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Youth-Like Precision of Slow Oscillation–Spindle Coupling Promotes Memory Consolidation Across the Adult Lifespan

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Abstract

Memory consolidation during sleep relies on the precisely timed interaction of rhythmic neural events. Here, we investigate differences in slow oscillations (SO) and sleep spindles (SP) and their coupling across the adult human lifespan and ask whether observed alterations relate to the ability to retain associative memories across sleep. We demonstrate that the fine-tuned SO–SP coupling that is present in younger adults diffuses with advanced age and shifts both in time and frequency. Crucially, we show that a 'youth-like' precision of SO–SP coupling promotes memory consolidation across the entire adult lifespan, and that brain integrity in source regions for the generation of SOs and SPs reinforces this beneficial SO–SP coupling in old age. Our results reveal age-related differences in SO–SP coupling in healthy elderly individuals. Furthermore, they broaden our understanding of the conditions and the functional significance of SO–SP coupling across the entire adult lifespan.

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Introduction

Research in animals and younger adults yields converging evidence that newly acquired information is reprocessed during deep non-rapid eye movement (NREM) sleep. According to the framework of system consolidation (Diekelmann & Born, 2010; Rasch & Born, 2013) declarative memories are initially processed by a fast learning system in the hippocampus that binds information into a transient representation (Simons & Spiers, 2003). Only repeated reactivation of memories in the hippocampus then eventually allows transfer to a long-term store in the neocortex (Born & Wilhelm, 2012; Gais & Born, 2004; Walker, 2009). But how does the brain ensure precise communication between cortical modules that allows for the reorganization of memory traces during sleep?

During sleep, effective communication is enabled by the fine-tuned hierarchical succession of several brain rhythms governed by large-amplitude, low-frequency oscillations, so-called slow oscillations (SO; 0.5–1 Hz) that mainly emerge from prefrontal brain areas (Achermann & Borbély, 1997; Cox, van Driel, de Boer, & Talamini, 2014; Murphy et al., 2009; Nir et al., 2011). Via cortico-thalamic projections, neurons in the thalamic reticular nucleus are activated during the depolarized up-states of SOs resulting in the initiation of fast sleep spindles (SP; 12–15 Hz) (Amzica & Steriade, 1998; Gennaro & Ferrara, 2003; Steriade, 2006; Steriade, Domich, Oakson, & Deschenes, 1987). These fast SPs, in turn, synchronize cortical activity in a precise spatiotemporal manner. As the excited neurons exhibit a massive influx of Ca^{2+}, synaptic changes become facilitated (Lüthi, 2014). Further nesting of hippocampal high-frequency bursts, known as sharp-wave ripples, within the excitable troughs of fast SPs (Clemens et al., 2007; Siapas & Wilson, 1998; Staresina et al., 2015) optimizes the hippocampo-neocortical dialogue. A second SP type, so-called slow SPs (9–12 Hz), occurs during a time window in which neural depolarization (i.e., the SO up-state) transitions into hyperpolarized down-states (Gennaro & Ferrara, 2003; Klinzing et al., 2016; Mölle, Bergmann, Marshall, & Born, 2011). A specific role of slow SPs in the consolidation of memories is not yet established (Barakat et al., 2011; Mölle et al., 2011; Rasch & Born, 2013).

Typically, SOs and SPs are studied with regard to their independent contribution to consolidation mechanisms. However, as system consolidation is assumed to rely on a tight coupling

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of SOs, SPs, and sharp-wave ripples (Born & Wilhelm, 2012; Marshall & Born, 2007), recent studies have started to focus on the exact timing of brain rhythms (Klinzing et al., 2016; Mölle, Marshall, Gais, & Born, 2002; Mölle, Eschenko, Gais, Sara, & Born, 2009; Mölle et al., 2011; Steriade, 2006) and its functional significance for sleep-dependent memory consolidation (eg., Latchoumane, Ngo, & Born, 2017; Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016; Mölle et al., 2009, 2011; Niknazar, Krishnan, Bazhenov, & Mednick, 2015). Recent experiments in rats demonstrated that reinforcing the coordinated pattern of SOs, SPs, and sharp-wave ripples boosts memory consolidation of object locations (Maingret et al., 2016), whereas suppression of these patterns has disruptive effects on sleep-dependent memory consolidation (Latchoumane et al., 2017). In humans, SO–SP coupling is enhanced by prior learning (Mölle et al., 2009, 2011) and is triggered by replaying previously learned material during sleep (Cairney, Guttesen, El Marj, & Staresina, in press). Although first studies have highlighted the involvement of SO–SP coupling in memory consolidation, particularly in humans, evidence for this link is still sparse. Further, it remains to be established under which circumstances the coordination of SOs and SPs is most beneficial in supporting the sleep-dependent reorganization and stabilization of memory contents.

SO–SP coupling, for instance, can be critically impaired in disrupted sleep. This is particularly common in elderly adults who often lack the deepest NREM sleep stage, so-called slow-wave sleep (Carrier et al., 2011; Mander, Winer, & Walker, 2017; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). In old age, SOs and SPs themselves appear less often and with reduced amplitudes (Crowley, Trinder, Kim, Carrington, & Colrain, 2002; Dubé et al., 2015; Fogel et al., 2012). Age-related changes in brain structure possibly contribute to the observed sleep alterations by impairing SO and SP generation and propagation (Dubé et al., 2015; Fogel et al., 2016; Landolt & Borbély, 2001; Mander et al., 2013; Varga et al., 2016). This may also impact SO–SP coupling itself, thereby resulting in impaired memory stabilization during sleep (see Helfrich, Mander, Jagust, Knight, & Walker, 2018 for most recent evidence). Indeed, several studies report age-related losses in overnight memory retention (Backhaus et al., 2007; Baran, Mantua, & Spencer, 2016; Cherdieu, Reynaud, Uhlrich, Versace, & Mazza, 2014), which can be linked to reduced slow-wave sleep (Mander et al., 2013;

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Varga et al., 2016) and a decline in SP occurrence (Seeck-Hirschner et al., 2012). In light of the growing interest in the interaction of SOs and SPs, very recent evidence highlights that SO–SP coupling is indeed dispersed in elderly adults, resulting in impaired overnight memory consolidation (Helfrich et al., 2018). As this disturbed nesting of SOs and SPs may constitute a possible target for clinical interventions (Ladenbauer et al., 2017), the preconditions and the functional significance of SO–SP coupling across the entire adult lifespan require investigation.

Following this rationale, it was our aim to examine age-related changes in the coupling of SOs and both slow and fast SPs. We asked whether observed alterations can be explained by structural brain atrophy in source regions of SO and SP generation and whether the resulting SO–SP dispersion negatively impacts the ability to retain associative memories across sleep. In the present study, younger and older adults completed an associative memory paradigm, consisting of a learning session of scene–word pairs on the first day and a delayed cued-recall task on the following day (Figure 1). During the nights before and after learning, sleep was monitored using ambulatory polysomnography (PSG). Structural brain integrity was assessed by voxel-based morphometry (VBM) of structural magnetic resonance images (MRI). By comparing the PSG recordings of younger and older adults, we identify age-related differences in the coordination of SOs and SPs. Using estimates of gray matter volume we further establish the role of structural brain integrity in the coordination of SOs and SPs. Finally, we relate the pattern of SO–SP coupling to the behavioral measure of overnight memory retention and show that the observed ‘aged’ SO–SP coordination indeed explains deficient memory consolidation in old age.

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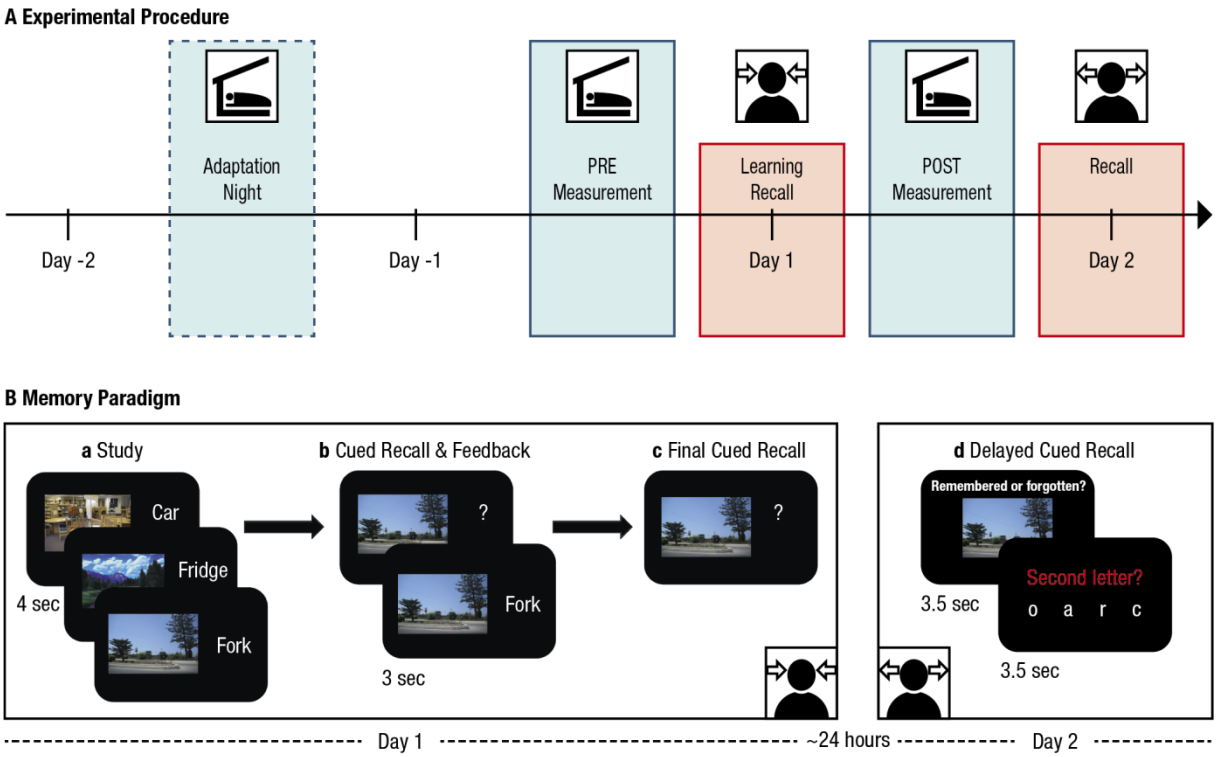

Figure 1. A. Experimental procedure. The memory task at the core of the experiment consisted of a learning phase and an immediate recall on Day 1 as well as a delayed recall approximately 24 hours later (red boxes). Sleep was monitored in the nights before (PRE) and after (POST) learning using ambulatory polysomnography (blue boxes). A prior adaptation night (dashed blue box) familiarized the participants with the sleep recordings. B. Memory paradigm (cf. Fandakova et al., in press). (a) During study, participants were instructed to remember 440 (younger adults) or 280 scene–word pairs (older adults). (b) During the cued-recall and feedback phase the scene was presented as a cue to recall the corresponding word. Irrespective of recall accuracy, the original pair was presented again to allow for re-study. The whole cued-recall and feedback cycle was performed once in younger and twice in older adults. (c) During final recall, scenes again served as cues to recall the corresponding word, but no feedback was provided. (d) Delayed cued-recall took place approximately 24 hours later. Participants were presented with the scenes only and had to indicate if they still remembered the associated word. Afterwards they had to select the corresponding second letter of the word to verify their true memory of the associate.

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Results

Rhythmic neural events during NREM sleep are affected by aging

Sleep architecture changes drastically across the adult lifespan (Ohayon et al., 2004). To capture these changes, we recorded electrical neuronal activity during sleep before and after learning scene–word pairs using ambulatory PSG devices at participants' homes (Methods). In the following, we focus on sleep after learning only. We found the anticipated decrease in the amount of slow-wave sleep in older adults, accompanied by an increase in the lighter NREM sleep stages 1 and 2 (Table 1; see Table 2 for the exact calculation of sleep variables). As almost one third of our older sample (n = 9) failed to meet the amplitude criteria of slow-wave sleep when visually scoring the PSG data (Iber, Ancoli-Israel, Chesson, & Quan, 2007), we combined all NREM sleep stages (i.e., stage 1, stage 2, and slow-wave sleep) for further analyses.

Within NREM sleep we were particularly interested in the occurrence of SOs (adapted SO detection algorithm by Mölle et al., 2002 and Ngo et al., 2013, cf. Methods), as well as slow and fast SPs (adapted SP detection algorithm by Ferrarelli et al., 2007, cf. Methods). In line with the previously reported topography of slow and fast SPs (Klinzing et al., 2016), we focused our analyses on frontal slow SPs and central fast SPs. Here, we observed the expected reduction in the occurrence of frontal SOs and slow SPs (SO number: $z = 2.41$, $p = .016$, $Md_{YA} = 1144.25$, $Md_{OA} = 995.50$; SO density: $z = 2.04$, $p = .042$, $Md_{YA} = 3.55$ events/min, $Md_{OA} = 3.11$ events/min; slow SP number: $z = 3.61$, $p < .001$, $Md_{YA} = 105$, $Md_{OA} = 55$; slow SP density: $z = 3.53$, $p < .001$, $Md_{YA} = 0.36$ events/min, $Md_{OA} = 0.16$ events/min) as well as central fast SPs (fast SP number: $z = 4.71$, $p < .001$, $Md_{YA} = 163$, $Md_{OA} = 63$; fast SP density: $z = 4.59$, $p < .001$, $Md_{YA} = 0.52$ events/min, $Md_{OA} = 0.17$ events/min).

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Table 1

Age differences in sleep architecture

	Younger Adults – Median [1st quartile; 3rd quartile]	Older Adults – Median [1st quartile; 3rd quartile]	*z*	*p*
TST (min)	457.00 [420.0; 508.5]	417.50 [370.75; 447.25]	2.60	.009
WASO (min)	3.43 [0.73; 5.66]	9.09 [4.96; 15.77]	-3.81	<.001
Stage 1 (%)	4.31 [3.07; 5.88]	7.57 [4.72; 10.20]	-3.19	.001
Stage 2 (%)	50.69 [44.96; 56.92]	63.99 [61.09; 69.96]	-5.45	<.001
SWS (%)	20.56 [16.62; 26.61]	3.80 [0.00; 12.67]	5.38	<.001
REM (%)	24.49 [21.6; 26.69]	21.10 [17.01; 24.53]	2.29	.022

Note. TST: total sleep time; WASO: wake after sleep onset; SWS: slow wave sleep; REM: rapid eye-movement sleep.

Slow and fast SPs show a comparable dependency on SOs in younger and older adults

To determine whether SP events indeed coincide with the detected SOs, we calculated the amount of SPs that occurred in an interval of ±1.2 s around the down peak of the identified SOs (Figure 2A). The time window was chosen to cover one whole SO cycle (0.5−1 Hz, i.e., 1−2 s). To cross-check, we also calculated the proportion of SOs with SPs occurring within ±1.2 s around the respective negative down peak of the oscillation (Figure 2B). In both age groups we identified a comparable percentage of SPs coupled to SOs (fast SPs: M_{YA} = 31.04 %, M_{OA} = 37.74 %; slow SPs: M_{YA} = 56.14 %, M_{OA} = 54.14 %). In older adults we found a reduced proportion of SOs occurring in coordination with both fast and slow SPs (fast SPs: $t(52)$ = 2.63, p = .011, M_{YA} = 6.68 %, M_{OA} = 3.58 %, slow SPS: $t(42)$ = 2.99, p = .005, M_{YA} = 6.75 %, M_{OA} = 3.60 %). This suggests a generally constant pattern of SP−SO coupling across adulthood with potentially the same mechanisms underlying SP generation. SOs might partly forfeit their ability to initiate SP generation in old age. However, those SPs that do occur in older adults, are still bound to the occurrence of SOs.

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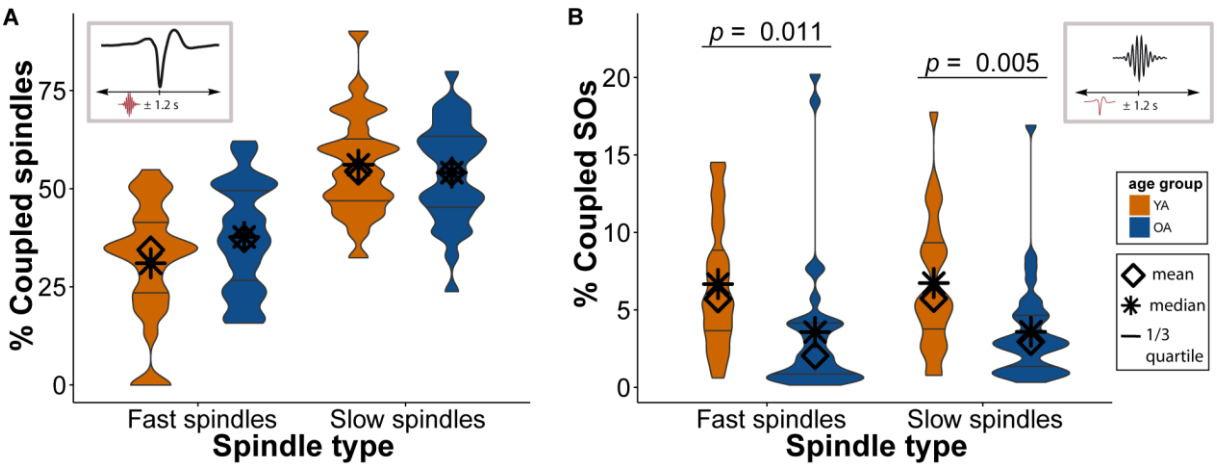

Figure 2. Fast and slow SPs coincide with SOs in both younger and older adults. (A) A high percentage of SPs is coupled to the occurrence of SOs. About one third of all fast SPs and half of all slow SPs occur within an interval of ± 1.2 s around the down peak of a SO. This proportion is similar for both age groups. (B) Only a small percentage of all appearing SOs is coupled to the occurrence of SPs. SOs in older adults (blue) occur less frequently within an interval of ± 1.2 s around fast and slow SP centers than in younger adults. YA: younger adults; OA: older adults; SO: slow oscillation; SP: spindle.

SO–SP coupling differentially changes for fast and slow SPs in younger and older adults

Having established the general presence of SO–SP coordination in old age, in the next step we focused on the precise temporal association between SOs and SPs. We compared the oscillatory power in the SP frequency range for time segments with and without SOs (cf. Methods). During SO trials (centered ± 1.2 s around the down peak of the respective SO), power in the SP frequency range indeed differed significantly from randomly selected intervals without SOs (for all clusters: $p < .001$, additional negative cluster in older adults at Pz: $p = .009$, Figure 3A and 3B, Supplementary Figure 1). This effect was present in both age groups and suggests a coupling of SPs to specific phases of the underlying SO. Nevertheless, each age group displayed a distinct modulation of the effect (Figure 3A and 3B, Supplementary Figure 1).

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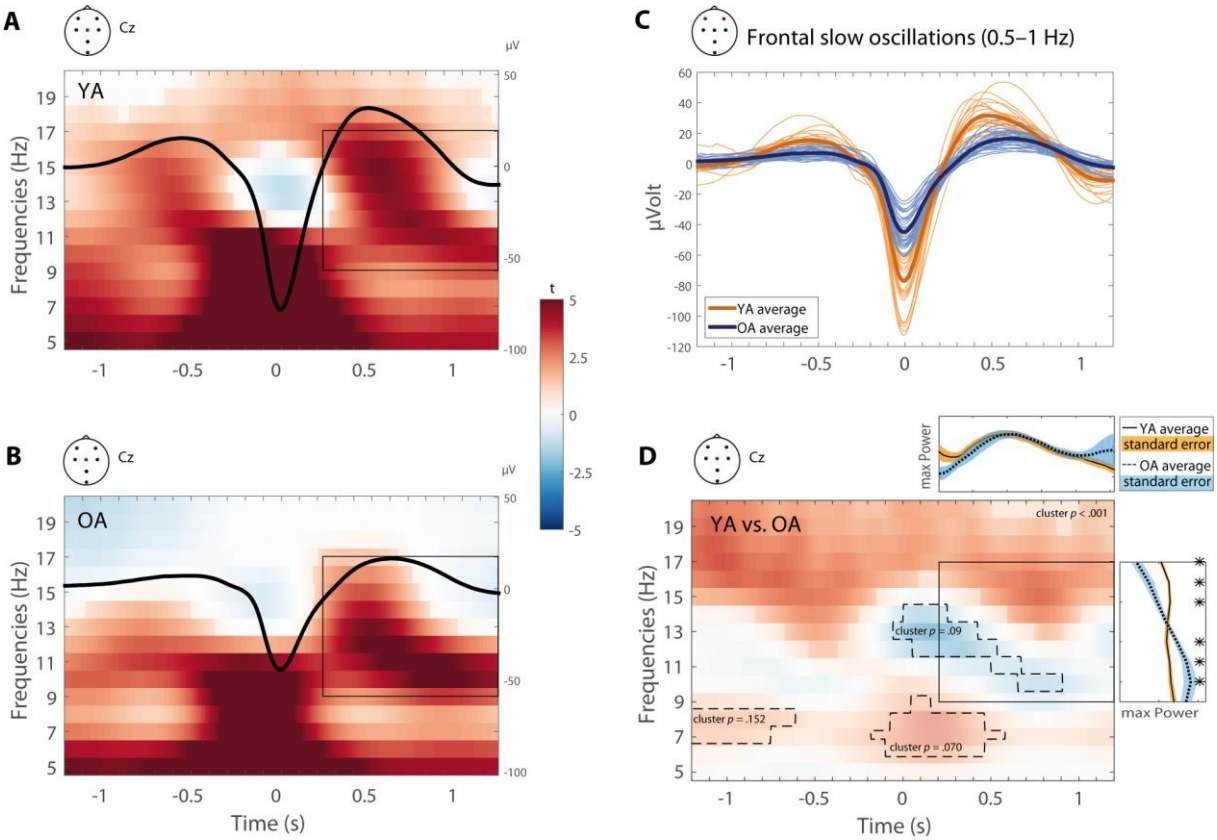

Figure 3. SO–SP coupling is differentially expressed in younger and older adults. (A + B) Differences in wavelet power for SO trials (respective down peak ± 1.2 s) compared to trials without SOs are depicted (in *t*-score units). Significant clusters (cluster-based permutation test, cluster $\alpha < 0.05$) are highlighted. The average frontal SO for each age group is inserted in black (the scale in µV is indicated on the right of each time–frequency graph). In both age groups, EEG power is modulated as a function of the SO phase. (A) In younger adults, fast SP activity (12–15 Hz) peaks during the up peak of the SO. Slow SP power (9–12 Hz) is strongest at the up-to down-state transition. (B) In older adults, power increases are shifted to lower frequencies as compared to younger adults. (C) Average frontal SOs are depicted for both age groups (thick lines) and for each younger (light orange) and older (light blue) individual. In older adults, the amplitude of SOs is reduced and the frequency is decreased. (D) The *t*-map of the time–frequency age comparison is displayed (significant clusters, cluster $\alpha < 0.05$, are highlighted, non-significant clusters marked by dashed line). Power distributions averaged across time and frequencies (reference window outlined in black) are displayed in the two line subplots (younger adults: black solid line and shaded orange standard errors; older adults: black dashed line and shaded blue standard errors). Significant clusters of the age comparison (cluster $\alpha < 0.05$) are marked by asterisks. Significant age-related reductions in fast SP power are tied to the SO up-state only (main plot, cluster $p < .001$). In older adults, power in fast SP frequencies during the SO up-state is reduced and slow SP power increased (right line plot, all clusters: $p \leq .002$). YA: younger adults; OA: older adults; SO: slow oscillation; SP: spindle.

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In younger adults, we observed increases in fast SP power (12–15 Hz) during the SO up-state but not during the down-state (Figure 3A). Power increased most strongly during and shortly after the SO up peak following the down-state (400 to 700 ms, SO up peak at 484 ms). Although this effect was visible across all chosen derivations (Supplementary Figures 1A and 1B), it was more pronounced over centroparietal sites. Frontal and central slow SP activity (9–12 Hz) was increased during the whole SO interval, but peaked during the up-to down-state transition (–500 to 200 ms).

In older adults, as expected, SOs themselves were expressed differently than in younger adults and showed a decreased amplitude and frequency (SO amplitude: $z = 5.69$, $p < .001$, $Md_{YA} = 123.66$ µV, $Md_{OA} = 74.85$ µV; SO frequency: $z = 2.73$, $p = .006$, $Md_{YA} = 0.79$ Hz, $Md_{OA} = 0.78$ Hz) (Figure 3B). But SO-modulated EEG activity also differed (Figure 3B). To identify age-specific characteristics of this global pattern we directly compared the time–frequency patterns of both age groups (Figure 3D). Further, as studies so far indicated SP activity during the SO up-state as being critical for memory consolidation (eg., Cairney et al., in press; Mölle et al., 2009), we precisely determined at which time points and at which frequencies EEG power was modulated most strongly during the SO up-state (cf. Methods). We thus compared the power distribution of frequencies between 9 and 17 Hz during the SO up-state (0.2–1.2 s after the SO down peak) between younger and older adults (line subplots above and to the right of Figure 3D).

Over all derivations, power in higher frequencies (16–20 Hz) was globally reduced in older adults whereas fast SP power was reduced during the SO up-state only (all clusters: $p \leq .003$, Figure 3D, Supplementary Figure 1). Over central sites the power peak during the up-state was more stretched in time and shifted to lower frequencies (9–13 Hz, i.e., the slow SP frequency band). This resulted in a strong increase in slow SP activity during the SO up-state in older adults (Figure 3B). This shift to lower frequencies failed to reach significance when tested within the global time–frequency pattern (negative, cold-colored cluster in Fig 3D, cluster $p = .09$), but became visible when comparing the slow and fast SP power distribution during the SO up-state (line subplot to the right of Figure 3D). Whereas younger adults showed an almost equal modulation of slow and fast SP power during the

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SO up-state, fast SP power was significantly reduced and slow SP power significantly increased in older adults (all clusters: $p \leq .002$).

Additional consideration of peri-event time histograms of SOs co-occurring with fast and slow SP events (Figure 4, Supplementary Figures 2 and 3, cf. Methods) revealed that the observed power changes in SP frequencies indeed reflected increases in the occurrence of SP events themselves (Figure 4, Supplementary Figures 2 and 3). The trajectory of frontal slow and central fast SP power (averaged *t*-values of the SO–baseline contrast within the respective frequency band) corresponded to the SO-modulated SP occurrence. Whereas in younger adults fast SPs predominantly appeared during and shortly after the SO up peak, in older adults they occurred before the up peak and their appearance was overall less specific (Figure 4D and 4E). Comparison of the fast SP power trajectories between younger and older adults highlighted largely reduced fast SP power values in older adults (controlled for multiple comparisons using a cluster-based permutation test, all clusters: $p < .019$) as well as an earlier peak during the SO up-state ($t(53) = 2.456$, $p = .017$, $M_{YA} = 573$ ms, $M_{OA} = 485$ ms; cf. Figure 4F). Slow SPs had a clear tendency to occur at the up-to down-state transition preceding the down peak in younger adults, a phenomenon that disappeared in older adults (Figure 4A and 4B). Age differences in slow SP power, however, were not significant (all clusters: $p = .100$; Figure 4C).

To summarize, we found a characteristic SO–SP coupling pattern in younger adults that was marked by a strong increase in fast SPs coupled to the SO up peak as well as an increase in slow SPs during the up-to down-state transition. This pattern changed significantly across the adult lifespan. Within this 'aged' SO–SP coupling, three characteristics were striking: First, fast SP modulation was overall reduced in the elderly. Second, if fast SPs occurred, they appeared earlier during the SO up-state. Together with an overall reduced frequency of SOs, fast SPs were thus no longer precisely tied to the SO up peak (SO up peak in older adults at 617 ms). Finally, slow SPs were similarly modulated in younger and older adults. Nevertheless, as fast SP power during the up-state was less increased in old age, slow SP power was proportionally more strongly increased in older adults, resulting in a pattern that was characterized by an increase in slow SP power at the end of the SO up-state.

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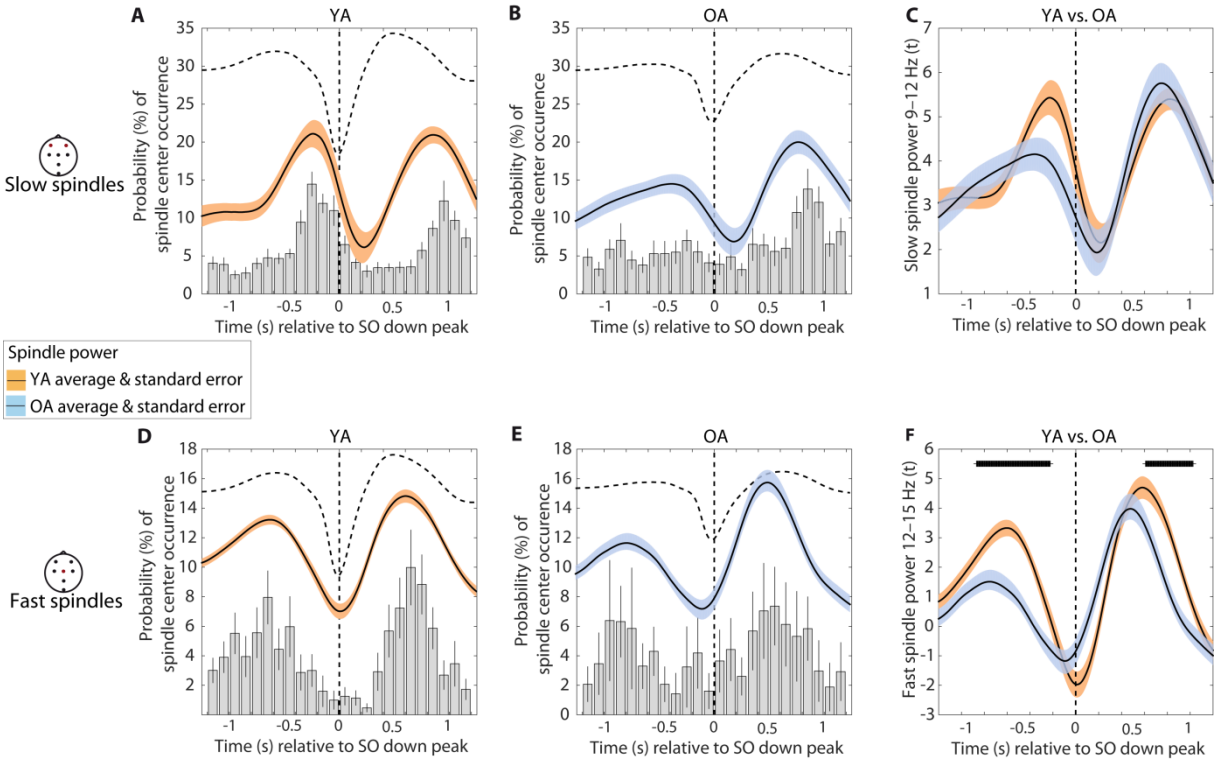

Figure 4. The occurrence of fast and slow SP events corresponds to the age-specific time–frequency profiles of fast and slow SP activity. Peri-event time histograms of fast and slow SPs co-occurring with frontal SOs are depicted for both age groups. Standard errors of the 100-ms bins are included as black vertical lines. Dashed lines mark the average SO of each age group as well as the SO down peak. The trajectory of slow and fast SP power (averaged *t*-values of the SO–baseline contrast within the respective frequency band at the respective electrodes) is inserted in black and its standard error is shaded in orange (younger adults) and blue (older adults). In general, slow and fast SP power corresponds to SO-modulated SP occurrence. (A) Frontal slow SPs in younger adults globally peak at the up-to down-state transition. (B) The frontal slow SP peak at the up-to down-state transition preceding the down peak observed in younger adults disappears in older adults. (C) Age comparison of slow SP power shows no significant differences (controlled for multiple comparisons using a cluster-based permutation test). (D) In younger adults, fast SPs prominently peak during and following the SO up peak. (E) In older adults, fast SPs are similarly modulated during the SO up-state as observed in younger adults but their occurrence is maximized before the SO has peaked. (F) Fast SP power in older adults is reduced during the SO up-state and peaks earlier (significant clusters marked in black). YA: younger adults; OA: older adults; SO: slow oscillation; SP: spindle.

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Reduced memory retention is associated with dispersed SO–SP coordination in younger adults

After establishing age-related changes in SO–SP coordination during the SO up-state, we asked how these alterations relate to the ability to retain memories across sleep. As central fast SP activity tied to the SO up-state is critically involved in memory consolidation (eg., Cairney et al., in press; Mölle et al., 2009), we focused our analyses on electrode Cz, where we observed a lack of SO–fast SP coupling in older adults (Figures 3B and 3D; for frontal channels and Pz, see Supplementary Figure 5). We focused on time–frequency patterns strongly modulated during the SO up-state (9–17 Hz, 0.2–1.2 s). To quantify memory retention, we measured each participant's ability to recall scene–word associations that had been successfully encoded the day before. We calculated the percentage of correctly recalled items during delayed recall relative to all items that were correctly retrieved during immediate recall before sleep. Whereas younger and older adults did not differ with regard to their learning performance on Day 1 ($t(59) = 1.62$, $p = .11$; $M_{YA} = 53.83$ %, $SD_{YA} = 20.80$ %; $M_{OA} = 45.80$ %, $SD_{OA} = 19.02$ %), memory consolidation was significantly reduced in older adults. Younger adults were almost perfect at retaining previously learned information on Day 2 ($M_{YA} = 90.58$ %, $SD_{YA} = 7.64$ %). Older adults, however, showed significantly worse memory retention across sleep ($M_{OA} = 71.15$ %, $SD_{OA} = 13.74$ %, $t(56) = 6.52$, $p < .001$; Figure 5 A).

Correlational analyses between time–frequency patterns and memory retention were conducted separately within each age group to prevent a bias of correlational estimates caused by strong age effects in both independent variables. While in the older sample there was no significant association of memory retention with EEG activity when controlling for multiple comparisons (cluster $p = .154$, Supplementary Figure 4B), we found a significant negative correlation cluster in younger adults (cluster $p = .019$, mean $r = -.52$, Figure 5B). Younger adults with an early peak in fast SP power (300 to 450 ms) and higher power in lower frequencies (9–12 Hz) at the end of the SO up-state showed worse overnight retention of memories. Critically, we did not find the expected positive relation between greater fast SP activity during the SO up peak and better memory retention. Instead, we observed that younger adults who did *not* display an 'age-typical' coupling pattern tended to be worse at retaining previously learned information overnight. More precisely, as

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illustrated in Figure 5C and 5D, we found that the negatively associated power increases in younger adults overlapped with the typical SO-related activity pattern of older adults. As a control, we ran the same analysis for a second time window (–500 to 200 ms) during the SO up- to down-state transition that reflects SO-modulated slow SP activity. Here, no significant associations with memory retention were observed after controlling for multiple comparisons (cluster p = .281) (Supplementary Figure 5).

To further illustrate the detected relation between SO–SP coupling and memory retention, we split our whole sample based on the ability to retain previously learned information (Figure 5A). The resulting four subgroups corresponding to the performance quartiles graded SO–SP coupling in a meaningful way (see Supplementary Figure 6 for the time–frequency patterns of the 4 subgroups). To check whether this gradient was also existent within each age group, we determined at which time points and at which frequencies EEG power was most modulated during the SO up-state for all behavioral subgroups within each age group (Methods). Given the low number of participants remaining within each of the subgroups – precluding meaningful statistical analyses – the following comparisons necessarily remain on a descriptive level. As displayed in the subplots of Figure 5C and 4D, we observed the same dissociation in both younger and older adults. Higher performing adults within both age groups showed a peak in fast SP frequencies during the respective SO up peak (SO up peak for younger adults at 484 ms, for older adults at 617 ms), that is, they exhibited a precise 'youth-like' SO–SP coupling (cf. Figure 3A). Lower performing adults within both age groups displayed maximal power values in lower frequencies at the end of the SO up-state, that is, they became more similar to the dispersed coupling pattern observed overall in older adults (cf. Figure 3B).

To conclude, we found evidence for an association between the precise coordination of SOs and SPs and memory retention. Our results suggest that inter-individual differences in SO–SP coupling as maximized *between* age groups also drive differences in memory retention *within* age groups. Dispersed SO–SP coupling, which was characteristic of older adults, already predicted worse memory retention at young ages. In contrast, 'youth-like' neuronal activity, i.e., high levels of fast SP power during the SO up peak, tended to coincide with better overnight retention of previously learned information.

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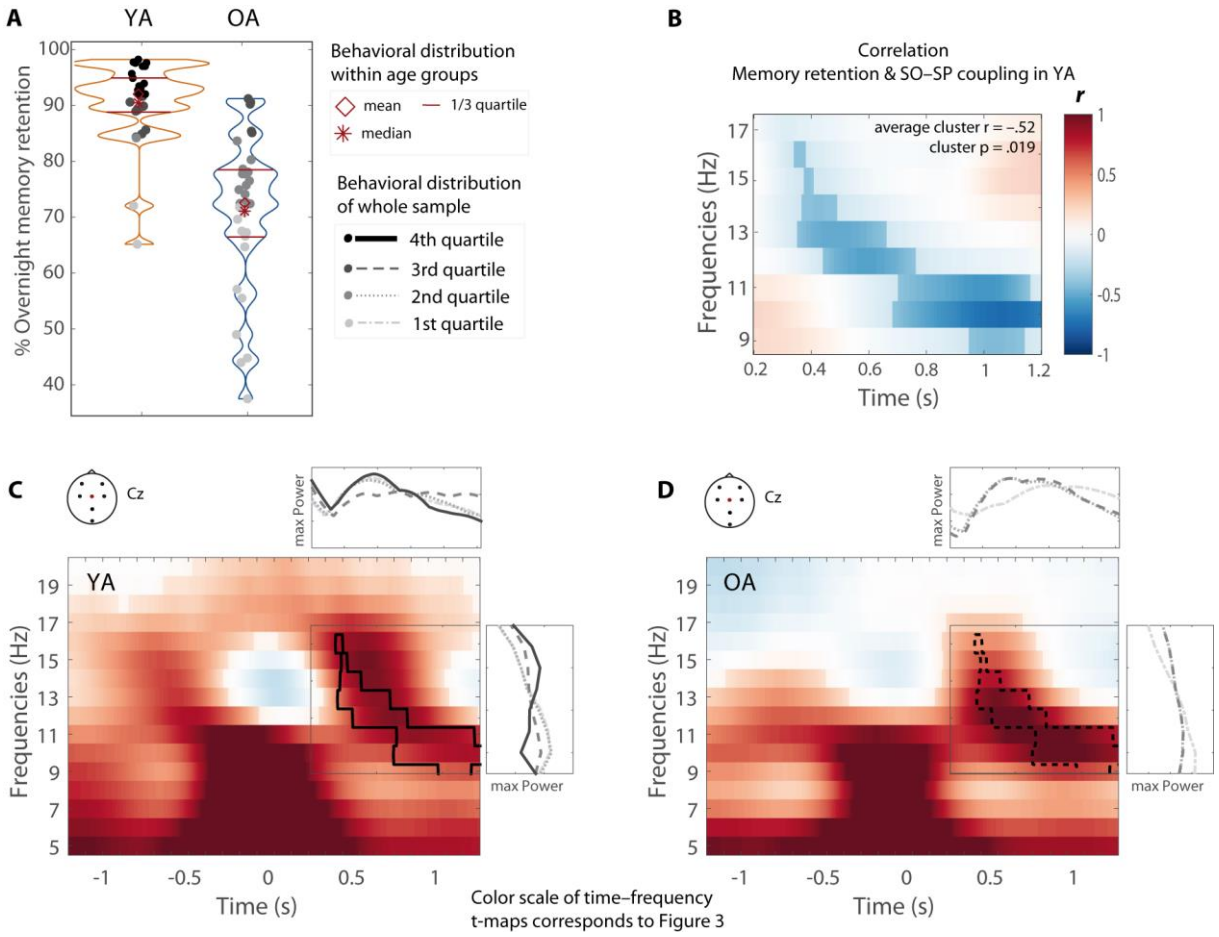

Figure 5. Dispersed SO–SP coordination predicts worse memory retention. (A) Each participant's ability to retain memories overnight is displayed (gray dots). The behavioral distribution within (red symbols) and across age groups (gray color shades) is depicted. Whereas younger adults almost completely retain previously learned information overnight, older adults' memory retention is reduced. (B) Pearson's correlation coefficients between memory retention and neuronal activity during SO up-states are displayed. In younger adults, a significant negative correlation cluster (highlighted) was detected (controlled for multiple comparisons using a cluster-based permutation test, cluster p = .019, mean r = –.52). More positive values in this cluster are associated with worse memory retention. (C) Younger adults' modulation of central SP activity during the SO up-state is shown (cf. Figure 3). The significant negative correlation cluster is outlined in black. (D) The significant cluster found in younger adults corresponds to the power increases observed in older adults (cluster outlined with dashed black line). For further illustration of this association, participants are grouped in quartiles (across both groups) with regard to their ability to retain memories overnight and the course of their power maxima is displayed within each age group (from 1st quartile – low performance – to 4th quartile – high performance, line subplots to C and D). In both age groups, more fast SP activity during the SO up peak is observed with increasing memory retention. YA: younger adults; OA: older adults; SO: slow oscillation; SP: spindle.

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Structural brain integrity in old age promotes 'youth-like' SO–SP coupling

In line with previous reports on the influence of age-related brain atrophy on the generation of sleep oscillations (eg., Mander et al., 2013; Varga et al., 2016), we finally asked whether the identified beneficial modulation of SP activity during the SO up-state is associated with measures of brain volume in specific regions of interest (ROI). As ROIs we included brain regions that are considered source regions for the generation of SOs and SPs (Nir et al., 2011; Steriade, 2006) and to be involved in memory processing during sleep (Gais & Born, 2004). We also included an occipital control region (Figure 6A). Again, we focused our analysis on frequencies between 9 and 17 Hz and a time window between 0.2 and 1.2 s after the SO down peak. Whereas the cluster-based permutation test did not indicate any significant association between brain volume and EEG power in younger adults (all clusters: $p \geq .082$; Supplementary Figure 7), we observed a very specific pattern in older adults. Larger medial prefrontal cortex (mPFC) and thalamus volume was associated with higher power in the fast SP range during the SO up peak (mean $r_{mPFC} = .42$, cluster $p_{mPFC} = .022$; mean $r_{thalamus} = .44$, cluster $p_{thalamus} = .02$) (see Figure 6). For hippocampus and entorhinal cortex even broader effects were observed. Greater volume in these regions was not only associated with higher fast SP power during the SO up peak, but in general with a more global neuronal activation during the SO up-state (mean $r_{hippocampus} = .45$, cluster $p_{hippocampus} = .002$; mean $r_{entorhinal\ cortex} = .46$, cluster $p_{entorhinal\ cortex} = .002$). As expected, no effect was detected when looking at medial occipital lobe volume (all clusters: $p \geq .201$). In other words, older adults with less age-related decline in mPFC and thalamus volume showed a more precise coupling between fast SPs and SOs time-locked to the SO up peak – precisely the pattern observed in younger adults. Less age-related decline in medial temporal lobe areas was moreover associated with overall enhanced neuronal activity during the SO up-state. We thus conclude that structural brain integrity in old age promotes 'youth-like' SO–SP coupling.

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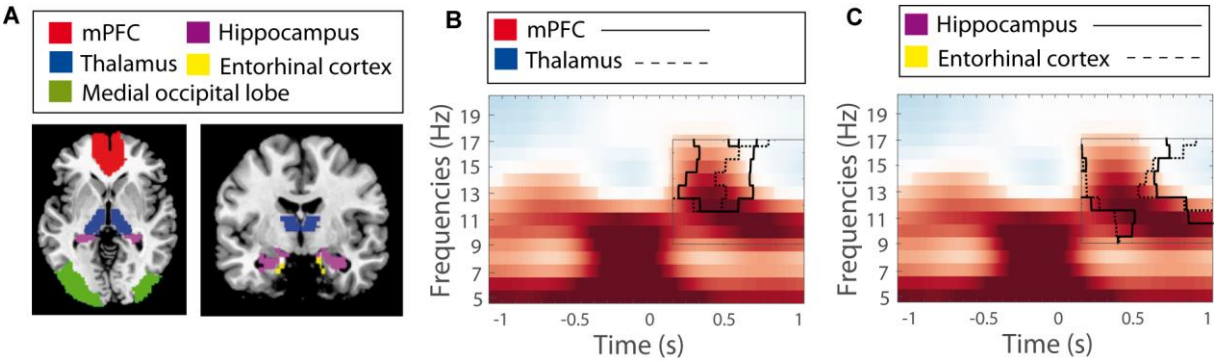

Figure 6. Structural brain integrity in old age promotes 'youth-like' SO–SP coupling. (A) VBM measures are extracted from ROIs to get individual values of brain volume (ROI masks overlaid in color). (B) In older adults, greater volume in the mPFC and the thalamus is associated with increased fast SP activity at the up peak of the SO. Significant positive correlation clusters (controlled for multiple comparison using a cluster-based permutation test, cluster α = 0.05) are outlined in solid (mPFC) and dashed black lines (thalamus). Underlying time–frequency profiles are only plotted for illustration. (C) Greater volume in the hippocampus (black solid line) and entorhinal cortex (black dashed line) is positively correlated with more global increases in EEG activity during the SO up-state. mPFC: medial prefrontal Cortex; VBM: voxel-based morphometry; ROI: region of interest; SO: slow oscillation; SP: spindle.

Discussion

This study investigated whether the coupling of SOs and SPs during sleep changes across the adult lifespan and how these alterations relate to the ability to retain associative memories across sleep. We demonstrate that older adults do not display the central fast SP power increase time-locked to the SO up peak that we observe in younger adults. Instead they exhibit an earlier but overall reduced fast SP peak and a shift to lower frequencies at the end of the SO up-state. We find evidence that this 'aged' coupling pattern coincides with worse memory consolidation, whereas a 'youth-like' precision of SO–SP coupling promotes memory consolidation across the entire adult lifespan. Moreover, greater structural integrity in brain regions involved in the generation of SOs and SPs relates to an intact 'youth-like' SO–SP coupling in old age. Overall, our results resonate well with a recent report on age-related differences in SO–SP phase–amplitude couplings (Helfrich et al., 2018). Together with Helfrich and co-authors, we are the first to demonstrate that an age-related dispersion of SO–SP coupling, as caused by structural brain atrophy, relates to impaired memory consolidation in old age.

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Age-related dispersion of SO–SP coupling

Effective communication during NREM sleep is governed by SOs that, during their up-states, initiate the generation of thalamic fast SPs (Steriade, 2006). This succession of neuronal events is mostly studied in healthy younger individuals (but see Helfrich et al., 2018; Ladenbauer et al., 2017; Piantoni et al., 2013). Here, we found that a generally constant pattern of SP–SO co-occurrence exists across adulthood (Figure 2). However, one should note that only a small percentage of SOs was accompanied by SPs in this study (Figure 2B). Moreover, merely one third of fast SPs co-occurred with SOs. This implies that: (1) Although it appears that thalamic SP generation are triggered by frontal SOs (Gennaro & Ferrara, 2003; Steriade, 2006), at least one other mechanism initiating SPs exists. (2) SO-induced SP initiation is not a necessity, but rather a rare occurrence. Nevertheless, if SOs and SPs co-occur, they do so in a precisely timed manner, as discussed next.

Consistent with a wide range of studies, we identified a precisely timed hierarchical structure of SOs and SPs in younger adults with fast SPs appearing during the highly depolarized SO up peak and slow SPs occurring at the up-to down-state transition (Klinzing et al., 2016; Mölle et al., 2011, 2002; Staresina et al., 2015). It is well established that, concurrent with decreased slow-wave sleep, the occurrence of SOs and SPs is dramatically reduced with advanced age (see Mander et al., 2017 for a review). Accordingly, we found fewer SOs, slow and fast SPs in older adults. SOs themselves change their appearance in old age and exhibit reduced amplitudes and slower frequencies in older adults (Figure 3C; cf. Carrier et al., 2011; Dubé et al., 2015). Flatter SOs have previously been associated with less synchronous neuronal switches between phases of depolarization and hyperpolarization (Fogel et al., 2012). As these phases precisely time the generation of SP events themselves, SO–SP coordination should, as a consequence, disperse in old age.

Indeed, in older adults EEG activity during SOs was differentially modulated than in younger adults. (1) Consistent with previously reported reductions in central fast SPs in old age (Crowley et al., 2002; Martin et al., 2013), fast SP increases during the SO up-state proved less pronounced in older adults. (2) If fast SPs appeared, they were no longer precisely tied to the SO up peak as observed in younger adults. Rather, they occurred before the up-state reached its maximum. (3)

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Over central sites modulation of EEG activity during the SO up-state dispersed, the power peak was stretched in time and shifted to lower frequencies (9–12 Hz). This 'aged' SO–SP coupling corresponds to the pattern recently described for healthy (Helfrich et al., 2018) and mildly cognitively impaired older adults (Ladenbauer et al., 2017). All things considered, we argue that even in older adults a very specific pattern of SO–SP coupling exists, although its appearance changes compared to younger adults, with more emphasis on lower frequencies occurring later during the SO up-state. Possible causes and mechanisms of this 'aged' pattern will be discussed next.

Structural correlates of SO–SP coupling

The process of SO–SP coupling involves intact communication between different brain regions (Steriade, 2006). SOs, generated mainly in prefrontal areas, propagate throughout the brain (Nir et al., 2011) and potentially trigger the initiation of fast SPs in the thalamus (Steriade, 2006). Here, we indicate that in old age structural integrity in the mPFC accounts for a 'youth-like' SO–SP coupling (Figure 6). This is in line with Helfrich and colleagues (2018) who recently proved that greater mPFC volume relates to a more precise coupling of fast SPs to the SO up peak. Expanding that observation, we demonstrate that additional brain regions are associated with inter-individual differences in SO–SP coupling. Greater thalamus volume, the main source region of fast SP generation (Steriade et al., 1987), related to more fast SP activity during the SO up peak. The precise pattern both in the time and in the frequency domain strongly suggest that structural integrity in both mPFC and thalamus is crucial for pacing a 'youth-like' SO–SP succession. In contrast, hippocampus and entorhinal cortex were linked to more diffuse neuronal activation during the SO up-state.

In our analysis, all associations between SO–SP coupling and VBM measures only held within the older sample. Importantly, this does *not* imply that the brain areas mentioned above do not contribute to an effective hierarchical nesting of neuronal oscillations during sleep in younger adults. We rather suggest that brain integrity in mPFC, thalamus and medial temporal lobe areas forms the basis for an effective 'youth-like' SO–SP coupling independent of age. Under conditions of impaired structural integrity in these regions, as the case in aging (Raz et al., 2005), the precise timing of SOs

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and SPs vanishes. This reasoning is in line with Nyberg and colleagues (2012) who argue that the individuals who experience fewer age-related structural brain changes are more likely to show neural activity patterns that resemble those of younger adults and are associated with better performance. The functional implications of an 'aged' SO–SP coupling will be discussed next.

Functional significance of precise SO–SP coupling

Current theory holds that hippocampo-neocortical communication during sleep is only enabled by the precise hierarchical coordination of SOs, SPs, and hippocampal sharp-wave ripples (Buzsáki, 1998; Logothetis et al., 2013). This is achieved by locking fast SPs to the SO up peak and further nesting sharp-wave ripples within the troughs of fast SPs (Staresina et al., 2015). Thus, memories initially dependent on a temporary store in the hippocampus become more reliant on neocortical areas, where they are permanently stored (Born & Wilhelm, 2012; Kitamura et al., 2017; Marshall & Born, 2007).

Here, we show that 'aged' SO–SP coupling was associated with worse memory retention (Figure 5). Vice versa, independent of the participants' age, higher fast SP activity during the SO up peak, i.e., a precise 'youth-like' SO–SP coupling, tended to coincide with better memory retention (Figure 5, Supplementary Figure 6). Our results support previous evidence showing that the precisely timed interaction of neural rhythms indeed supports sleep-dependent memory consolidation (Cairney et al., in press; Helfrich et al., 2018; Ladenbauer et al., 2017; Latchoumane et al., 2017; Maingret et al., 2016; Niknazar et al., 2015). Brain activity is globally synchronized during the SO up-state and maximized during the SO up peak (Amzica & Steriade, 1998). This constitutes a moment of effective interregional brain communication. Fast SPs occurring at this very moment induce a massive influx of Ca^{2+} into excited neurons. This enables synaptic plasticity and promotes the stabilization and integration of memory representations (Bergmann & Born, 2018). As most recently demonstrated, fast SPs are misaligned in older adults, resulting in worse memory retention (Helfrich et al., 2018). But what is it that makes the 'aged' SO–SP coupling detrimental?

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First, the temporal dispersion of 'aged' SO–SP coordination in older adults is striking. In older adults, the fast SP power increase during the SO up-state reaches its maximum *before* the SO up peak (Figures 3 and 4). This may be explained in two ways: (1) During flatter SOs, as observed in older adults, the switch between up- and down-states is more variable (Fogel et al., 2012) and as a result SP initiation is also less precise. (2) The mechanism initiating SPs might be similarly timed in younger and older adults, but as SOs are slower in older adults, fast SPs appear too early during the SO up-state. Here, global brain synchrony has not reached its maximum yet and interregional brain communication might not be optimal for reorganization of memories on a brain system level. Indeed, in both younger and older adults with high memory retention, fast SP activity *during* the SO up peak was enhanced whereas high values of fast SP activity *before* the SO up peak were associated with worse memory retention (Figure 5). Importantly, this implies that the beneficial effects of a precise SO–SP coupling are not specific to younger adults, but rather constitute a general mechanism that can be observed across the entire adult lifespan.

The second characteristic of 'aged' SO–SP coupling is a power shift to lower frequencies in the slow SP band at the end of the SO up-state (Figure 3). At young age already, this shift related to worse memory retention (Figure 5). Recent evidence suggests that fast and slow SPs are generated via distinct mechanisms (Ayoub et al., 2013; Timofeev & Chauvette, 2013) and have different functional significances. While the occurrence of fast SPs probably reflects thalamo-cortical information processing necessary for memory transfer, slow SPs may mirror cortico-cortical communication (Doran, 2003). Slow SPs per se may not be sufficient to enable effective memory consolidation during sleep (Barakat et al., 2011; Cairney et al., in press; Mölle et al., 2011; Rasch & Born, 2013). When focusing our analysis on the up-to down-state transition, where slow SPs preferentially occur (Klinzing et al., 2016; Mölle et al., 2011), no association with memory retention was detected (Supplementary Figure 5). Rather than carrying any functional significance for memory consolidation, slow SPs may thus occur as a by-product of SOs as a consequence of network depolarization (Ayoub et al., 2013; Klinzing et al., 2016; Mölle et al., 2011).

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In our analysis, the statistical association between SO–SP coupling and memory retention was only present in younger adults. Given the high inter-individual variance in the ability to retain memories across sleep in older adults, it is indeed surprising that no stable association was present in the elderly. Importantly, memory consolidation does not only rely on intact SO–SP coupling, but on multiple factors that are prone to aging effects (Harand et al., 2012). For instance, in old age, an adverse neurochemical state during NREM sleep might generally hinder the interregional brain communication necessary for memory consolidation (Buckley & Schatzberg, 2005). Further, structural brain atrophy, as described above, might not only impede the hippocampo-neocortical dialogue enabled by SO–SP coordination, but could also impact hippocampal memory reactivation in the first place (Gerrard, Burke, McNaughton, & Barnes, 2008). Age differences in the oscillatory dynamics in older adults during sleep may thus be insufficient to fully explain the complex age-related deficits in memory retention. Indeed, as recently demonstrated, enhancement of fast SPs coupled to the SP up peak in elderly people has only small, though significant impacts on memory consolidation itself (Ladenbauer et al., 2017). In line with this, we show that memory retention differs as a function of SO–SP dispersion in old age, but that the functionality of SO–SP coupling is only fully revealed in younger adults, where brain structure and neuromodulation form suitable conditions for sleep-dependent memory processing.

To conclude, our results replicate the finding that a precise 'youth-like' SO-fast SP coupling is beneficial for memory consolidation (Helfrich et al., 2018; Ladenbauer et al., 2017). Vice versa,'aged' coupling coincides with worse memory consolidation already in young adulthood already. This lines up with the concept of "brain maintenance" (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012) stating that cognitive functioning is not only determined by maintained structural integrity across the adult lifespan, but also by the preservation of functionally specific processes and networks (Düzel, Schütze, Yonelinas, & Heinze, 2010; Fandakova, Lindenberger, & Shing, 2015; Nyberg et al., 2012). Maintenance of 'youth-like' processing during both encoding (Düzel et al., 2010) and memory retrieval (Fandakova et al., 2015) has previously shown to relate to better long-term memory in older

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adults. Here we complement this view by demonstrating that consolidation processes also benefit from maintained brain mechanisms during sleep.

Methods

Participants and procedure

Participants

Thirty-four healthy younger adults (19–28 years) and 41 healthy older adults (63–74 years) participated in the experiment. Due to technical failures, data collection from 4 younger and 4 older adults could not be completed. Accordingly, the final sample for our behavioral analysis consisted of 30 younger (M_{age} = 23.7 years, SD_{age} = 2.6; 17 females) and 37 older adults (M_{age} = 68.92 years, SD_{age} = 3.04; 16 females). For some participants parts of the neural data (PSG or MRI) were missing or of bad quality. Final PSG analyses were hence conducted with 24 younger (M_{age} = 23.61 years, SD_{age} = 2.55; 13 females) and 31 older adults (M_{age} = 68.63 years, SD_{age} = 3.10; 15 females), VBM analyses with 24 younger (M_{age} = 23.61 years, SD_{age} = 2.55; 13 females) and 29 older adults (M_{age} = 68.64 years, SD_{age} = 3.10; 14 females). The different samples did not differ with regard to any behavioral measure.

All participants were right-handed native German speakers with no reported history of psychiatric or neurological disease, or any use of psychoactive medication. To screen for cognitive impairments in the sample of the elderly, all older adults completed the Mini-Mental State Examination (MMSE; *M* = 29.24, *SD* = 1.12, *Range*: 26–30; Folstein, Folstein, & McHugh, 1975) and passed a brief memory screening beforehand. General subjective sleep quality was controlled by assessing the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989) and did not show differences between the two age groups. The study was approved by the Ethics Committee of the *Deutsche Gesellschaft für Psychologie* (DGPs) and conducted at the *Max Planck Institute for Human Development* in Berlin. After being informed about the complete study procedure, all participants gave written consent to their participation in the experiment.

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Experimental Procedures

The present data were derived from a series of studies investigating age-related differences in the encoding, consolidation, and retrieval of associative memories (see Fandakova et al., in press, for the effects of age and memory quality on false memory retrieval). Core of the experimental design was an associative scene–word pair memory paradigm, consisting of a learning session on the first day (Day 1) as well as a delayed cued-recall task approximately 24 hours later (Day 2) (see Figure 1, for illustration of the study procedure). During the nights before and after learning (experimental nights PRE and POST) sleep was monitored at participants' home using ambulatory PSG. Prior to the first experimental night an adaptation night familiarized the participants with the PSG procedure. Structural MRI data were collected on Day 2. Furthermore, EEG was recorded during learning on Day 1. Additionally, functional MRI data were collected during delayed recall on Day 2. Neither the EEG nor the fMRI data are included in the present report.

Day 1 – Encoding and immediate cued-recall

During initial study, scene–word pairs were presented on a black background for 4000 ms. Scene–word pairs were randomized combinations of indoor and outdoor scenes and concrete nouns. Participants were instructed to remember the scene–word pair using a previously trained imagery strategy and to indicate how well they were able to form an integrated image of the scene–word pair. Cued-recall blocks followed immediately after the initial learning phase. Scenes served as cues for participants to verbally recall the associated word. Recall time was not constrained. Independent of recall accuracy, the correct scene–word pair was presented again for 3 seconds and participants were instructed to use this opportunity to remember the word–scene pair by forming an integrated image of the two. Finally, participants completed a final cued-recall test without feedback at the end of Day 1. This phase served as a measure of learning performance. Importantly, task difficulty was adjusted between the age groups to achieve comparable recall success of approximately 50 % in each age group. This was done in two ways. First, younger adults learned 440 pairs, whereas older

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adults learned 280 pairs on Day 1. Second, younger adults completed one cued-recall block with feedback, whereas older adults completed two cued-recall blocks with feedback. Further details about the encoding task and the stimulus set are described by Fandakova et al. (in press).

Day 2 – Delayed cued-recall

Delayed cued-recall of the scene–word pairs consisted of four blocks of 70 experimental trials each and was conducted inside a 3T MRI scanner. For the older age group, all of the 280 studied pairs were presented. For younger adults items were chosen with regard to their learning history. This resulted in a selection of pairs, half of which had been recalled in the criterion cued-recall the day before. The 280 pictures were displayed for 3500 ms. Meanwhile participants had to decide via keypress if they still remembered the corresponding word ("remembered" vs. "forgotten"). Afterwards, four letters were presented for 3500 ms. One of these was the second letter of the correct word and had to be selected by pressing the corresponding key. If the according word had been forgotten or none of the letters fitted their remembered answer word, participants were told to choose one of the letters at random.

Sleep EEG data acquisition and analyses

Data acquisition

During the two experimental nights before (PRE) and after learning (POST), sleep was recorded using an ambulatory PSG device (SOMNOscreen plus; SOMNOmedics, Germany). Eight scalp electrodes were attached according to the international 10–20 system for electrode positioning (Fz, F3, F4, C3, C4, Cz, Pz, Oz) along with two electrodes on the mastoids A1 and A2 that later served as the offline reference. All impedances were kept below 6 kΩ. Data were recorded using Cz as the online reference for all EEG derivations and AFz as ground. Additionally, a bilateral electrooculogram (EOG) was assessed. Two submental electromyogram channels (EMG) were positioned left and right inferior of the labial angle and referenced against one chin electrode. Electrical activity of the heart was recorded using two electrocardiogram channels (ECG). All electrodes were attached to a small

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recorder fixed with two straps either to the front or back of the torso depending on the participant's sleep habits. EEG channels were recorded between 0.2–75 Hz with a sampling rate of 128 Hz.

EEG pre-processing

Data was preprocessed using *BrainVision Analyzer 2.1* (Brain Products, Germany). Here, all EEG channels were re-referenced against the average of A1 and A2. Afterwards, sleep stages 1 and 2, slow-wave sleep, REM sleep, awakenings, and body movements were visually scored in 30-second epochs according to the standard criteria suggested by the American Academy for Sleep Medicine (AASM; Iber et al., 2007). Participants provided markers for switching the light off and on again, narrowing the time period to be analyzed. Visual determination of sleep onset and offset took place when participants did not remember to set the markers (n = 5). Global sleep parameters were estimated based on the visually scored sleep data (Table 2).

Table 2

Estimation of Sleep Variables

Variable Name	Variable Definition
TST (min)	Time spent in stage 1, 2, SWS, and REM in minutes
WASO (min)	Time awake between sleep onset and final morning awakening in minutes
Stage 1 (%)	Time spent in stage 1 / TST
Stage 2 (%)	Time spent in stage 2 / TST
SWS (%)	Time spent in SWS / TST
REM (%)	Time spent in REM sleep / TST

Note. TST: total sleep time; SWS: slow-wave sleep; REM: rapid eye movement sleep; WASO: wake after sleep onset; NREM: non-rapid eye movement sleep.

Further analyses of the sleep EEG data were conducted using *Matlab* R2014b (Mathworks Inc., Sherbom, MA) and the open-source toolbox *Fieldtrip* (Oostenveld, Fries, Maris, & Schoffelen, 2011). Bad EEG channels were visually rejected. For the remaining channels, artefact detection was

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implemented on segments of 1 second, marking segments that were visually scored as body movement or exhibited power differences of more than 500 µV. To further exclude segments that strongly deviated from the observed overall power distribution, mean power differences for each segment were *z*-standardized within each channel. Segments with a *z*-score of more than 5 in any of the channels were excluded.

Spindle detection

SPs were detected using the established algorithm by Ferrarelli et al. (2007) in conjunction with recommended adaptations by Warby et al. (2014). For all NREM epochs (i.e., stage 1, stage 2, and slow-wave sleep), EEG data were band-pass filtered using a 6th-order Butterworth filter (in forward and backward direction to prevent phase distortions) between 9 and 12 Hz for the detection of slow SPs, respectively 12 and 15 Hz for fast SPs. A Hilbert-transform was applied to the band-pass filtered signal to estimate the instantaneous amplitude time series. To increase sensitivity and specificity of our algorithm (Coppieters ’t Wallant, Maquet, & Phillips, 2016), we accounted for individual differences in EEG amplitude by anchoring the SP identification on individually determined amplitude thresholds. The lower/upper threshold was set to two/six times the average amplitude of the total Hilbert-transformed time series (cf. Warby et al., 2014). Whenever the signal amplitude exceeded the upper threshold, a potential SP was tagged. Start and end of the respective putative SP were determined as the preceding and following time points at which the amplitude dropped below the lower threshold. Only events with durations between 0.5 and 2 seconds were considered SPs. SPs with boundaries closer than 0.25 seconds were eventually merged in the following way: in each processing run, starting with the smallest boundary difference, two SPs were merged if the resulting SP event remained within the time limit of 2 seconds. As soon as a SP was combined with another one, it could not be merged with another SP in the very same run anymore. Only if all boundary differences were revised and no further merging of putative SPs was possible, the new resulting SP events were processed in a next run. Starting again with the smallest boundary difference, two putative SPs could be merged if the merged event remained within the required time limit. These

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runs were repeated until no further merging was possible. Finally, only SPs not overlapping with previously marked artefact segments were considered SPs.

Slow oscillation detection

Detection of SOs at frontal electrodes was based on Mölle et al. (2002) and Ngo et al. (2013). For all NREM epochs, EEG data was band-pass filtered between 0.2 and 4 Hz using a 6th-order Butterworth filter (in forward and backward direction). The whole signal was then divided into negative and positive half-waves that were separated by zero-crossings of the filtered signal. The combination of a negative half wave with the succeeding positive half wave was considered a putative SO when its frequency was between 0.5 and 1 Hz. The amplitude of each potential slow wave was calculated as the distance between the down peak and up peak, defined as its maximal negative respectively positive potential. As in the SP detection, individualized amplitude thresholds were defined for SO detection: Putative SOs exceeding a down peak of 1.25 times the mean down-peak potential of all putative SOs as well as amplitudes of 1.25 times the average amplitude of all potential SOs, were marked. Only artefact-free SOs were considered in further analyses.

Statistical analysis

Not all sleep variables used in our analysis followed a normal distribution. To identify age differences in the sleep architecture and the expressed sleep oscillations between younger and older adults, non-parametric Mann-Whitney U Tests for independent samples were calculated and median and quartile values of the variables were reported.

To describe the temporal association between SPs and SO, we selected 6-second long artefact-free trials from the EEG data, centered ±3 s around the down peak of the SOs. The longer time segments were selected to prevent filter artefacts during later analysis steps (e.g., due to wavelet filtering). All analyses described in the following were first conducted separately for SOs detected at the two frontal derivations F3 and F4, and then averaged. Time–frequency analyses were performed at frontal electrodes as well as at electrodes Cz and Pz. For baseline contrasts we

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randomly selected 6-second trials without SOs. To obtain time–frequency representations of trials with and without SOs, we applied a Morlet-wavelet transformation (12 cycles) to the unfiltered EEG data of SO and baseline trials between 5 Hz and 20 Hz in steps of 1 Hz and 2 ms. First, we contrasted trials with and without SOs for each subject with independent-sample *t*-tests. The resulting *t*-maps reflect the increase/decrease in both the fast and slow SP frequency range for trials with SOs, compared to trials without. Next, *t*-maps were averaged across F3 and F4 SOs for each participant before subjecting the results to group-level analyses. Separately for each age group, *t*-maps were tested against zero using a cluster-based permutation test with 5000 permutations in a time window of –1.2 to 1.2 s (Maris & Oostenveld, 2007). The time window was chosen to cover one whole SO cycle (0.5–1 Hz, i.e., 1–2 s).

Age differences in SO-modulated EEG activity were quantified in two ways: (1) The time–frequency *t*-maps (SO vs. baseline trials) of both age groups were compared using a cluster-based permutation test with 5000 permutations. (2) We compared at which time points and in which frequencies EEG power was most modulated during the SO up-state. As power was most regulated between 9 and 17 Hz from 0.2 to 1.2 s after the SO down peak (see Figure 3A and 3B) we focused our computations on this time–frequency window. Within it, we determined the maximal power value for each frequency across the whole time interval, respectively for each time point across all frequencies. We then normalized these values within the whole power course to add up to 100 %. The resulting power distributions were then compared using a cluster-based permutation test with 5000 permutations.

To verify that the detected time–frequency pattern really reflected alterations in the occurrence of SP events themselves, we compared the trajectories of SP power within the respective frequency bands with peri-event time histograms (PETHs) of SOs co-occurring with fast and slow SPs. SP power was quantified as averaged *t*-values of the SO-baseline contrast within the respective frequency band (slow SPs: 9–12 Hz; fast SPs: 12–15 Hz) at each time point during the SO (± 1.2 s around the down peak). For the same time interval around the down peak (target event) of the respective SO we identified the occurrence of slow and fast SP centers (seed events). Probabilities of

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seed event occurrence were summed within bins of 100 ms and normalized to add up to 100 %. Following the same pipeline, PETHs were also calculated for intervals of ±5 s to demonstrate the general specificity of SP appearance to the actual presence of SOs (Supplementarys Figure 2 and 3).

As we aimed to identify the functional significance of the detected SO–SP association, we then correlated each participant's individual time–frequency *t*-maps for the comparison with/without SOs with the participant's ability to retain previously learned information overnight. For each time–frequency point a Pearson's correlation with the behavioral outcome variable was computed. Control for multiple comparisons was achieved using a cluster-based permutation approach with 5000 bootstrap samples to create the reference distribution.

MRI data acquisition and structural MRI analyses

Whole-brain MRI data was acquired with a Siemens Magnetom 3T TimTrio machine. For each participant a high-resolution T1-weighted MPRAGE sequence (TR = 2500 ms, TE = 4.77 ms, FOV = 256 mm, voxel size = 1 × 1 × 1 mm^3) was collected. To get estimates of brain volume in regions of interest (ROI) we conducted voxel-based morphometry (VBM) using statistical parametric mapping software (SPM12, http://www.fil.ion.ucl.ac.uk/spm) and the Computational Anatomy Toolbox (CAT 12, http://www.neuro.uni-jena.de/cat). Images were normalized to Montreal Neurological Institute (MNI) space and segmented into gray matter, white matter, and cerebrospinal fluid. Data were then modulated, i.e., corrected by the volume changes due to spatial normalization. For this, each voxel value was multiplied with the Jacobian determinant derived from the spatial normalization step. Afterwards images were smoothed with a 8 mm full width at half maximum (FWHM) kernel. Total intracranial volume (TIV) was estimated by summing volume of gray matter, white matter, and cerebrospinal fluid. Due to their involvement in sleep-dependent memory processes and especially in the generation of SPs and SOs (Gais & Born, 2004; Nir et al., 2011a; Steriade, 2006), we selected bilateral medial prefrontal cortex (mPFC), thalamus, entorhinal cortex, hippocampus, and, as a control region, the medial occipital lobe (Figure 7A). The mPFC mask was kindly provided by Bryce A. Mander (cf. Mander et al., 2013). All other ROIs were defined using the WFU PickAtlas toolbox

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(http://fmri.wfubmc.edu/software/pickatlas). Measures of gray matter volume in all ROIs were extracted using the REX toolbox (http://web.mit.edu/swg/rex/rex.pdf) and adjusted for differences in TIV based on the formula provided by Raz et al. (2005) (adjusted volume = raw volume – b x (TIV – mean TIV), where b is the slope of the regression of ROI volume on TIV). Similar to the method described above, we finally conducted a cluster-based permutation test with 5000 bootstrap samples, relating each participant's individual time–frequency *t*-map to gray matter volumes in the different ROIs.

Code availability

The custom code used for these analyses is available upon reasonable request from the corresponding authors.

Data availability

The data that our results are based on are available upon reasonable request from the corresponding authors.

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Author Contribution

MCS, YF, THG, YLS, and MWB designed the study; BEM performed the experiments; BEM and MWB analyzed the data; BEM and MWB wrote the manuscript; BR and MCS gave conceptual advice. All authors revised the manuscript.

Competing interests

The authors declare no competing interests.

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