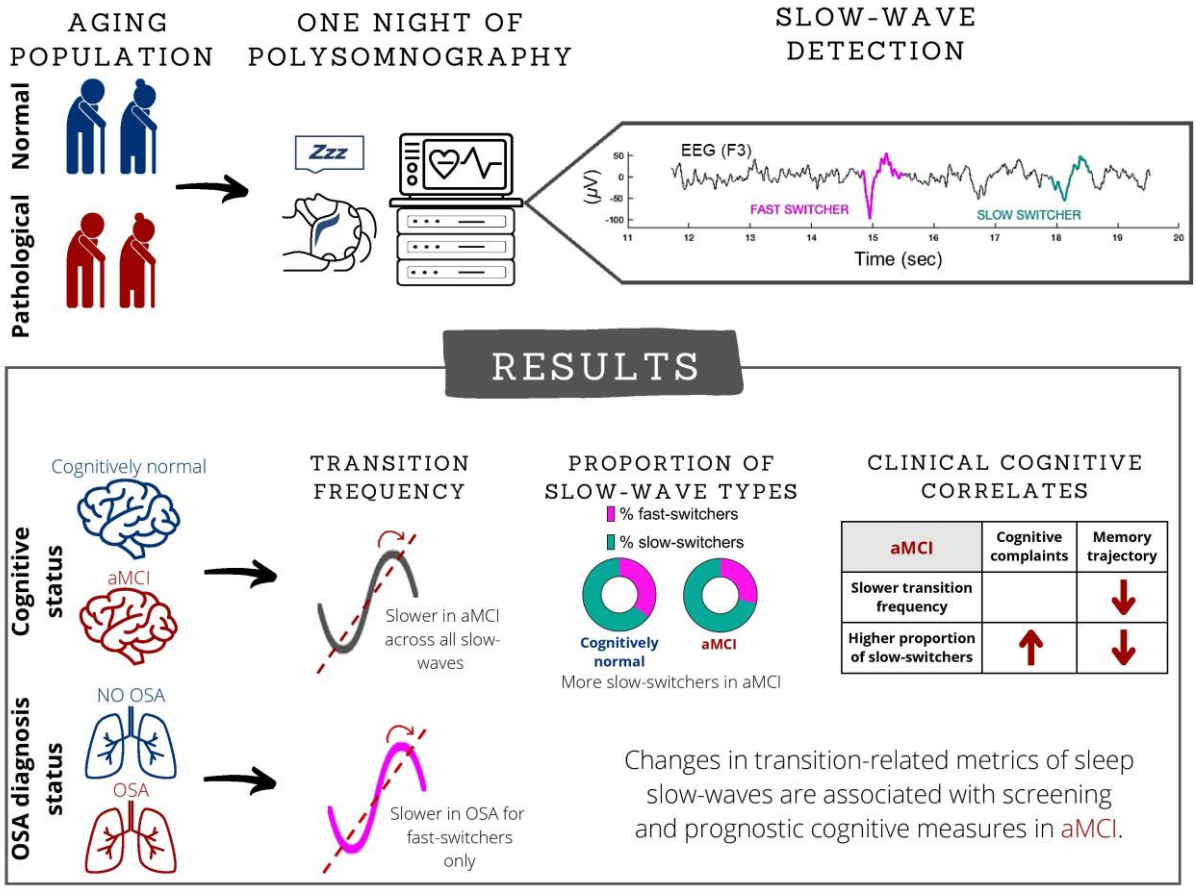
ABSTRACT

The sleep slow wave (SW) transition between negative and positive phases is thought to mirror synaptic strength and likely depends on brain health. This transition shows significant age-related changes but has not been investigated in pathological aging. The present study aimed at comparing the transition speed and other characteristics of SW between older adults with amnestic mild cognitive impairment (aMCI) and cognitively normal (CN) controls with and without obstructive sleep apnea (OSA). We also examined the association of SW characteristics with the longitudinal changes of episodic memory and executive functions and the degree of subjective cognitive complaints. aMCI (no/mild OSA=17; OSA=15) and CN (no/mild OSA=20; OSA=17) participants underwent a night of polysomnography (PSG) and a neuropsychological evaluation at baseline and 18 months later. Participants with aMCI had a significantly slower SW negative-to-positive-phase transition speed and a higher proportion of SW that are “slow-switchers” than CN participants. These SW measures in the frontal region were significantly correlated with memory decline and cognitive complaints in aMCI and cognitive improvements in CN participants. The transition speed of the SW that are “fast-switchers” was significantly slower in OSA compared to nOSA participants. The SW transition-related metrics showed opposite correlations with the longitudinal episodic memory changes depending on the participants' cognitive status. These relationships were particularly strong in participants with aMCI. As the changes of the SW transition-related metrics in pathological aging might reflect synaptic alterations, future studies should investigate whether these new metrics covary with biomarker levels of synaptic integrity in this population.

Keywords: Slow waves, Sleep, Mild cognitive impairment, Obstructive sleep apnea, Cognitive decline.

Statement of Significance: Healthy brain functioning depends on synaptic integrity, which is significantly disrupted in Alzheimer's disease (AD). The transition between negative and positive phases of sleep slow waves (SW) was proposed to be the most direct electroencephalographic measure of synaptic strength. Thus, we investigate this SW transition in a population of older adults at higher risk of developing AD. Our results show that different characteristics linked to this transition were differently affected by the status of amnestic mild cognitive impairment (aMCI) and obstructive sleep apnea. These changes were also related to a longitudinal decline in memory in individuals with aMCI. Our study reveals that early alterations linked to the SW negative-to-positive-phase transition have a prognostic value for memory decline in pathological aging.

Graphical_Abstract



INTRODUCTION

Electroencephalographic (EEG) oscillations occurring during non-rapid eye movement (NREM) sleep are postulated to play a crucial role in sleep-related cognitive processes[1-4] and have been associated with neurocognitive performance across the human lifespan[5,6]. Among these oscillations are the sleep slow waves (SW). Electrophysiological studies in animals showed that SW, when recorded on the scalp, are the reflection of an underlying cortical slow oscillation rhythm (SO; <1 Hz)[7,8]. At the intracellular level, the SO emerges from neurons' membrane potential transitions between hyperpolarized (DOWN-state) and depolarized (UP-state) states. At the extracellular level, this SO translates as synchronous neuron populations' firing patterns transitioning between silent (OFF-state) and active (ON-state) states. At the scalp level, SW represent a broad manifestation of highly synchronized neuronal networks alternating between a widespread state of hyperpolarization (negative phase in surface EEG) and depolarization (positive phase in surface EEG). This alternation oscillates in the delta frequency range (<4 Hz). Scalp-SW can then be characterized by nightly occurrence (e.g., SW density), morphological features (e.g., amplitude, frequency, phases duration) and spectral power in the delta range, which is also known as slow-wave activity (SWA). As an attempt to capture the cortical SO activity, the delta frequency range is also, sometime, dichotomized into two oscillatory components, distinguishing faster (≈ 1-4 Hz) versus slower (≈ <1 Hz) oscillations[9].

Different theories have attributed a pivotal role to SW in brain plasticity processes supporting cognition[7,10,11]. For example, it is postulated that the SO (and by extension, slower scalp-SW in surface EEG studies) coordinate the oscillatory activity of thalamic sleep spindles and hippocampal sharp-wave/ripples during NREM sleep to support long-term memory consolidation[3,12-15]. It is also posited that SW contribute to synaptic renormalization, promoting future learning capabilities[10,16]. As sleep SW result from synchronic neuronal activity involved in putative sleep-dependent cognitive processes, they may thus have value as a potential marker of cognitive health later in life. In this regard, sleep SW undergo several changes throughout healthy aging, showing lower density and amplitude, smoother

slope, longer negative and positive phase durations, and lower spectral power in the delta range[17,18]. In cognitively healthy older adults, SWA and SW morphological characteristics, particularly from the slower frequency range (<2 Hz), have been associated with memory and executive functions performance[1,19-21]. Furthermore, age-related medial prefrontal cortex (mPFC) atrophy[22] and mPFC amyloid-β (Aβ) accumulation[23] were both linked to lower frontal SWA, which in turn predicted poorer memory consolidation. Reduced frontal SWA was also associated with higher levels of tau pathology in cognitively normal and mildly impaired older adults[24]. In these studies, SWA in the slower delta range (<2 Hz) were most sensitive to markers of Aβ and tau pathology[23,24]. In sum, research from the last decade has shown that SW-related measures, particularly from the frontal region and slower delta frequency range, could potentially be valuable markers of neurocognitive deficits and levels of Aβ and tau pathology. Hence, SW measures could help monitoring the onset of Alzheimer's disease (AD)[25,26].

In the context of pathological aging, overnight memory consolidation is altered in participants with amnestic mild cognitive impairment (aMCI)[27], multiple-domain MCI[28] and AD[29]. aMCI corresponds to a prodromal phase between the cognitive changes of normal aging and Alzheimer dementia[30-32]. Given the close relationship suspected between sleep SW and AD pathology, aMCI thus represents an opportunity to identify SW characteristics able to detect early brain changes in individuals at higher risk of developing AD[33-37]. There are, however, very few studies investigating sleep microarchitecture in older adults with MCI[38]. One small study[27] showed that patients with aMCI (*n* = 8) had significantly lower nighttime NREM SWA (0.5-4.5 Hz) in central-to-occipital regions compared to cognitively healthy older adults (*n* = 16). A more recent study did not replicate such a difference for the central area either for global SWA (0.5-4.5 Hz) or slower SWA (0.25-1 Hz)[28]. Moreover, no significant differences between healthy older adults and patients with aMCI were observed during a diurnal nap for the SWA in the slower delta range (0.5-1 Hz)[39]. The same was observed for the count and amplitude of SW in the slower frequency range (0.5-1.25 Hz). On one hand, these studies collectively underscore the clinical relevance to deepen our understanding of sleep neurophysiology in the context of pathological

cognitive aging. On the other hand, they also incite the development of novel sleep EEG measures to identify sensitive and reliable markers of early cognitive decline.

The SW's transition from negative to positive phases has been described as reflecting synaptic strength and neuronal synchrony[8,40-43]. This transition has been previously measured by the SW slope, which becomes smoother with aging and suggests lower neuronal synchrony[17]. Because the SW amplitude influences the slope measure, our team recently developed the transition frequency metric[44]. The latter captures the transition speed between the SW negative and positive phase, regardless of amplitude. This new metric highlighted two distinct types of SW in the delta frequency spectrum. The first one had a slow depolarization transition ("slow-switchers"), whereas the second one had a fast transition ("fast-switchers"). Several age-related changes in SW were observed using the transition frequency metrics. Most importantly, compared to younger adults, healthy older adults produced a higher proportion of slow-switchers and showed lower EEG functional connectivity along the SW negative-to-positive-phase transition. Changes pertaining to the SW negative-to-positive-phase transition is thus sensitive to the process of healthy aging. It remains, however, to determine whether the transition frequency metrics could be markers of brain health, distinguishing healthy from pathological aging. As the rate of the SW depolarization transition is thought to be closely related to synaptic strength[42,43] and that synaptic alterations are central to AD pathology[45], we propose that measures derived from the SW transition frequency could serve as markers of pathological aging.

Some sleep disorders prevalent with advancing age have been linked to cognitive impairment and neurodegeneration[46-49]. Among them, obstructive sleep apnea (OSA) has been associated with a higher risk of developing MCI or AD[50,51], with cognitive decline at an earlier age[52], and with biomarkers of Aβ and tau pathologies[50,53]. OSA has also been reported to induce a detrimental effect on sleep-dependent memory processing, potentially via sleep fragmentation, which was hypothesized to entail fewer opportunities to produce SW and sleep spindles[54]. This is coherent with the reduction of global SWA seen in patients with OSA[55-57], although it remains unknown whether more fragmented sleep is

directly related to reduced SW density in this population. Furthermore, a recent study has shown that OSA severity in patients with MCI was associated with cerebrospinal fluid AD-biomarkers[58]. This implies that OSA may contribute to the development of AD in patients with MCI. However, whether OSA and aMCI interact to alter SW characteristics is unknown. Such an investigation is particularly relevant given the high prevalence of OSA in older individuals with MCI[59] and the proximal relationship between sleep SW and AD-related markers.

This study aimed at investigating characteristics of different types of SW in individuals with aMCI compared to cognitively normal (CN) controls and testing the effect of OSA on this association. Instead of using a blurred cut-off in the frequency domain to dichotomize SW, we applied a data-driven approach dividing SW based on their negative-to-positive-phase transition speed (i.e., one of the most characteristic features of this oscillatory event). This led to the study of the characteristics of three types of SW: slow-switcher, fast-switcher, all-combined SW. We also examined the relationship between the SW characteristics and the longitudinal changes of episodic memory and executive functions over a 1.5-year follow-up. As cognitive complaints are usually the inaugural symptom prompting clinical examination, we also tested the association between subjective cognitive complaints and SW features[45,60]. We hypothesized that SW characteristics, particularly measures derived from the SW transition frequency, would be altered in aMCI compared to CN older adults. Alterations would be more significant in aMCI participants with OSA. We also hypothesized that the sleep fragmentation in patients with OSA would result in fewer opportunities to produce SW, thus reducing their density during NREM sleep. Finally, we predicted that SW characteristics altered in pathological aging would be associated with objective and subjective cognitive measures.

METHODS

Participants and protocol overview

Thirty-four participants with aMCI and 37 CN older adults matched for age, sex, education, and OSA diagnosis were selected from a longitudinal study's cohort on OSA and cognition. Given the nature of the cohort and that OSA is more prevalent in men[61], the total sample is primarily composed of males (≈95%). The recruitment procedure, study protocol, and inclusion/exclusion criteria are described in detail in prior studies[62-64]. In brief, participants between 55 and 85 years old were recruited from the waiting list at the Hôpital du Sacré-Coeur de Montréal's sleep apnea clinic and by advertisements in local newspapers. Exclusion criteria were: (1) central nervous system disorders (e.g., dementia, neurological diseases, history of stroke, brain tumor, epilepsy) or any major psychiatric disorders; (2) uncontrolled diabetes, hypertension or pulmonary diseases; (3) body mass index (BMI) > 40 kg/m^2; (4) use of psychotropic medications (including drugs or alcohol abuse) that can impact sleep or cognition; (5) treatment with continuous positive airway pressure (CPAP) or other types of treatment such as a mandibular advancement device at baseline; and (6) sleep disorders other than OSA.

The study was approved by the CIUSSS du Nord-de-l'Île-de-Montréal Ethics' Committee. All participants provided written consent and were compensated financially for their participation in the study. They filled out the following questionnaires: Pittsburgh Sleep Quality Index[65], Epworth Sleepiness Scale[66], Insomnia Severity Index[67], Beck Depression Inventory-II[68], Beck Anxiety Inventory[69], and the Vascular Burden Index[70]. Participants underwent one full-night of in-laboratory polysomnography (PSG) recording, followed by a 3-h neuropsychological assessment the next morning. A subset of 44 participants came back 18 months later for a longitudinal follow-up, including a second 3-h neuropsychological evaluation. Among the CN participants, 17 nOSA and 11 OSA participants were tested at follow-up. Among the participants with aMCI, nine nOSA and seven OSA participants were tested at follow-up. Of these 44 participants, 16 (i.e., 36.4%) had started an OSA

treatment between the baseline and follow-up visits (18 months later). Participants were considered as "users" if they had started an OSA treatment after the baseline and continued to use it at the follow-up according to medical notes. Participants who had not started an OSA treatment or had started one but stopped after a few weeks were considered "non-users". Fifteen participants used a CPAP treatment, while one used a mandibular advancement device. Twelve participants belonged to the CN groups and four to the aMCI groups.

Neuropsychological assessment, objective, and subjective cognitive scores

Five cognitive domains were evaluated[71]: attention and processing speed, executive functions, visual and verbal episodic learning and memory, visuospatial abilities, and language (see Table S1 in Supplementary Material, Methods section, for the list of tests). All cognitive tasks were administered by a neuropsychologist or a psychometrician in the same order for all participants. Raw scores were converted to z-scores according to the best available clinical norms. A performance with a z-score ≤ 1.5 standard deviation below normative data on at least two measures in the same cognitive domain was defined as an objective cognitive impairment. Participants were diagnosed with aMCI based on the following criteria[72]: 1) an objective cognitive impairment; 2) preservation of independence in daily activities assessed by the Activities of Daily Living Inventory[73] and during an interview; and 3) the cognitive impairment was not better explained by a medical or psychiatric condition or medication use. Participants with aMCI had to have a predominant cognitive memory impairment, alone or with coexistent impairment in another cognitive domain. CN participants had to be exempt of objective cognitive impairment in all areas. Participants with non-aMCI were not included in the present study.

Cognitive composite scores have been shown to be robust proxies of cognitive capacities[74,75]. Based on their clinical relevance to assess AD-related cognitive decline[76,77], we computed a composite score for the domains of episodic memory and executive functions, which reflect the longitudinal change in cognition from the first visit to the second one 18 months later (see Supplementary Material, Methods section). Given that only a subset of participants had a longitudinal neuropsychological follow-

up, a reduced sample (*n* = 44) was used for the analyses using these composite scores. Moreover, four participants lacked either one test or subtest at either time point for one of the composite scores. Their composite score was thus computed based on the remaining available tests or subtests (for more details, see Supplementary Material, Methods section).

The degree of subjective cognitive complaint was assessed with the Cognitive Difficulties Scale (CDS) [78]. This questionnaire contains 37 questions on a 5-point Likert scale (0 = never to 4 = very often), where a higher score depicts greater cognitive complaints. Two versions of the CDS were administered in this cohort. Only the same 35 items of both versions were summed to define the total score. Figures S1 to S3 depict descriptive statistics for all cognitive scores for each group.

Polysomnographic recording and scoring

The PSG recording was conducted in a sleep laboratory, starting and ending according to each participant's habitual sleep schedule[62,63]. We used the international 10–20 system with a 17-channel EEG montage (Fz, F3, F4, F7, F8, Cz, C3, C4, T7, T8, Pz, P3, P4, P7, P8, O1, O2) with a linked mastoid reference. Sleep was recorded with a Grass Technologies Model 15A54 Polygraph (amplifier gain, 7.5 µV/mm; bandpass filter, 0.3–100 Hz). All signals were digitized at a sampling rate of 256 Hz using a commercial software (Harmonie). In addition, the PSG included an electrooculogram, a submental electromyogram, and an electrocardiogram. A bilateral anterior tibialis muscle electromyogram was used to measure periodic leg movements. Thoracoabdominal strain gauges, oronasal thermistors and cannula were utilized to monitor respiration. A transcutaneous finger pulse oximeter measured oxygen saturation.

Sleep recording and scoring were performed by experienced medical electrophysiology technologists according to standard methods[79]. Apneic episodes were defined as a reduction of ≥ 90% from baseline airflow, lasting ≥ 10 seconds. Hypopneic episodes were defined as a reduction in airflow amplitude of ≥ 30% from baseline for ≥10 seconds, which was accompanied either by an oxygen

desaturation of ≥ 3% or by an electroencephalogram arousal. The apnea-hypopnea index (AHI) represents the sum of apneas and hypopneas divided by the total number of hours of sleep; an AHI was also computed for the time spent in NREM sleep (N2+N3). The mean oxygen saturation values were extracted for the whole night and NREM sleep. The microarousal index is the sum of microarousals divided by the total number of hours of sleep. The number of NREM stage transitions towards the N1 and waking stages was also calculated.

The apneic status was defined using the AHI as follows: no or mild OSA (< 15 events/h) and moderate to severe OSA (≥ 15 events/h). Twenty CN participants had no/mild OSA and 17 had moderate to severe OSA, while 19 participants with aMCI had no/mild OSA and 15 had moderate to severe OSA. For future references, the groups with no/mild OSA will be termed "nOSA groups", and the groups with moderate to severe OSA will be termed "OSA groups".

Slow-wave detection

Slow waves were automatically detected on artifact-free epochs of NREM sleep (N2 and N3) on nine channels of interest (i.e., Fz, F3, F4, Cz, C3, C4, Pz, P3, P4). Beforehand, EEG artifacts were detected automatically according to Brunner and collaborators[80]' approach. A validation by visual inspection was then conducted, and adjustments were applied if needed. Subsequently, we applied a conservative method whereby we rejected all 30-second epochs of NREM sleep in which artifacts were detected on any of our EEG channels of interest. This ensured that SW were detected on similar epoch length (30 seconds) and that an equivalent number of NREM sleep epochs was analysed for each channel. Using two-way ANOVAs with two independent factors (two cognitive status × two OSA diagnosis status), we examined whether the groups differed in their quantity of remaining NREM sleep stages (i.e., duration and number of epochs) following artifact rejection. As shown in the Table S2 (Supplementary Material, Methods section), this step revealed that the quantity of remaining NREM sleep stages were not significantly different between the groups. Based on this observation, we

considered that the amount of NREM EEG data subjected to SW detection should not impact subsequent analytical steps and results interpretation.

Then, before the SW detection, we used a previously published methodology developed by our laboratory[81] to adapt SW amplitude criteria to putative age differences (for more details, see Supplementary Material, Methods section). This data-driven approach defined the peak-to-peak amplitude threshold at 61 µV and the negative amplitude threshold at 33 µV, consistent with our prior findings[81]. SW were detected on the filtered signal using these adapted criteria: (1) peak-to-peak amplitude ≥ 61 µV; (2) negative amplitude ≥ 33 µV; (3) duration of negative deflection ≥ 125 and ≤ 1500 ms; and (4) duration of positive deflection ≤ 1000 ms. Following the preliminary artifact rejection, one participant had to be excluded due to persistent artifacts in the EEG across the night on one channel of interest.

Slow-wave characteristics

Using a mixture of two Gaussians to model the SW transition frequency distribution, we previously identified two types of SW[44]: one showing a "slow" transition and the other a "fast" transition. We used the same methodology to classify SW into slow- and fast-switchers (for more details, see Supplementary Material, Methods section). Briefly, we calculated the transition frequency of each SW, which is defined as $f_\tau = \frac{1}{2\tau}$, with τ denoting the time from the negative-phase to the positive-phase peak (see Figure 1A). Then, we estimated the distribution of all SW transition frequencies drawn from the combined EEG derivations of interest for each group separately. As presented in Figure 1B, the probability distribution of the two types of SW can be obtained using a sum of weighted Gaussians:

$$p(f_\tau) = p(SlowSw)\, p(f_\tau \mid SlowSw) + p(FastSw)\, p(f_\tau \mid FastSw)$$

where $p(SlowSw) + p(FastSw) = 1$.

In this equation, $p(f_\tau \mid SlowSw)$ and $p(f_\tau \mid FastSw)$ are Gaussian distributions describing the probability to transit with the frequency f_τ, depending on the SW type, that is "slow-switcher" or "fast-switcher". $p(SlowSw)$ and $p(FastSw)$ are the SW's probability of being either a slow-switcher or a fast-switcher, respectively. We then estimated for each group the parametric model of $p(f_\tau)$ utilizing the Expectation-Maximization algorithm to fit the distribution. From this mixture of Gaussians, we can define the frequency f^* where the two Gaussians intersect: a SW is labeled as a slow-switcher if $f_\tau < f^*$, that is if $p(f_\tau \mid SlowSw) \geq p(f_\tau \mid FastSw)$ and a fast-switcher otherwise. As shown in Figure 1B, the separation frequency f^* was very similar across the four groups.

Several characteristics of SW during NREM (i.e., N2+N3) sleep were derived: SW density (number of SW per minute of NREM sleep), proportion of slow- and fast-switchers (percentage), SW peak-to-peak amplitude (difference in voltage between the negative-phase and positive-phase peaks of the filtered signal expressed in µV), SW frequency (number of cycles per second expressed in Hz), and SW transition frequency ('speed' of the negative-to-positive-phase transition expressed in Hz). SW characteristics were averaged over all-night NREM sleep for frontal (average of F3, F4 and Fz), central (average of C3, C4 and Cz) and parietal (average of P3, P4 and Pz) derivations, as well as across the type of SW (slow-switcher, fast-switcher, and all-combined SW). One participant did not produce enough parietal fast-switchers to compute characteristic estimates and was thus not considered for the group comparison analyses including this type of SW. These analyses were conducted using MATLAB (R2018b).

Statistical analyses

All variables were examined for normality and homogeneity of variance using measures of skewness and kurtosis, the Shapiro–Wilk test, visual inspection of standardized residual plots, and the F_{max} test [82,83]. When a deviation from normality for the clinical descriptive, sleep macroarchitecture and PSG variables were observed, a square root transformation was performed to correct it while a log

transformation was used for SW measures. Beforehand, outlier values at ± 3 standard deviations from the mean, which showed a clear discontinuity with preceding values, were winsorized to the next highest value that was not an outlier. Participants who displayed values beyond ± 4 SD were removed from the analyses. For correlational analyses, bivariate outliers were identified using a standardized residual score of > 2 SD and Cook's distance to assess the degree of influence of each data point.

In the CN groups, six of the 55 objective sleep variables, including the SW features probed at different topographies, had one data point winsorized. In the aMCI groups, 23 of the 55 sleep variables had one data point winsorized mainly due to two participants who displayed recurrent outlier values for similar variables (e.g., densities, classical frequencies) and across topographies. One participant was excluded from all analyses as she showed consistent extreme values (z-scores at more than ± 3 SD from the mean on 20% of sleep microarchitecture variables), whereas several of them were higher than ± 4 SD and exhibited a clear discontinuity (>1 SD) with the preceding z-values when ordered in rank. One participant was further removed from correlation analyses involving the episodic memory score as he was a bivariate outlier (standardized residual score > 2 SD) and an influential case (Cook's distance > 1). Accordingly, the resultant sample sizes specific to each analysis are displayed in the results tables.

A chi-squared test was conducted to assess group differences in sex prevalence. Two-way ANOVAs with two independent factors (two cognitive status × two OSA diagnosis status) were performed on sociodemographics, clinical and PSG variables. When an interaction was found significant, a simple effect analysis was performed. To evaluate group differences on SW characteristics, three-way mixed ANOVAs with two independent factors (two cognitive status × two OSA diagnosis status) and one repeated measure (three topographical regions) were conducted. *P*-values for repeated measures with more than two levels were adjusted for sphericity according to Girden [84]'s recommendations: when ε > .75, the Huynh-Feldt correction was applied; when ε < .75, the Greenhouse-Geisser correction was applied. Post-hoc pairwise comparisons with Bonferroni

adjustment were conducted when the main within-subjects effect of the topographical region (i.e., repeated measure) was found significant. For all ANOVAs, effect sizes were quantified by the partial eta² (η^2p) and reported for significant effects.

When group differences were observed on SW characteristics, within-group Pearson's correlations were carried out to assess the relationships between these SW characteristics and the cognitive scores. Previous studies highlighted the frontal slow-wave sensitivity to AD pathology and cognitive performance in aging[19,22,23,85]. Based on this *a priori* sensitivity of the frontal region, correlational analyses focused on the relationships between cognition and frontal SW characteristics. Using the PROCESS macro for SPSS v4.0[86], exploratory moderation analyses were performed, when applicable, with continuous predictor variables mean-centred prior to analysis. Moderating effects were verified by testing significant interaction between the predictor and the moderator, as well as the degree of variance it explained. In a second step, we performed these analyses again but with statistical control for OSA treatment between the baseline and follow-up visits. The OSA treatment control variable was dichotomous (treatment: user or non-user). A $p < 0.05$ (two-sided) was used as the significance threshold for all statistical analyses. All statistical analyses were carried out using IBM Statistical Packages for Social Sciences v27 (SPSS, 2021) and figures were produced using GraphPad Prism v9.2.0 (2021) for Windows.

RESULTS

Sociodemographic and descriptive variables

Table 1 shows sociodemographic and clinical descriptive variables (mean and SD), and results from statistical comparisons. The nOSA groups had significantly lower BMI and reported less daytime sleepiness than the groups with OSA. A significant interaction between the cognitive status × OSA diagnosis status for the PSQI total score was found. A simple effect analysis revealed that the CN-nOSA group reported better sleep quality than the CN-OSA group ($F(1,65) = 13.29$, $p < .001$, $\eta^2p =$

.17); no other significant differences were observed. Both groups with aMCI exhibited significantly lower global cognitive functioning compared to the CN groups. There were no group differences for age, education, vascular burden, insomnia severity, mood, and anxiety. No group differences were observed for sex ($\chi^2(3) = 0.49$, $p = .92$).

Characteristics of polysomnographic variables

Table 2 displays PSG variables (means and SD) and results from statistical comparisons. Compared to the CN groups, the groups with aMCI showed significantly shorter total sleep duration and lower sleep efficiency. Compared to the nOSA groups, the groups with OSA exhibited a significantly higher proportion of N1 sleep stage, lower proportion of REM sleep, higher microarousal index, more NREM stage transitions to N1 and wakefulness, more severe AHI (across all night and during NREM sleep) and lower mean oxygen saturation (across the night and during NREM sleep). No significant interaction between cognitive and apneic status was found.

SW characteristics for all-night NREM sleep

Table 3 displays the groups' means and SD for SW characteristics. There were no significant group differences or interactions for any type of SW (i.e., all-combined SW, slow-switchers, and fast-switchers) regarding the measures of density, peak-to-peak amplitude, and classical frequency. By contrast, aMCI groups showed a significantly higher proportion of slow-switchers, and incidentally a lower proportion of fast-switchers ($F(1,65) = 6.07$, $p = .016$, $\eta^2p = .085$; Figure 2A) compared to the CN groups. The groups with aMCI also showed a significantly slower transition frequency for the all-combined SW in comparison to the CN groups ($F(1,65) = 4.01$, $p = .049$, $\eta^2p = .058$; Figure 2B). Finally, the OSA groups exhibited a significantly slower transition frequency for the fast-switchers compared to the nOSA groups ($F(1,64) = 6.31$, $p = .015$, $\eta^2p = .090$; Figure 2C). No significant interactions were found between group factors (cognitive status and OSA diagnosis status) and EEG topographic regions for any SW characteristics. In other words, the observed group differences were independent of the

topographical region. Tables S3 and S4 (Supplementary Material, Results section) present all the results from statistical comparisons on SW characteristics.

OSA-related sleep fragmentation and its association with SW densities

We tested whether the magnitude of sleep fragmentation in the OSA groups could be associated with SW densities. These analyses focused on the frontal region due to its relevance for SW generation [7,17,87]. They were conducted on the group of patients with OSA, and the groups split according to the cognitive status. No significant associations were detected between the frontal SW densities (i.e., all-combined SW, slow-switchers, fast-switchers) and the microarousal index in any groups (all *p*'s > .19). For the number of NREM stage transitions to N1 and wakefulness, there were no significant associations with frontal SW densities (i.e., all-combined SW, slow-switchers, fast-switchers) for the whole and CN-OSA groups (all *p*'s > .058), but strong relationships were observed for the aMCI-OSA group (all-combined SW: $r = -0.73$, $p = .002$; slow-switchers: $r = -0.77$, $p < .001$; fast-switchers: $r = -0.56$, $p = .030$; see Figures 3A and 3B).

SW characteristics and their associations with cognition

As shown in Figures 4A and 4B, the SW transition frequency and slow-switchers proportion in the frontal region significantly correlated with the composite score of episodic memory in the CN and aMCI groups. A slower SW transition frequency and higher slow-switcher proportion in the frontal region were associated with an improvement in episodic memory in CN participants but with a memory decline in aMCI participants. Significant correlations were observed for the composite score of the executive functions with the frontal SW transition frequency and slow-switchers proportion in the CN groups only (Figure 4C and 4D). A higher slow-switcher proportion and slower SW transition frequency in the frontal area were also associated with an improvement in executive functions in this group. Of note, the abovementioned correlations remained significant and of similar magnitude when conducting partial correlations to control for the effect of OSA treatment (see Table S5). Finally, the frontal

proportion of slow-switchers was positively correlated to the degree of subjective cognitive complaints at baseline in the aMCI groups only (Figure 4E). Table S5 (Supplementary Material, Results section) presents the results from all correlational analyses between SW characteristics showing group differences and the cognitive scores in these groups.

To explore the antagonistic relationships mentioned above, we conducted exploratory moderation analyses to determine whether the cognitive status is a moderator. As presented in Figure 5A, a moderation analysis showed that the interaction term between the cognitive status and the frontal SW transition frequency induced a significant increase in explained variance (ΔR^2 = .30, $F_{(1,39)}$= 16.51, p = .0002) of the composite score of episodic memory. This confirms an antagonistic moderating effect of the cognitive status. This result was also preserved when controlling for the effect of OSA treatment (ΔR^2 = .31, $F_{(1,38)}$= 16.98, p = .0002). Similarly, a moderation analysis confirmed a moderating effect of the cognitive status (ΔR^2 = .32, $F_{(1,39)}$= 18.27, p = .0001) on the relationship between the frontal slow-switcher proportion and the composite score of episodic memory (Figure 5B). Again, this effect was preserved when controlling for OSA treatment (ΔR^2 = .33, $F_{(1,38)}$= 18.69, p = .0001).

Regarding the within-group correlational analyses based on the OSA diagnosis status, no significant associations were detected between the frontal fast-switcher transition frequency with objective and subjective measures of cognition (all p's > .15; see Table S6). Controlling for OSA treatment did not change the results of the cognitive composite scores (all p's > .16).

DISCUSSION

This is the first study to examine NREM SW characteristics in the context of aMCI, OSA, and their potential interaction. We also introduced the concept of SW transition frequency and its derived measures to study pathological aging. Contrary to our prediction that aMCI combined with OSA would be associated with greater alterations of sleep SW, no significant interaction between both conditions was detected. Although classical SW characteristics did not significantly discriminate normal from pathological aging, the transition frequency of all-combined SW was slower and the proportion of slow-

switchers was higher in aMCI compared to CN participants. These SW characteristics in the frontal area were also associated with the longitudinal changes of cognition over time. A slower SW transition frequency and a higher proportion of slow-switchers were associated with cognitive improvements in the CN groups and a memory decline in the aMCI groups. A greater cognitive complaint was also uniquely related to a higher frontal proportion of slow-switchers in participants with aMCI. The fast-switcher transition frequency was significantly slower in OSA compared to nOSA participants, although not associated with cognitive measures.

Cognitive status, SW characteristics and cognitive correlates

The absence of a significant difference in the proportion of N2 and N3 sleep stages and the reduction of total sleep duration and sleep efficiency in the aMCI compared to the CN groups corroborate the results of a recent meta-analysis[38]. Previous studies highlighted an association between Aβ deposition with shorter self-reported sleep duration and lower sleep quality[88], as well as with lower sleep efficiency measured with actigraphy[89] and EEG[90] in CN older adults. Together, these results suggest that global subjective and objective measures of sleep quality and quantity covary with Aβ pathology, with a possible complex bi-directional influence[37]. Furthermore, our results align with recent studies showing that classically-defined SW characteristics are similar between the CN and aMCI groups[28,39], warranting the development and use of new sleep EEG measures.

In this study, we applied novel SW characteristic measures[44] to the investigation of pathological aging. We found that participants with aMCI displayed a significantly slower averaged transition frequency of the all-combined SW in addition to a higher proportion of the slow-switchers (and inversely, a diminished portion of fast-switchers) compared to the CN groups. These metrics are closely related to the SW negative-to-positive-phase transition. The former measures the speed of change of the SW phase (negative to positive), while the latter is a proportion measure of the SW type based on a preferred rate of transition (slow or fast). Numerous studies have suggested that the rate at which the

transition occurs from the SW negative-phase to positive-phase, mirrors synaptic strength and neuronal synchrony[8,40,42,43]. Therefore, we hypothesize that the slowing of the slow-wave transition frequency and the higher proportion of slow-switchers could reflect synaptic alterations in individuals with aMCI. Indeed, synaptic alterations are a key feature of AD[45,91-93], which is already evident in the MCI phase[94-97]. Early AD-related synaptic depletion might hamper the synaptic activity at the neuronal populations' level during sleep, leading to less synchronic transitioning between both SW phases. In this respect, N-methyl-D-aspartate (NMDA)-type glutamate receptors play an essential role in long-term synaptic plasticity[98] and are postulated to be involved in AD-related synaptic disruption[99-101]. In partial support of our hypothesis, a group recently observed a slower negative-to-positive slope of SW (considered here as negative half-waves) during the first hour of NREM sleep, as well as a smaller overnight reduction of the slope, in young participants with anti-NMDA receptor encephalitis (i.e., showing NMDA receptor deficiency) compared to age-matched healthy controls[102]. Additionally, idiopathic rapid eye movement sleep behavior disorder (iRBD) represents a prodromal stage for α-synucleinopathy neurodegeneration[103]. A recent study found that slowing of the slope of slower-range SW (0.5-1.25 Hz) was the most significant difference in SW characteristics between patients with iRBD compared to controls[104]. Collectively, these findings are in alignment with the idea that a slower negative-to-positive-phase transitioning may be a marker of synaptic alterations and degenerative processes in clinical populations.

Various aspects of sleep have been associated with cognition across the lifespan[5,25,105]. In this study, we observed significant relationships between the frontal transition frequency of all-combined SW and the frontal proportion of slow-switchers with the composite score of episodic memory in both groups. Associations with frontal SW features were also observed for the cognitive complaints in the groups with aMCI, and the executive function score in the CN groups. Together, these results support a sensitivity of frontal SW measures to clinically relevant cognitive markers in aging. Most interesting, however, was the observation of opposite relationship directions between both cognitive status groups

for the composite score of episodic memory. In the CN groups, a slower averaged transition frequency of SW and a higher proportion of slow-switchers in the frontal region were associated with cognitive improvements (i.e., episodic memory and executive functions). This is reminiscent of the relationships observed between the low-frequency component (<1 Hz) of the SW spectral range with cognition in healthy older individuals[19,23,39]. More low-range SWA is usually related to better memory and executive functions in healthy aging. Similarly, it was recently showed that a higher proportion of <1 Hz frontal SWA predicted lower cortical Aβ burden in CN older adults [85], in addition to forecasting a lower rate of cortical Aβ deposition longitudinally[90].

Conversely, in the group with aMCI, a slower transition frequency of SW and a higher proportion of slow-switchers in the frontal region were linked to a decline of episodic memory over time. Earlier research has indicated that synapse loss is the best neuropathological correlate of cognitive deficits in the context of AD[106-108], which was recently confirmed by synaptic PET imaging[109]. The observation of a declining memory trajectory accompanying the slowing of the SW negative-to-positive-phase transition in participants with aMCI could potentially reflect the AD-related synaptic alterations. Such synaptic disruptions may lead to an above-normal slowing of the SW negative-to-positive-phase transition, thus explaining the antagonistic moderating effect of the cognitive status. Moreover, it was previously shown that subjectively-measured sleep symptomatology and problems were associated with the extent of subjective cognitive complaints[110,111]. Complementarily, we observed that the frontal proportion of slow-switchers, an objective sleep measure, was related to the level of subjective cognitive complaints in the groups with aMCI only. This suggests that more SW with a "slow negative-to-positive transition" are associated with both greater current subjective cognitive difficulty and more future objective decline of memory, i.e., two clinically relevant measures in the context of AD. Indeed, the cognitive complaint usually prompts the initial referral and investigation in clinical settings, while the memory decline marks advancements in degenerative processes. It thus appears that the proportion of

slow-switchers has screening and prognosis value for cognitive health in this group at higher risk of progressing to AD.

OSA diagnosis status and SW characteristics

A recent review[112] underlined the presence of significant alterations in NREM sleep EEG microstructure in participants with OSA, including reduced SWA and sigma spectral power. Our study adds to this line of research by showing a significant slowing of the averaged transition frequency of fast-switchers in OSA compared to nOSA patients. Interestingly, we previously showed that the fast-switchers underwent a steeper decline across the overnight sleep cycles compared to the slow-switchers in healthy young and older adults[44]. This suggests that the fast-switchers type may be a more sensitive marker of homeostatic sleep processes. Along the same line, a previous study[113] showed that patients with sleep-disordered breathing, compared to control participants, displayed a significantly slower exponential decay of SWA (i.e., a well-known marker of sleep homeostasis) across a night of sleep. One could thus speculate that the OSA-related slowing we observed might mark alterations in brain networks underlying sleep homeostatic responses to wakefulness.

More broadly, we previously observed differences between fast-switchers and slow-switchers in terms of connectivity dynamics along their negative-to-positive-phase transition[44]. Thus, one hypothesis is that both SW types might implicate different structural and functional brain networks in their generation. Therefore, another possible explanation could be that the OSA-related slowing of the fast-switcher transition frequency illustrates an underlying loss of neuronal synchrony in those networks. At the macroscale, a recent study showed a global reduction of phase-based EEG synchronization in patients with OSA, compared to healthy controls, in the delta frequency band (0.5-4 Hz) during N2 and N3 sleep stages[114]. In other words, patients with OSA displayed a diminished level of long-range EEG functional connectivity in the spectral range of SW during NREM sleep. Of note, altered patterns of functional connectivity in patients with OSA were observed in multiple frequency bands and sleep stages, suggesting potential complex and extended alterations. SW and, more generally, slow-wave

sleep are related to brain integrity[115,116]. As OSA leads to structural and functional brain changes[117,118], it would be of keen interest to determine whether these alterations are linked to fast-switchers transition frequency. At the group level, the frontal transition frequency of fast-switchers was not significantly linked to the temporal course of cognition. This suggests that fast-switchers could be more involved in processes independent of the cognitive trajectories of patients with OSA. It could also suggest that the cognitive decline could occur later (beyond 18 months), thus masking any associations within the temporal window covered by the current study.

Few studies have formally looked into OSA-related disruptions of the sleep macroarchitecture. Our results showing an increase in the N1 sleep stage (%) are consistent with previous findings[55,119-121]. More inconsistent results are reported for the impact of OSA on the proportion of the REM sleep stage. However, the latter was shown to be significantly decreased in more severe OSA (AHI ≥ 30)[119,121]. This finding is coherent with the reduction in the REM sleep stage (%) that we observed in the groups with OSA, which have a mean AHI ≥ 30 events per hour. In this study, we were also interested in whether more sleep fragmentation in patients with OSA would induce a reduction in SW density during NREM sleep[54]. We observed that the number of NREM stage transitions to N1 and wakefulness was negatively correlated to frontal SW densities (i.e., all-combined SW, slow-switchers, fast-switchers) in aMCI-OSA participants only. These findings suggest that the CN-OSA group exhibit some degree of resilience of the mechanisms of SW production relative to sleep fragmentation, as more fractionated sleep was not linked to a disruption of SW density. Such resilience could be impeded in the aMCI-OSA group. Indeed, the more fragmented their NREM sleep, the lower is their density of SW. This susceptibility to sleep fragmentation also appears to be stronger for the slow-switchers density. Together, these results highlight a unique vulnerability of this clinical population and the relevance to test whether they would benefit from non-invasive brain stimulation to modulate their SW activity[122]. In a promising study[123], a transcranial direct current stimulation was applied at a low frequency (i.e., 0.75 Hz) to modulate NREM sleep oscillations in aMCI patients. Using this technique, they were able to

intensify <1 Hz SW and sleep spindle activity over frontal and centroparietal regions. They also observed a heightened synchronization between these two oscillations which tended to accompany better offline memory consolidation. Future studies should investigate whether such manipulation would benefit aMCI patients with OSA.

Limitations and future directions

The National Institute on Aging and Alzheimer's Association's (NIA-AA) research framework proposed to define the different stages of the AD continuum using established biomarkers[124], which were not accessible in this study. Thus, the main limitation of our study refers to the use of a syndromic rather than a biological definition of MCI. This may have favoured the presence of heterogeneous aetiologies that caused the cognitive impairments in our participants with aMCI. Moreover, only 64% of the sample performed a second neuropsychological assessment 18 months after the baseline testing. The sub-sample of participants who were tested a second time did not, however, differ from the ones who were not tested in terms of sociodemographic variables, episodic memory and executive function scores at baseline, subjective cognitive complaints, and SW characteristics showing group differences. Nonetheless, we invite a cautious interpretation of our correlational analyses as they are not based on the whole sample. The fact that our sample is mainly composed of males constitutes another limitation. Future studies should thus validate our results in a larger sample, with a more balanced prevalence of males and females, including participants with MCI presenting an AD-related biomarker profile.

Moreover, our hypotheses and results interpretation are largely based on previous works having proposed the speed of SW state transitions as a manifestation of synaptic strength and neuronal synchrony. This conception was first demonstrated via computational modelling of a large-scale thalamocortical system during sleep[43]. The latter showed that synaptic strength determined the degree of network synchronization and neuronal recruitment rate, which translated into the slope steepness of SW from local field potentials. Then, the model's predictions were tested in animals[8,42] and humans[40] and were shown to be supported. This model did not, however, discriminate between types of SW.

From the model's point of view, all SW are the realization of the same process, i.e., the SO rhythm. However, evidence from animals[13,125] and humans[126-128] suggests the existence of distinct oscillatory components in the delta frequency range (<4 Hz) that could integrate the scalp-SW domain. Our studies are coherent with this view[44]. Therefore, it is currently unknown whether the model[43]'s prediction of the link between synaptic strength and SW negative-to-positive-phase transition holds similarly for every SW entity. This is an important consideration to keep in mind when interpreting our results and calls for further investigations. Future studies will also be required to elucidate the possible relationship between the measures derived from the SW transition frequency and the already-known SW entities (e.g., SWA in the low versus high delta range).

Finally, our statistical comparisons and correlational analyses did not account for multiple testing, increasing the probability of making type-1 errors. However, given our modest sample size and limited statistical power, applying adjustments for multiple testing can also inflate the type-2 errors probability. Thus, trying to find a balance between managing the probabilities of making type-1 or type-2 errors, we favoured the latter based on the novelty brought by our study. Consequently, we invite researchers to see our significant results as initial evidence of the effects of pathological aging, which need confirmation via experimental replication[129].

CONCLUSION

The current findings expose the dissociated effects of the cognitive and apneic status on sleep architecture and SW characteristics. Even with the recent progress to identify and develop biomarkers of AD neuropathology, the prediction and tracking of cognitive trajectory in individuals at risk of converting to AD remain clinically challenging[130]. The SW transition frequency metrics showed specific correlational patterns with the temporal course of episodic memory depending on the participants' cognitive status, with particularly strong relationships in participants with aMCI. Future studies should investigate whether the general slowing observed at the SW negative-to-positive-phase transition level

in pathological aging covaries with biomarkers levels of synaptic integrity. If so, it would greatly support the recourse to a night of EEG recordings as a broadly accessible, non-invasive, and affordable tool for the early screening of cognitive decline and AD pathology instalment.

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The data underlying this article will be shared on reasonable request to the corresponding author.

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Figure Captions

Figure 1. Transition frequency and the slow- and fast-switcher distributions. (A) Representation of the SW phases with the transition between the negative-phase and positive-phase colored in red. The delay of the negative-to-positive-phase transition is denoted by τ. (B) Normalized histograms of each group's transition frequencies $1/(2\tau)$ (red line) for slow waves detected in N2+N3. The fit of the distributions can be expressed as a mixture of two Gaussians: one distribution for slow-switchers (cyan), another one for the fast-switchers (dark blue). The dashed line represents the separation frequency at the intersection between the two Gaussian distributions. The gray line depicts the empirical distribution.

Figure 2. Group estimated marginal means (± SEM) of altered SW characteristics across topographical regions. (A) Mean values of the percentage of slow-switchers based on the cognitive status. (B) Mean values of the averaged transition frequency of SW based on the cognitive status. (C) Mean values of the averaged transition frequency of fast-switchers (FS) based on the OSA diagnosis status.

Figure 3. Sleep fragmentation and SW densities in OSA groups. (A-B) Correlations between the frontal slow-switchers (SS) density / fast-switchers (FS) density and the number of NREM transitions to N1 and waking stages.

Figure 4. Significant relationships between frontal SW transition-related metrics and clinically relevant cognitive measures in the groups split according to the cognitive status. (A-B) Correlations between the frontal SW transition frequency / percentage of slow-switchers (SS) and the

score of episodic memory in both groups. (C-D) Correlations between the frontal SW transition frequency / percentage of slow-switchers and the score of executive functions in the CN group. (E) Correlation between the frontal percentage of slow-switchers and the level of subjective cognitive complaint in the aMCI group.

Figure 5. Moderating effect of the cognitive status on the relationship between SW transition-related metrics and the longitudinal change of episodic memory. (A-B) Relationships between the frontal SW transition frequency / percentage of slow-switchers (SS) and the composite score of episodic memory.

Note. The SW characteristic variable (predictor) is mean-centered ; the three points on the regression slope are set at the mean (0) ± 1SD of the SW characteristic variable.

Table 1. Sociodemographic and clinical variables: results from group comparisons.

	CN		aMCI		ANOVA				
Variables	nOSA n = 20	OSA n = 17	nOSA n = 17	OSA n = 15	Cognitive status	Apneic status	Interaction	Effect	η^2p[b]
Sex	18M; 2F	15M; 2F	16M; 1F	14M; 1F	-	-	-		
Age, years	63.7 (6.8)	64.4 (5.0)	65.1 (6.3)	64.2 (7.9)	$F = 0.17$, $p = .68$	$F = 0.005$, $p = .95$	$F = 0.26$, $p = .61$		
Education, years	16.1 (3.1)	15.4 (2.7)	13.8 (4.1)	15.1 (3.7)	$F = 2.41$, $p = .13$	$F = 0.20$, $p = .66$	$F = 1.48$, $p = .23$		
BMI, kg/m^2	25.8 (4.2)	29.5 (3.6)	26.9 (2.2)	28.3 (2.1)	$F < 0.001$, $p = 1.0$	**$F = 10.5$, $p = .002$**	$F = 2.20$, $p = .15$	nOSA < OSA	0.139
VBI[a]	0.95 (1.1)	1.1 (1.1)	1.1 (1.2)	1.3 (1.2)	$F = 0.43$, $p = .52$	$F = 0.54$, $p = .47$	$F = 0.08$, $p = .79$		
PSQI[a]	3.3 (2.2)	6.3 (3.1)	4.4 (2.4)	4.9 (2.5)	$F = 0.05$, $p = .83$	**$F = 8.22$, $p = .006$**	**$F = 4.42$, $p = .039$**	CN-nOSA < CN-OSA	0.064
ESS[a]	7.5 (4.7)	9.5 (5.0)	6.4 (4.7)	9.1 (3.0)	$F = 0.18$, $p = .68$	**$F = 6.16$, $p = .016$**	$F = 0.15$, $p = .70$	nOSA < OSA	0.087
ISI	5.8 (4.5)	8.2 (5.1)	6.9 (4.2)	7.1 (5.1)	$F = 0.002$, $p = .97$	$F = 1.37$, $p = .25$	$F = 0.90$, $p = .35$		
BDI-II[a]	4.4 (5.3)	8.4 (6.0)	7.7 (6.2)	6.9 (4.9)	$F = 0.44$, $p = .51$	$F = 2.10$, $p = .16$	$F = 2.45$, $p = .12$		
BAI[a]	2.6 (3.3)	2.8 (3.0)	2.9 (3.6)	5.1 (6.5)	$F = 1.13$, $p = .29$	$F = 1.07$, $p = .31$	$F = 0.34$, $p = .56$		
MoCA[a]	28.6 (1.2)	27.8 (1.6)	26.0 (2.2)	25.9 (3.0)	**$F = 19.9$, $p < .001$**	$F = 0.77$, $p = .39$	$F = 0.83$, $p = .37$	CN > aMCI	0.235

Note. Results are presented as means (standard deviation). Bold-colored results identify significant results at $p < .05$. CN, cognitively normal; aMCI, amnestic mild cognitive impairment; nOSA, no or mild obstructive sleep apnea; OSA, moderate to severe obstructive sleep apnea; BMI, body mass index; VBI, Vascular Burden Index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; BDI-II, Beck Depression Inventory II; BAI, Beck Anxiety Inventory; MoCA, Montreal Cognitive Assessment.

[a] The variable was subjected to a square root transformation. Original pre-transformation data are presented.

[b] The effect sizes are reported only for the significant effects.

Table 2. Polysomnographic variables: results from group comparisons.

	CN		aMCI		ANOVA				
Variables	nOSA n = 20	OSA n = 17	nOSA n = 17	OSA n = 15	Cognitive status	Apneic status	Interaction	Effect	η²p[b]
Sleep macroarchitecture									
Sleep latency[a], minutes	12.7 (8.5)	12.5 (13.7)	18.0 (13.0)	13.2 (11.4)	*F* = 1.31, *p* = .26	*F* = 1.68, *p* = .20	*F* = 0.28, *p* = .60		
Total sleep time, minutes	369.2 (57.2)	380.3 (65.7)	342.0 (61.4)	332.8 (64.8)	***F* = 6.18, *p* = .015**	*F* = 0.004, *p* = .95	*F* = 0.46, *p* = .50	aMCI < CN	0.087
Sleep efficiency, %	79.5 (8.4)	82.5 (8.8)	73.6 (10.4)	74.7 (15.0)	***F* = 7.01, *p* = .01**	*F* = 0.67, *p* = .42	*F* = 0.13, *p* = .72	aMCI < CN	0.097
Stage N1 sleep, %	18.6 (6.8)	22.7 (4.2)	20.1 (7.3)	27.7 (12.3)	*F* = 2.69, *p* = .11	***F* = 9.17, *p* = .004**	*F* = 0.82, *p* = .37	nOSA < OSA	0.124
Stage N2 sleep, %	57.8 (6.7)	55.8 (6.1)	55.8 (7.6)	54.4 (10.2)	*F* = 0.83, *p* = .37	*F* = 0.80, *p* = .38	*F* = 0.03, *p* = .87		
Stage N3 sleep[a], %	6.4 (7.0)	6.2 (5.4)	7.6 (8.0)	6.1 (6.8)	*F* = 0.02, *p* = .90	*F* = 0.05, *p* = .83	*F* = 0.20, *p* = .65		
Stage REM sleep, %	17.2 (6.3)	15.2 (4.4)	16.6 (5.3)	11.9 (5.6)	*F* = 2.27, *p* = .14	***F* = 6.34, *p* = .014**	*F* = 1.13, *p* = .29	nOSA > OSA	0.089
Polysomnographic variables									
AHI, events/h	8.0 (4.1)	31.0 (10.5)	5.8 (4.2)	33.6 (11.8)	*F* = 0.01, *p* = .91	***F* = 165.8, *p* < .001**	*F* = 1.49, *p* = .23	nOSA < OSA	0.718
AHI during NREM, events/h	4.8 (3.0)	19.4 (8.7)	3.7 (4.2)	24.8 (12.2)	*F* = 1.35, *p* = .25	***F* = 94.4, *p* < .001**	*F* = 3.20, *p* = .08	nOSA < OSA	0.592
Microarousal index, events/h	13.5 (6.2)	18.6 (6.2)	13.2 (5.5)	19.3 (6.5)	*F* = 0.02, *p* = .90	***F* = 14.5, *p* < .001**	*F* = 0.10, *p* = .76	nOSA < OSA	0.182
Number of NREM transitions to N1 and wakefulness	69.0 (26.9)	90.9 (27.4)	62.7 (19.7)	87.4 (32.6)	*F* = 0.57, *p* = .45	***F* = 13.0, *p* < .001**	*F* = 0.05, *p* = .83	nOSA < OSA	0.166
Mean Sp_{O2}, %	95.3 (1.2)	93.8 (1.1)	95.0 (1.2)	94.4 (0.99)	*F* = 0.16, *p* = .69	***F* = 14.8, *p* < .001**	*F* = 2.65, *p* = .11	nOSA > OSA	0.190
Mean Sp_{O2} during NREM, %	95.2 (1.2)	93.7 (1.1)	94.8 (1.2)	94.2 (1.0)	*F* = 0.03, *p* = .87	***F* = 16.0, *p* < .001**	*F* = 2.39, *p* = .13	nOSA > OSA	0.203

Note. Results are presented as means (standard deviation). Bold-colored results identify significant results at $p < .05$. AHI, apnea-hypopnea index; AHI during NREM, apnea-hypopnea index during NREM sleep; Sp_{O2}, oxygen saturation; Sp_{O2} during NREM, oxygen saturation during NREM sleep.

[a] The variable was subjected to a square root transformation. Original pre-transformation data are presented.

[b] The effect sizes are reported only for the significant effects.

Table 3. SW characteristics for each group.

	CN-nOSA			CN-OSA			aMCI-nOSA			aMCI-OSA		
Variables	Frontal	Central	Parietal	Frontal	Central	Parietal	Frontal	Central	Parietal	Frontal	Central	Parietal
Density (events / minute)												
SW	6.0 (4.2)	4.4 (3.3)	2.5 (2.4)	6.4 (3.6)	4.5 (3.2)	2.4 (2.4)	6.2 (3.8)	4.4 (2.9)	2.5 (2.3)	5.2 (3.1)	3.4 (2.2)	1.8 (1.9)
SS	3.7 (2.4)	2.3 (1.9)	1.7 (1.7)	4.2 (2.7)	2.6 (2.0)	1.8 (1.7)	4.3 (2.8)	2.7 (1.8)	1.9 (1.7)	3.6 (2.3)	2.2 (1.4)	1.4 (1.4)
FS	2.3 (1.9)	2.0 (1.7)	0.8 (0.8)	2.2 (1.5)	1.9 (1.4)	0.6 (0.7)	2.0 (1.4)	1.7 (1.4)	0.6 (0.7)	1.7 (1.4)	1.4 (1.4)	0.5 (0.5)
Proportion of switchers (%)												
SS	64.6 (9.4)	60.0 (13.1)	71.4 (12.3)	62.1 (15.9)	57.4 (14.5)	71.4 (13.5)	68.5 (13.1)	65.5 (15.3)	80.0 (10.5)	70.2 (10.6)	66.0 (10.9)	78.4 (6.4)
FS	35.4 (9.4)	40.0 (13.1)	28.6 (12.3)	37.9 (15.9)	42.6 (14.5)	28.6 (13.5)	31.5 (13.1)	34.5 (15.3)	20.0 (10.5)	29.8 (10.6)	34.0 (10.9)	21.6 (6.4)
Amplitude (μV)												
SW	88.9 (7.6)	82.4 (6.5)	78.9 (7.1)	88.8 (5.9)	81.6 (4.6)	77.2 (4.4)	86.5 (8.5)	80.4 (6.3)	76.9 (5.6)	87.0 (7.3)	80.5 (6.8)	76.6 (5.5)
SS	91.5 (9.2)	84.0 (7.9)	80.4 (8.1)	90.3 (6.6)	82.0 (5.7)	77.7 (5.0)	88.6 (9.8)	81.8 (7.3)	77.6 (6.2)	89.0 (8.7)	82.0 (8.1)	77.6 (6.3)
FS	83.8 (7.1)	79.9 (5.1)	75.2 (5.4)	84.5 (5.0)	80.2 (4.2)	75.5 (3.9)	81.2 (7.3)	77.5 (5.4)	74.6 (4.3)	82.0 (6.1)	77.3 (5.2)	73.1 (3.8)
Frequency (Hz)												
SW	1.25 (0.09)	1.35 (0.15)	1.21 (0.14)	1.27 (0.12)	1.35 (0.14)	1.22 (0.13)	1.25 (0.12)	1.32 (0.14)	1.19 (0.10)	1.23 (0.11)	1.30 (0.11)	1.19 (0.09)
SS	1.12 (0.07)	1.14 (0.08)	1.07 (0.07)	1.14 (0.08)	1.15 (0.08)	1.09 (0.08)	1.12 (0.07)	1.13 (0.05)	1.09 (0.06)	1.12 (0.08)	1.13 (0.06)	1.07 (0.06)
FS	1.49 (0.11)	1.64 (0.14)	1.52 (0.15)	1.47 (0.09)	1.61 (0.12)	1.55 (0.14)	1.53 (0.15)	1.66 (0.17)	1.62 (0.25)	1.48 (0.11)	1.61 (0.11)	1.58 (0.23)
Transition frequency (Hz)												
SW	1.43 (0.12)	1.51 (0.18)	1.33 (0.18)	1.45 (0.19)	1.51 (0.19)	1.32 (0.18)	1.38 (0.15)	1.43 (0.19)	1.23 (0.15)	1.37 (0.15)	1.43 (0.16)	1.24 (0.11)
SS	1.10 (0.06)	1.07 (0.05)	1.01 (0.05)	1.11 (0.06)	1.08 (0.05)	1.03 (0.07)	1.10 (0.06)	1.07 (0.05)	1.01 (0.05)	1.10 (0.06)	1.08 (0.05)	1.01 (0.05)
FS	2.04 (0.07)	2.15 (0.09)	2.11 (0.11)	1.98 (0.09)	2.09 (0.09)	2.06 (0.09)	2.05 (0.07)	2.15 (0.10)	2.13 (0.13)	2.03 (0.06)	2.11 (0.09)	2.09 (0.12)

Note. Results are presented as means (SD). SW, all-combined slow waves; SS, slow-switchers; FS, fast-switchers.

Figure 1

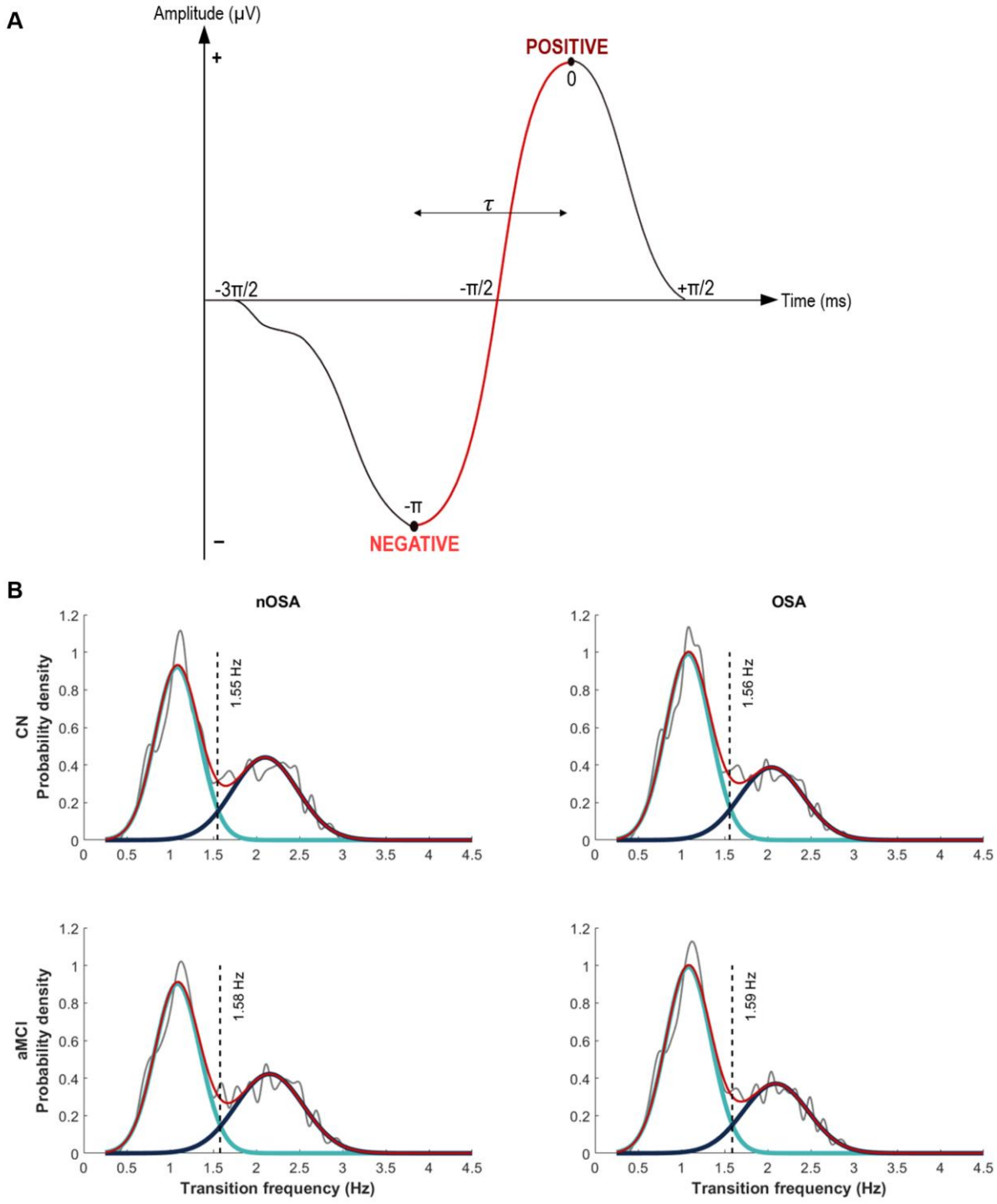

Figure 2

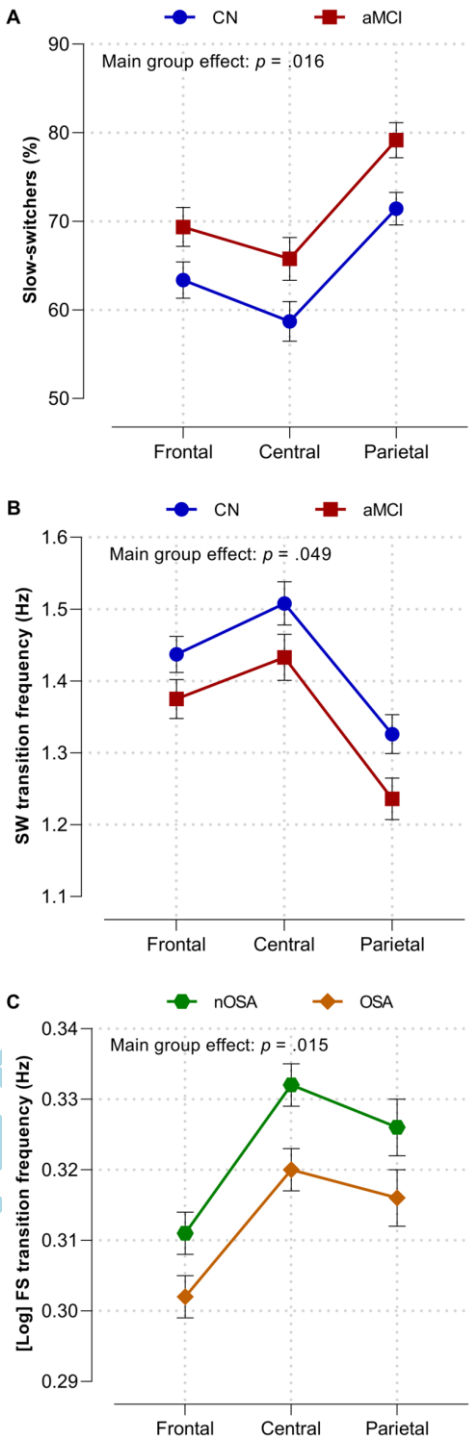

Figure 3

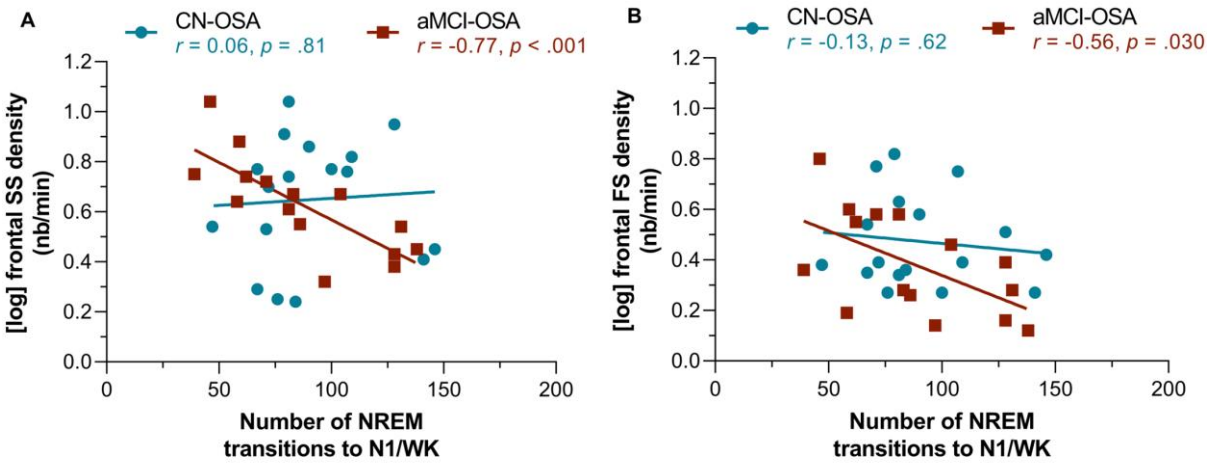

Figure 4

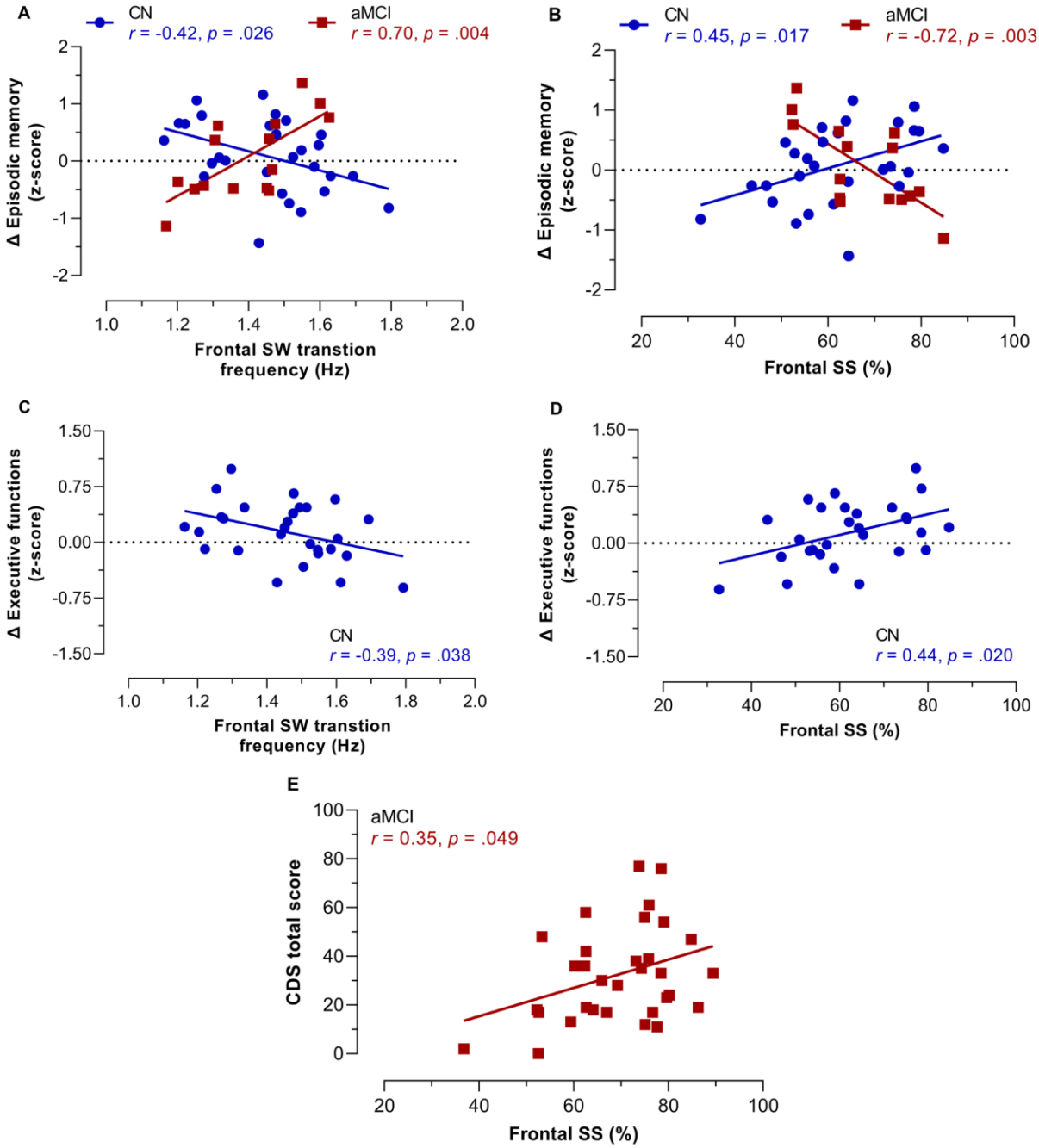

Figure 5