Received: 18 December 2019 | Revised: 17 March 2020 | Accepted: 10 April 2020

DOI: 10.1111/jsr.13062

Journal of Sleep Research | ESRS

REGULAR RESEARCH PAPER

Hippocampal and medial prefrontal cortical volume is associated with overnight declarative memory consolidation independent of specific sleep oscillations

Lukas Frase[1] | Wolfram Regen[1] | Stéphanie Kass[1] | Albena Rambach[1] | Chiara Baglioni[1] | Bernd Feige[1] | Jürgen Hennig[2] | Dieter Riemann[1] | Christoph Nissen[1,3] | Kai Spiegelhalder[1]

[1]Department of Psychiatry and Psychotherapy, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[2]Department of Radiology – Medical Physics, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[3]University Hospital of Psychiatry and Psychotherapy, Bern, Switzerland

Correspondence
Lukas Frase, Department of Psychiatry and Psychotherapy, Medical Center – University of Freiburg, Hauptstr. 5, 79104 Freiburg, Germany.
Email: Lukas.frase@uniklinik-freiburg.de

Funding information
FP7 Ideas: European Research Council, Grant/Award Number: FP7-PEOPLE-IEF-2008

Summary

The current study was designed to further clarify the influence of brain morphology, sleep oscillatory activity and age on memory consolidation. Specifically, we hypothesized, that a smaller volume of hippocampus, parahippocampal and medial prefrontal cortex negatively impacts declarative, but not procedural, memory consolidation. Explorative analyses were conducted to demonstrate whether a decrease in slow-wave activity negatively impacts declarative memory consolidation, and whether these factors mediate age effects on memory consolidation. Thirty-eight healthy participants underwent an acquisition session in the evening and a retrieval session in the morning after night-time sleep with polysomnographic monitoring. Declarative memory was assessed with the paired-associate word list task, while procedural memory was tested using the mirror-tracing task. All participants underwent high-resolution magnetic resonance imaging. Participants with smaller hippocampal, parahippocampal and medial prefrontal cortex volumes displayed a reduced overnight declarative, but not procedural memory consolidation. Mediation analyses showed significant age effects on overnight declarative memory consolidation, but no significant mediation effects of brain morphology on this association. Further mediation analyses showed that the effects of age and brain morphology on overnight declarative memory consolidation were not mediated by polysomnographic variables or sleep electroencephalogram spectral power variables. Thus, the results suggest that the association between age, specific brain area volume and overnight memory consolidation is highly relevant, but does not necessarily depend on slow-wave sleep as previously conceptualized.

KEYWORDS

ageing, hippocampus, learning, mirror-tracing, slow oscillations, word pairs

Christoph Nissen and Kai Spiegelhalder contributed equally to this study.

1 | INTRODUCTION

Traditionally, learning and memory are conceptualized to comprise three distinct phases. During *encoding*, new memory traces are generated, which are then strengthened and stabilized during *consolidation*. Stored memory information is retrieved during *recall*. This general concept is regularly applied on different types of memory systems, including declarative and procedural memory (Squire & Zola, 1996). The importance of specific sleep characteristics and brain regions for each of these phases has been partially delineated for differing memory systems, but the interplay between brain morphology, sleep oscillatory activity and memory formation remains to be further examined (Klinzing, Niethard, & Born, 2019).

Various studies in animal models and in patients with specific brain lesions have shown that structures in the medial temporal lobe are crucial for declarative memory encoding and retrieval (Davachi, Mitchell, & Wagner, 2003; Suzuki & Amaral, 2004). Specifically, input from other cortical sources is processed in the perirhinal and parahippocampal cortices (PHC; Fernandez, Klaver, Fell, Grunwald, & Elger, 2002; Ricci et al., 1999; Suzuki & Amaral, 2004). These cortices then provide the main input to the entorhinal cortex, which integrates information and relays to the hippocampus (Krause et al., 1999; Witter & Amaral, 1991). Recent studies suggest a specific but time-limited role of the hippocampus in storage and retrieval of declarative memory, and emphasize the crucial role of a hippocampal–cortical replay that gradually strengthens cortico-cortical connections allowing memories to become hippocampus-independent (Frankland & Bontempi, 2005; McClelland, McNaughton, & O'Reilly, 1995). During this *consolidation* process, and later during memory *recall*, the medial prefrontal cortex (mPFC) has been repeatedly shown to be of high relevance for remote memory (Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999; Buckner, Kelley, & Petersen, 1999; Maviel, Durkin, Menzaghi, & Bontempi, 2004; Takehara, Kawahara, & Kirino, 2003). Some authors hypothesize that the mPFC mirrors hippocampal function in recent memories for remote memories (Frankland & Bontempi, 2005). In addition, the hippocampus appears to be inhibited during recall of remote memories. It has been speculated that the source of this inhibition lies in the mPFC itself thereby preventing re-encoding of already learned memory traces (Frankland & Bontempi, 2005).

Since the beginning of the 20th century, studies have hinted at the special role of sleep for memory *consolidation* (Yang et al., 2014). The broadly accepted "active system consolidation theory" states that active neuronal replay of memory representations takes place during slow-wave sleep (SWS) and strengthens memory traces encoded during preceding wakefulness (Klinzing et al., 2019); in addition, continuous downscaling of unsustainable high synaptic strength during sleep enables efficient use of grey matter space (Ngo & Born, 2019; Tononi & Cirelli, 2006; Vyazovskiy, Walton, Peirson, & Bannerman, 2017). Hippocampal reactivation supposedly gets triggered and synchronized by sleep electroencephalogram (EEG) slow oscillations (slow waves, SW, < 1 Hz), which originate mainly in prefrontal areas (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004; Molle, Yeshenko, Marshall, Sara, & Born, 2006; Murphy et al., 2009; Sirota, Csicsvari, Buhl, & Buzsaki, 2003). In addition, SW synchronize thalamic activity, where specific fast oscillations (spindles, sigma frequency, 12–16 Hz) originate, that then feedback to cortical areas (Molle, Bergmann, Marshall, & Born, 2011). Cortical spindles are thought to enhance plasticity and facilitate integration of new memories in cortical areas (Bergmann, Molle, Diedrichs, Born, & Siebner, 2012; Holz et al., 2012; Ribeiro et al., 2007; Schabus et al., 2004).

In summary, hippocampal–cortical replay between the hippocampus and mPFC during non-rapid eye movement (NREM) sleep, mediated by SW (Molle et al., 2006) and sleep spindles (Lustenberger, Wehrle, Tushaus, Achermann, & Huber, 2015), represents a broadly accepted model of sleep-dependent declarative memory consolidation.

Besides that, the system consolidation theory has been questioned lately to an inability to integrate newer findings on memory and forgetting (Yonelinas, Ranganath, Ekstrom, & Wiltgen, 2019). For episodic memory, a "contextual binding theory" has been formulated that challenges the timeframe of hippocampal recent and neocortical remote memory. Instead, the hippocampus supposedly stores the connection between item information and context information continuously with support of the MTL. Instead of memory consolidation, the theory highlights the importance of interference for forgetting, and states absence of interference as the most relevant effect of sleep-related memory benefits (Yonelinas et al., 2019).

The importance of specific sleep stages, such as SW sleep or rapid eye movement (REM), for memory consolidation has been discussed for a long time due to conflicting evidence. A recent analysis using a large sample size failed to find significant correlations between sleep stages and overnight memory consolidation in a picture memory task (Ackermann, Hartmann, Papassotiropoulos, Quervain, & Rasch, 2015). The authors discuss their findings as hinting at a supporting role of sleep for memory without supporting common theories about the importance of specific sleep characteristics.

For ageing, a decline in the structural (Sowell et al., 2003) as well as functional (van Cauter, Leproult, & Plat, 2000) components of these consolidation models has been described, leading to the hypothesis that SW sleep disruption, mediated by mPFC atrophy, might represent a major contributing factor of age-related cognitive decline (Mander et al., 2013). In addition, a recent review on literature regarding sleep, age and memory came to the conclusion that variability in sleep parameters does not relate to cognitive functioning as described for younger subjects in older adults (Scullin & Bliwise, 2015). Contrary to Mander et al., the authors discuss SW sleep as an epiphenomenon that declines with reduced cognitive ability, without causing or mediating deficits in sleep-related memory consolidation.

The current study was designed to further clarify the interconnected but not fully understood influence of brain morphology, sleep oscillatory activity and age on memory consolidation. Specifically, the primary hypothesis was that smaller volumes of hippocampus, PHC and mPFC negatively impact declarative

memory consolidation operationalized as retention rate in the paired-associate word list task (WP). Encoding as well as early retrieval and consolidation of procedural memory were hypothesized to be independent of the targeted brain areas as they rather depend on the basal ganglia, cerebellum and supplementary motor cortex (Matthews, 2015). Explorative analyses were conducted to analyse whether a decrease in SW activity negatively impacts declarative memory consolidation, and whether hippocampus, PHC and mPFC as well as EEG spectral power mediate age effects on memory consolidation.

2 | METHODS

2.1 | Participants

Thirty-eight healthy participants were recruited through local advertisements as part of a larger study on structural and functional brain changes in insomnia and healthy controls (Baglioni et al., 2014; Reinhard et al., 2014; Spiegelhalder et al., 2013, 2014, 2016), and provided written informed consent prior to inclusion in the analysis (17 male, 21 female, age: 39.5 ± 9.1 years, range 27–57 years; body mass index 23.2 ± 3.4 kg m^{-2}). Two additional participants were excluded because of pathological magnetic resonance imaging (MRI) scans. All participants underwent a semi-standardized interview and a standardized physical examination by an experienced psychiatrist to rule out any history or prevalence of a somatic, psychiatric or sleep disorder. In addition, electrocardiogram, EEG and routine blood sampling (haematology; liver, renal and thyroid function) as well as self-report questionnaires for sleep quality (Pittsburgh Sleep Quality Index; total sum score 3.9 ± 1.9; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), depression (Beck Depression Inventory; total sum score 3.5 ± 3.3; Beck, Steer, & Brown, 1996) and excessive daytime sleepiness (Epworth Sleepiness Scale; total sum score 6.7 ± 3.9; Johns, 1991) were assessed. All participants were right-handed and free of any psychoactive medication for at least 2 weeks prior to and during the study, and refrained from alcohol, caffeine and daytime naps during the recording days. Participants with an irregular sleep–wake rhythm, for example shift workers, periodic leg movements during sleep (periodic leg movements with arousal index > 5 per hr), sleep apnea (apnea–hypopnea index > 5 per hr) or with MRI-specific exclusion criteria such as metallic implants or pregnancy were excluded.

2.2 | Study design

The study design is visualized in Figure 1. All participants underwent 2 consecutive nights of polysomnography from 23:00 hours to 07:00 hours in the sleep laboratory at the Department of Psychiatry and Psychotherapy, Medical Center – University of Freiburg. One adaptation night to rule out any sleep disorder and to prevent first-night effects was followed by one experimental night, which was used for the current analysis. An acquisition session prior to polysomnographic recorded sleep (baseline) at 21:00 hours comprising a learning and an early retrieval phase was followed by one late retrieval session in the morning after polysomnography at 09:00 hours. Declarative memory was assessed with the WP (Marshall, Molle, Hallschmid, & Born, 2004), while procedural memory was tested using the mirror-tracing task (MT; Plihal & Born, 1997). All participants underwent high-resolution MRI at the Department of Radiology – Medical Physics, Medical Center – University of Freiburg, following polysomnography with a mean interval of 30.2 ± 19.8 days. The study was conducted in accordance with the Declaration of Helsinki,

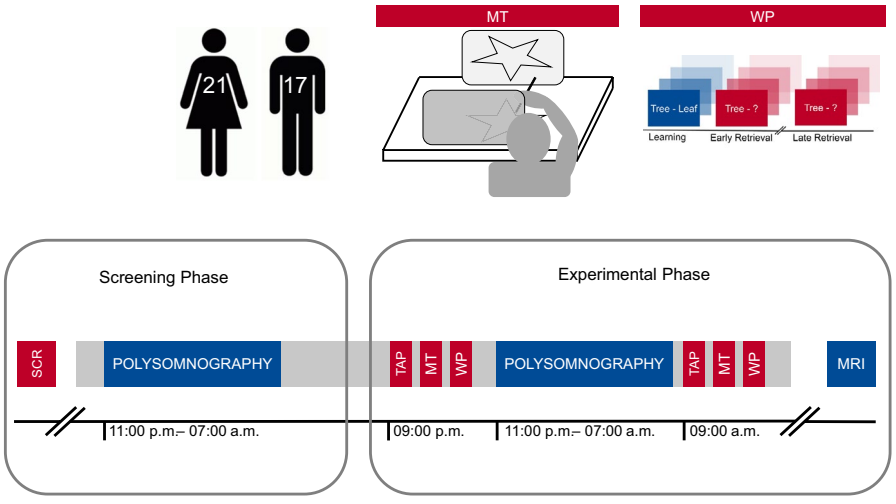

FIGURE 1 Study design. Thirty-eight healthy participants (17 male) underwent a thorough screening process including polysomnography to rule out any history or prevalence of a somatic, psychiatric or sleep disorder. An acquisition session for three tasks (attentional performance, procedural memory – mirror-tracing task [MT], declarative memory – paired-associate word list task [WP]) prior to the experimental night at 21:00 hours was followed by one retrieval session in the morning at 09:00 hours. All participants underwent high-resolution magnetic resonance imaging (MRI) on a 3-Tesla scanner following polysomnography with a mean interval of 30.2 ± 19.8 days. MT, mirror-tracing task; WP, paired-associate word list task; SCR, screening session; MRI, magnetic resonance imaging

and was approved by the Institutional Review Board of the Medical Center – University of Freiburg (No. 6/08).

2.3 | Paired-associate word list task

Forty-six semantically related word pairs (e.g. tree–leaf) were presented in a randomized order on a 15″ computer screen for 5,000 ms, followed by a 100-ms blank screen using the Presentation® software (Version 0.70, www.neurobs.com; word pair list and procedures from Marshall et al., 2004). Four additional word pairs at the beginning and end served to buffer primacy and recency effects. This set of stimuli was presented repeatedly until participants remembered at least 60% in a cued recall test. Memory encoding was assessed as the number of correctly retrieved words in the last acquisition trial. During retrieval, participants performed a cued recall test without prior presentation of the word pairs. Memory consolidation was calculated as the difference of correctly retrieved words in the morning referred to the number of correctly encoded words in the evening session.

2.4 | Mirror-tracing task

Participants were required to trace different line-drawn figures using a stylus with an electronic light sensor that measures draw time to finish the figure and number of deviations from template (errors). During the task, visual access was limited to a mirror reflection. The test set-up and figure templates were identical to those originally described (Plihal & Born, 1997). During the learning phase in the evening, a star was repeatedly used as a template until participants completed the figure with a maximum of six errors. During early and late retrieval, the same six differing templates different to the ones during learning were presented consecutively, and the mean draw time and errors were aggregated and used as the main outcome parameters. Overnight improvement of each outcome parameter was calculated as the difference between early and late mean draw time/errors of all the six templates.

2.5 | Sleep recordings

All recordings included EEG (sampling rate: 200 Hz; bandpass filter: 0.53–70 Hz), electrooculogram, submental electromyogram, electrocardiogram, abdominal and thoracic movement sensors, nasal airflow, oxymetry and bilateral tibialis anterior electromyogram, and were visually scored off-line by experienced raters according to standard criteria (Berry et al., 2017; Reinhard et al., 2014). The following sleep continuity parameters were assessed: sleep-onset latency (SOL), defined as the period between turning the lights off and the first 30 s epoch of stage 2 sleep (N2), SWS (N3) or rapid eye movement; total sleep time (TST), defined as the time spent in stage 1 or 2 sleep, SWS or REM sleep after sleep onset; amounts of stages 1 and 2, SWS and REM sleep as a percentage of sleep period time (SPT).

Sleep EEG spectral analysis was carried out to assess power spectra as described previously (Frase et al., 2016; Holz et al., 2012). The analysis was performed on the C3-A2 derivation in 30-s epochs for which sleep stages had been determined. Spectral estimates for each epoch were obtained by averaging 22 overlapping fast Fourier transform (FFT) windows (512 data points, 2.56 s) covering a 30-s epoch to obtain the spectral power within that epoch, resulting in a spectral resolution of 0.39 Hz. A Welch taper was applied to each FFT window after demeaning and detrending the data in that window. The spectral power values were then log-transformed (base e). All subsequent steps including statistical analysis were performed on these logarithmic values, which have a more symmetrical distribution of errors as compared with raw spectral power. Rejection of artefacts was conducted by an automatic, data-driven method. The total and gamma band log power of each epoch was related to the corresponding median-filtered value (the median of values in the 5 min preceding and 5 min following the epoch), and an epoch was excluded if the deviation was larger than the difference between the median and the first quartile of all median-filtered values across the night (Feige et al., 2002; Frase et al., 2019). The log spectra of the remaining epochs were averaged across all NREM sleep epochs. Spectral band power was calculated for the following frequency ranges: delta 0.1–3.5 Hz; theta 3.5–8 Hz; alpha 8–12 Hz; sigma 12–16 Hz; beta 16–24 Hz; and gamma 24–50 Hz. Note that these are nominal ranges; due to analogue filtering and FFT spectral resolution, actual sensitivity for delta between 0.1 and 0.5 Hz is low.

2.6 | Magnetic resonance imaging acquisition and voxel-based morphometry

High-resolution T1-weighted MRI datasets were acquired on a 3-Tesla scanner (Magnetom TIM-Trio, Siemens, Erlangen, Germany) using an MPRAGE sequence (TR 2.2 s; TE 2.6 ms; 160 sagittal slices of 256 × 256 voxels, 1.0 × 1.0 × 1.0 mm^3; Mugler & Brookeman, 1990). All scans were inspected for motion artefacts and pathological findings by a neurologist under the supervision of a board-certified neuroradiologist. Voxel-based morphometry was performed using Statistical Parametric Mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Structural images were segmented into grey matter, white matter and cerebrospinal fluid (CSF) using the standard segmentation procedure in SPM8, and the results were checked by visual inspection. A grey matter population template with a 1.5-mm cubic resolution was generated using DARTEL (diffeomorphic anatomical registration through exponentiated Lie algebra; Ashburner, 2007). DARTEL-registered data were affine-transformed to Montreal Neurological Institute space (http://www.mni.mcgill.ca/). Then, all images were modulated to correct for volume changes during normalization, and smoothed with an 8-mm full-width at half-maximum Gaussian

smoothing kernel, thereby shifting the interpretation of the values from relative grey matter densities to absolute grey matter volumes. The Automated Anatomical Labelling (AAL) atlas was used to calculate values for hippocampus (AAL regions 37 and 38), PHC (AAL regions 39 and 40) and mPFC (AAL regions 25, 26, 27, 28, 31 and 32) for each participant (Figure 2).

2.7 | Statistical analyses

Three linear regression models were used to analyse the primary hypothesis that brain morphology (hippocampus, PHC and mPFC) was significantly associated with word pair retention in the WP. To control for unspecific effects, associations between brain morphology and performance in the MT task were also analysed using regression models, as well as associations between brain morphology and recent memory encoding (WP: number of trials in the evening and number of pairs encoded in the last acquisition trial; MT: number of errors and total draw time in the last acquisition trial) and early memory consolidation following encoding in the evening (MT: number of errors and total draw time). Mediation analyses (Sobel tests) were used to analyse whether age effects on overnight memory consolidation were mediated by brain morphology. Furthermore, in exploratory regression models, the effects of spectral power in different frequency bands (delta, theta, alpha, sigma, beta, gamma) on overnight memory consolidation (WP: word pair retention; MT: improvement in number of errors and improvement in draw time) were investigated. To control for sex effects, sex was used as a covariate in all analyses. To control for unspecific effects of total brain volume, all analyses including brain morphology parameters included total CSF corrected brain volume as an additional covariate. The statistical threshold was set at $p < .05$.

3 | RESULTS

In summary, all participants demonstrated good results for encoding in both tasks with relatively few needed acquisition trials to meet the task specifications (Table 1). Retrieval in the WP demonstrated a slight, non-significant decrease in the amount of correct word pairs ($F = 1.5$; $p = .223$; $pETA^2 = 0.041$). Retrieval in the MT showed clear overnight improvements in number of errors ($F = 5.7$; $p = .023$; $pETA^2 = 0.152$) and draw time ($F = 8.8$; $p = .005$; $pETA^2 = 0.217$; Table 1).

Besides showing only a slight decrease, overnight memory consolidation in the WP was significantly correlated with brain morphology (Figure 3; Table 2). Specifically, participants with

TABLE 1 Memory task results

	Mean ± *SD*
Declarative memory – WP	
Encoding, word pairs encoded	35.0 ± 9.1
Encoding, number of trials	1.4 ± 0.7
Retrieval, word pairs remembered	33.5 ± 5.5
Procedural memory – MT	
Encoding, number of errors	2.7 ± 1.7
Encoding, total draw time, s	101.9 ± 55.4
Encoding, trials needed	3.0 ± 2.0
Early retrieval, number of errors	8.4 ± 7.2
Early retrieval, total draw time, s	104.5 ± 38.4
Late retrieval, number of errors	2.3 ± 2.7
Late retrieval, total draw time, s	70.1 ± 23.8

Means ± *SD*.

MT, mirror-tracing task; WP, paired-associate word list task.

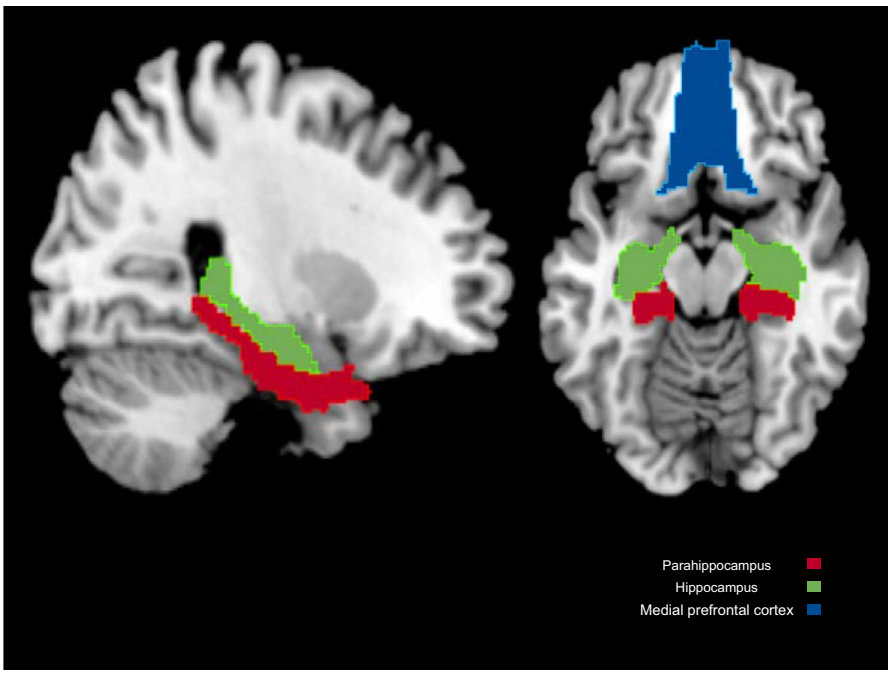

FIGURE 2 Brain morphometry. The Automated Anatomical Labelling (AAL) atlas was used to calculate average volume values for the hippocampus (AAL regions 37 and 38; *green*), parahippocampal (PAH) cortex (AAL regions 39 and 40; *red*) and medial prefrontal cortex (mPFC; AAL regions 23, 24, 25, 26, 27 and 28; blue) for each participant

smaller hippocampus, PHC and mPFC volumes displayed a reduced overnight declarative memory consolidation. As predicted, the control experiment did not show any significant effects of brain morphology on overnight procedural memory consolidation in the MT (Table 2). Furthermore, brain morphology had no effect on recent memory encoding and early memory recall besides a positive correlation between hippocampus volume and draw time (Table 3).

As there were minor volumetric associations with number of trials to encode the word pairs, we reanalysed the sample using number of trials as an additional covariate. The results remained significant with only a minor influence of the additional control variable (PHC: β = 0.765, p = .005; mPFC: β = 0.750, p = .002).

Age correlated significantly with brain morphology, with higher age being associated with smaller hippocampus (β = −0.223, p = .031), PHC (β = −0.287, p = .007) and mPFC volumes (β = −0.418, p = <.001). Mediation analyses showed significant age effects on overnight declarative memory consolidation (β = −0.352; p = .041), but no significant mediation effects of brain morphology on this association (hippocampus: Sobel's z = −0.695, p = .487; PHC: Sobel's z = −1.301, p = .193; mPFC: Sobel's z = −1.877, p = .060).

All participants included in this analysis demonstrated regular night sleep in the experimental night, characterized by a SOL of 17.8 ± 16.5 min, a TST of 416.3 ± 24.0 min and a regular sleep architecture (Stage 1: 8.7 ± 4.5% SPT; Stage 2: 53.8 ± 5.9% SPT; SW sleep: 8.9 ± 7.2% SPT; REM: 19.5 ± 3.8% SPT). Neither of the

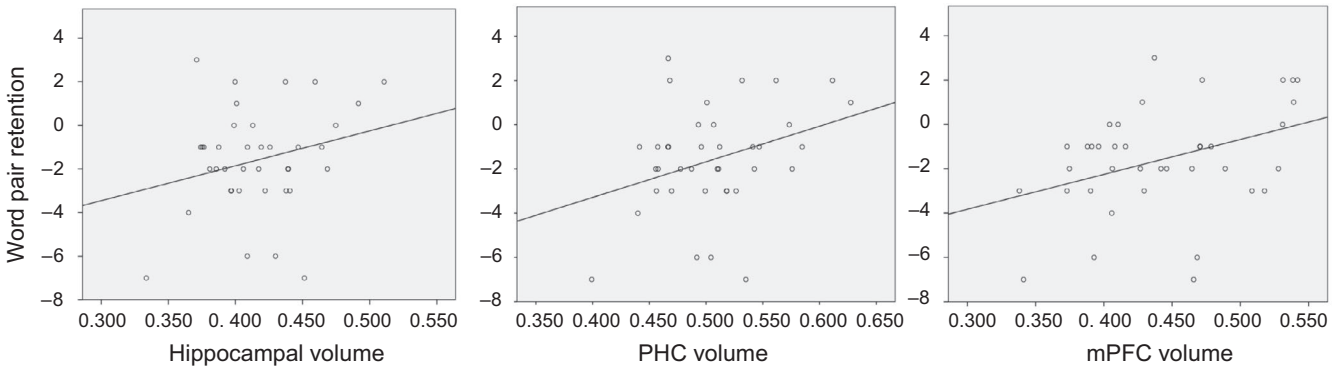

FIGURE 3 Main results. Overnight memory consolidation in the paired-associate word list task (WP) was significantly correlated with medial prefrontal cortex (mPFC), parahippocampus (PHC) and hippocampus volume. Specifically, participants with smaller hippocampus, PHC and mPFC volumes displayed a reduced overnight declarative memory consolidation

TABLE 2 Linear regression analysis of brain morphology effects on overnight memory consolidation

	Declarative memory		Procedural memory			
	WP - word pair retention		MT - number of errors improvement		MT - total time (s) improvement	
	β	p	β	p	β	p
Hippocampus	0.577	**.041**	0.271	.373	−0.499	.086
PHC	0.745	**.004**	0.420	.148	−0.423	.134
mPFC	0.747	**.001**	0.176	.504	−0.103	.687

mPFC, medial prefrontal cortex; MT, mirror-tracing task; PHC, parahippocampal cortex; WP, paired associate word list task; β, standardized beta coefficient. Bold font indicates statistical significance.

TABLE 3 Linear regression analysis of brain morphology effects on recent memory encoding and early consolidation

	Declarative memory Encoding				Procedural memory Encoding				Procedural memory Early retrieval			
	WP - number of trials		WP - word pairs encoded		MT - number of errors		MT - total draw time, s		MT - number of errors		MT - total draw time, s	
	β	p	β	p	β	p	β	p	β	p	β	p
Hippocampus	−0.443	.124	0.333	.251	−0.335	.267	0.433	.155	−0.220	.459	0.584	**.044**
PHC	−0.374	.175	0.124	.655	−0.338	.247	0.324	.273	−0.368	.194	0.496	.078
mPFC	−0.212	.402	0.231	.359	−0.375	.148	−0.042	.874	−0.186	.468	0.020	.937

mPFC, medial prefrontal cortex; MT, mirror-tracing task; PHC, parahippocampus; WP, paired-associate word list task; β, standardized beta coefficient. Bold font indicates statistical significance.

polysomnographic variables or derived sleep EEG spectral power variables displayed correlations with overnight memory consolidation (all $p > .05$; Table 4). Further mediation analyses showed that the effects of age and brain morphology on overnight declarative memory consolidation were not mediated by polysomnographic variables or sleep EEG spectral power variables either. In particular, SW sleep and EEG delta power did not mediate the effects of age (SW sleep: Sobel's $z = 0.153$, $p = .878$; EEG delta power: Sobel's $z = 0.005$, $p = .996$) and brain morphology (SW sleep: hippocampus: Sobel's $z = 0.142$, $p = .887$; PHC: Sobel's $z = -0.253$, $p = .800$; mPFC: Sobel's $z = -0.177$, $p = .859$; EEG delta power: hippocampus: Sobel's $z = 0.158$, $p = .874$; PHC: Sobel's $z = -0.083$, $p = .934$; mPFC: Sobel's $z = 0.227$, $p = .820$) on overnight declarative memory consolidation.

TABLE 4 Linear regression analysis of NREM sleep EEG spectral power effects on overnight memory consolidation

	Declarative memory		Procedural memory			
	WP – word pair retention		MT - number of errors, improvement		MT - total time (s), improvement	
	β	*p*	*β*	*p*	*β*	*p*
Delta	0.091	.635	0.071	.728	−0.140	.488
Theta	−0.027	.895	−0.295	.163	0.005	.982
Alpha	0.011	.952	−0.287	.139	−0.106	.588
Sigma	0.189	.270	−0.108	.562	0.043	.814
Beta	0.216	.206	−0.247	.176	−0.107	.562
Gamma	0.205	.226	−0.346	.051	−0.014	.937

MT, mirror-tracing task; WP, paired-associate word list task; *β*, standardized beta coefficient.

4 | DISCUSSION

As a main finding, this study demonstrates overnight memory consolidation in the WP to be significantly correlated with hippocampus, PHC and mPFC volumes. The direct correlation of mPFC with consolidation effects added to the growing body of evidence for the importance of a hippocampal–neocortical dialogue for memory consolidation (Klinzing et al., 2019).

To control for unspecific cognitive effects of mPFC, PHC and hippocampus volumes, the study shows that learning/encoding was not correlated with any of the analysed brain regions, thereby characterizing the main effects to be specific for consolidation. Improvement in procedural memory consolidation, conceptualized as error rate and draw time gains in a MT, did not show any correlation with the analysed regions, distinguishing the main results to be specific for hippocampus-dependent declarative memory formation.

Interestingly, clear age effects on memory consolidation and mPFC volume were detected in a middle-aged study population. The findings further strengthen the conceptualization of age-related cognitive decline as an ongoing process throughout the lifespan rather than a challenge limited to old age (Sowell et al., 2003). In addition, the results support that structural differences in specific brain volumes can be directly linked to functional decline, as described for example for PFC engagement during working memory tasks (Onoda, Ishihara, & Yamaguchi, 2012; Yaple, Stevens, &

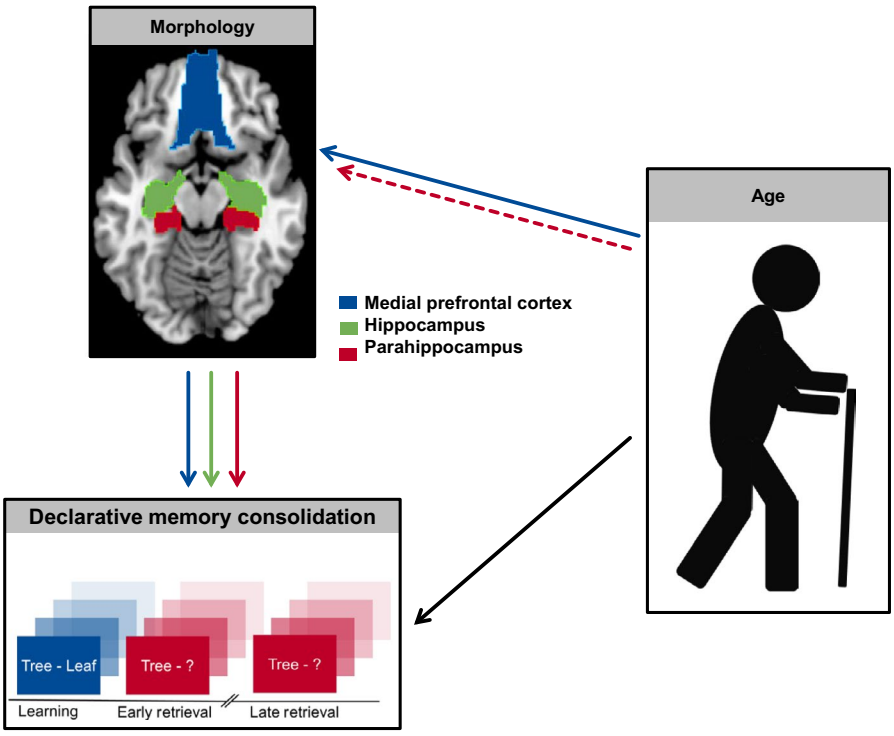

FIGURE 4 Model schematic. Lesser volumes of hippocampus, parahippocampal (PHC) cortex and medial prefrontal cortex (mPFC) are correlated with reduced overnight declarative memory consolidation. In addition, age is negatively associated with declarative memory consolidation as well as volumes of the mPFC and PHC cortex (trend). However, mediation analyses demonstrated that age effects on memory consolidation were not significantly mediated by brain morphology. Straight line, significant correlation; dotted line, non-significant correlation (trend)

Arsalidou, 2019). While in this study higher age correlated with lesser mPFC volume (and PHC volume on trend level) and all three targeted brain regions correlated positively with overnight memory consolidation, age effects were not mediated by brain morphology. This can be interpreted as brain area volume contributing to a decline in memory consolidation that occurs in addition to other negative effects of aging. For a schematic depiction of the proposed interaction of age, morphology and overnight declarative memory consolidation, refer to Figure 4.

The correlation between brain morphology and memory consolidation demonstrated in this study has been found in the absence of an association of one of the variables with slow-wave activity or any other sleep variable. Thus, the results suggest that the association between mPFC volume and memory consolidation does not necessarily depend on slow-wave activity (delta range, 0.1–3.5 Hz) as it is commonly conceptualized (Mander et al., 2013). One possible explanation can be found in analysing typical age groups in neuropsychological studies. A recent review summarizes nocturnal sleep and napping to promote memory consolidation and sleep deprivation to cause cognitive impairments in young adults more pronounced than in older adults (Scullin & Bliwise, 2015). It can be speculated that the involved mechanisms and brain areas change during the lifespan.

To fully clarify this finding though, a wake control condition with the same circadian and timeframe between learning and recall would have been needed to fully exclude sleep to be the driving influence behind the demonstrated effects on consolidation. In addition, it is possible that sleep supports memory consolidation, but inter-individual variance in specific sleep characteristics does not reflect these benefits (Ackermann et al., 2015). As another limitation, due to the cross-sectional nature of the study, final conclusions about causality cannot be drawn. Our study applies state of the art methods for investigating sleep, overnight memory consolidation and brain morphology though, leading to a reliable study design.

Some authors discuss whether other characteristics besides the distinction between declarative memory and procedural memory might be of higher relevance for finding memory-enhancing effects of sleep. While our study found no influence of sleep on overnight memory consolidation of semantically related word pairs, such effects might be stronger for unrelated word pairs where some aspects, for example integration or reorganization of memory, might be more challenging and/or important (Landmann et al., 2015; Payne et al., 2012).

In summary, the results suggest that the association between age, brain morphology and overnight memory consolidation is highly relevant, but does not necessarily depend on SWS.

ACKNOWLEDGEMENTS

The authors wish to thank the sleep laboratory staff at the Department of Psychiatry and Psychotherapy, Freiburg, for their help in conducting the study.

CONFLICT OF INTEREST

The described work was supported by funding from the European Community's Seventh Framework Programme (People, Marie Curie Actions, Intra-European Fellowship, FP7-PEOPLE-IEF-2008; http://cordis.europa.eu/fp7/home_en.html) under grant agreement n. 235,321. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. CB and DR received funding from the European Community's Seventh Framework Programme. CN has served as a consultant for Vifor and Lundbeck. None of the other authors declare any conflict of interest.

AUTHOR CONTRIBUTION

CB, JH, DR, CN and KS conceived and designed the experiments. WR, SK and AR collected the data. BF and JH contributed data or analysis tools. LF, KS and BF performed the statistical analysis. All authors interpreted the data and results. LF, KS and CN wrote the paper with support of and revising by all authors. All authors approved the final version to be published.

ORCID

Lukas Frase https://orcid.org/0000-0002-0841-3630
Chiara Baglioni https://orcid.org/0000-0003-3150-7755
Bernd Feige https://orcid.org/0000-0002-9436-1258
Dieter Riemann https://orcid.org/0000-0002-1968-6220
Christoph Nissen https://orcid.org/0000-0001-9809-0275

REFERENCES

Ackermann, S., Hartmann, F., Papassotiropoulos, A., de Quervain, D.-J.-F., & Rasch, B. (2015). No associations between interindividual differences in sleep parameters and episodic memory consolidation. *Sleep*, *38*(6), 951–959. https://doi.org/10.5665/sleep.4748

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007

Baglioni, C., Spiegelhalder, K., Regen, W., Feige, B., Nissen, C., Lombardo, C., … Riemann, D. (2014). Insomnia disorder is associated with increased amygdala reactivity to insomnia-related stimuli. *Sleep*, *37*(12), 1907–1917. https://doi.org/10.5665/sleep.4240

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Bergmann, T. O., Molle, M., Diedrichs, J., Born, J., & Siebner, H. R. (2012). Sleep spindle-related reactivation of category-specific cortical regions after learning face-scene associations. *NeuroImage*, *59*(3), 2733–2742. https://doi.org/10.1016/j.neuroimage.2011.10.036

Berry, R. B., Brooks, R., Gamaldo, C., Harding, S. M., Lloyd, R. M., Quan, S. F., … Vaughn, B. V. (2017). AASM scoring manual updates for 2017 (Version 2.4). *Journal of Clinical Sleep Medicine*, *13*(5), 665–666. https://doi.org/10.5664/jcsm.6576

Bontempi, B., Laurent-Demir, C., Destrade, C., & Jaffard, R. (1999). Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature*, *400*(6745), 671–675. https://doi.org/10.1038/23270

Buckner, R. L., Kelley, W. M., & Petersen, S. E. (1999). Frontal cortex contributes to human memory formation. *Nature Neuroscience*, *2*(4), 311–314. https://doi.org/10.1038/7221

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for

psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Davachi, L., Mitchell, J. P., & Wagner, A. D. (2003). Multiple routes to memory: Distinct medial temporal lobe processes build item and source memories. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(4), 2157–2162. https://doi.org/10.1073/pnas.0337195100

Feige, B., Voderholzer, U., Riemann, D., Dittmann, R., Hohagen, F., & Berger, M. (2002). Fluoxetine and sleep EEG: Effects of a single dose, subchronic treatment, and discontinuation in healthy subjects. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *26*(2), 246–258. https://doi.org/10.1016/S0893-133X(01)00314-1

Fernandez, G., Klaver, P., Fell, J., Grunwald, T., & Elger, C. E. (2002). Human declarative memory formation: Segregating rhinal and hippocampal contributions. *Hippocampus*, *12*(4), 514–519. https://doi.org/10.1002/hipo.10050

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nature Reviews Neuroscience*, *6*(2), 119–130. https://doi.org/10.1038/nrn1607

Frase, L., Piosczyk, H., Zittel, S., Jahn, F., Selhausen, P., Krone, L., … Nissen, C. (2016). Modulation of total sleep time by transcranial direct current stimulation (tDCS). *Neuropsychopharmacology*, *41*(10), 2577–2586. https://doi.org/10.1038/npp.2016.65

Frase, L., Selhausen, P., Krone, L., Tsodor, S., Jahn, F., Feige, B., … Nissen, C. (2019). Differential effects of bifrontal tDCS on arousal and sleep duration in insomnia patients and healthy controls. *Brain Stimulation*, *12*(3), 674–683. https://doi.org/10.1016/j.brs.2019.01.001

Holz, J., Piosczyk, H., Feige, B., Spiegelhalder, K., Baglioni, C., Riemann, D., & Nissen, C. (2012). EEG Sigma and slow-wave activity during NREM sleep correlate with overnight declarative and procedural memory consolidation. *Journal of Sleep Research*, *21*(6), 612–619. https://doi.org/10.1111/j.1365-2869.2012.01017.x

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, *14*(6), 540–545. https://doi.org/10.1093/sleep/14.6.540

Klinzing, J. G., Niethard, N., & Born, J. (2019). Mechanisms of systems memory consolidation during sleep. *Nature Neuroscience*, *22*(10), 1598–1610. https://doi.org/10.1038/s41593-019-0467-3

Krause, B. J., Horwitz, B., Taylor, J. G., Schmidt, D., Mottaghy, F. M., Herzog, H., … Müller-Gärtner, H.-W. (1999). Network analysis in episodic encoding and retrieval of word-pair associates: A PET study. *The European Journal of Neuroscience*, *11*(9), 3293–3301. https://doi.org/10.1046/j.1460-9568.1999.00723.x

Landmann, N., Kuhn, M., Maier, J.-G., Spiegelhalder, K., Baglioni, C., Frase, L., … Nissen, C. (2015). REM sleep and memory reorganization: Potential relevance for psychiatry and psychotherapy. *Neurobiology of Learning and Memory*, *122*, 28–40. https://doi.org/10.1016/j.nlm.2015.01.004

Lustenberger, C., Wehrle, F., Tushaus, L., Achermann, P., & Huber, R. (2015). The multidimensional aspects of sleep spindles and their relationship to word-pair memory consolidation. *Sleep*, *38*(7), 1093–1103. https://doi.org/10.5665/sleep.4820

Mander, B. A., Rao, V., Lu, B., Saletin, J. M., Lindquist, J. R., Ancoli-Israel, S., … Walker, M. P. (2013). Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nature Neuroscience*, *16*(3), 357–364. https://doi.org/10.1038/nn.3324

Marshall, L., Molle, M., Hallschmid, M., & Born, J. (2004). Transcranial direct current stimulation during sleep improves declarative memory. *The Journal of Neuroscience*, *24*(44), 9985–9992. https://doi.org/10.1523/JNEUROSCI.2725-04.2004

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The sleep slow oscillation as a traveling wave. *The Journal of Neuroscience*, *24*(31), 6862–6870. https://doi.org/10.1523/JNEUROSCI.1318-04.2004

Matthews, B. R. (2015). Memory dysfunction. *Continuum*, *21*(3), 613–626. https://doi.org/10.1212/01.CON.0000466656.59413.29

Maviel, T., Durkin, T. P., Menzaghi, F., & Bontempi, B. (2004). Sites of neocortical reorganization critical for remote spatial memory. *Science (New York, N.Y.)*, *305*(5680), 96–99. https://doi.org/10.1126/science.1098180

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, *102*(3), 419–457. https://doi.org/10.1037/0033-295X.102.3.419

Molle, M., Bergmann, T. O., Marshall, L., & Born, J. (2011). Fast and slow spindles during the sleep slow oscillation: Disparate coalescence and engagement in memory processing. *Sleep*, *34*(10), 1411–1421. https://doi.org/10.5665/SLEEP.1290

Molle, M., Yeshenko, O., Marshall, L., Sara, S. J., & Born, J. (2006). Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. *Journal of Neurophysiology*, *96*(1), 62–70. https://doi.org/10.1152/jn.00014.2006

Mugler, J. P. 3rd, & Brookeman, J. R. (1990). Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). *Magnetic Resonance in Medicine*, *15*(1), 152–157. https://doi.org/10.1002/mrm.1910150117

Murphy, M., Riedner, B. A., Huber, R., Massimini, M., Ferrarelli, F., & Tononi, G. (2009). Source modeling sleep slow waves. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(5), 1608–1613. https://doi.org/10.1073/pnas.0807933106

Ngo, H.-V.-V., & Born, J. (2019). Sleep and the balance between memory and forgetting. *Cell*, *179*(2), 289–291. https://doi.org/10.1016/j.cell.2019.09.007

Onoda, K., Ishihara, M., & Yamaguchi, S. (2012). Decreased functional connectivity by aging is associated with cognitive decline. *Journal of Cognitive Neuroscience*, *24*(11), 2186–2198. https://doi.org/10.1162/jocn_a_00269

Payne, J. D., Tucker, M. A., Ellenbogen, J. M., Wamsley, E. J., Walker, M. P., Schacter, D. L., & Stickgold, R. (2012). Memory for semantically related and unrelated declarative information: The benefit of sleep, the cost of wake. *PLoS ONE*, *7*(3), e33079. https://doi.org/10.1371/journal.pone.0033079

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience*, *9*(4), 534–547. https://doi.org/10.1162/jocn.1997.9.4.534

Reinhard, M. A., Regen, W., Baglioni, C., Nissen, C., Feige, B., Hennig, J., … Spiegelhalder, K. (2014). The relationship between brain morphology and polysomnography in healthy good sleepers. *PLoS ONE*, *9*(10), e109336. https://doi.org/10.1371/journal.pone.0109336

Ribeiro, S., Shi, X., Engelhard, M., Zhou, Y., Zhang, H., Gervasoni, D., & Nicolelis, M. A. L. (2007). Novel experience induces persistent sleep-dependent plasticity in the cortex but not in the hippocampus. *Frontiers in Neuroscience*, *1*(1), 43–55. https://doi.org/10.3389/neuro.01.1.1.003.2007

Ricci, P. T., Zelkowicz, B. J., Nebes, R. D., Meltzer, C. C., Mintun, M. A., & Becker, J. T. (1999). Functional neuroanatomy of semantic memory: Recognition of semantic associations. *NeuroImage*, *9*(1), 88–96. https://doi.org/10.1006/nimg.1998.0386

Schabus, M., Gruber, G., Parapatics, S., Sauter, C., Klösch, G., Anderer, P., … Zeitlhofer, J. (2004). Sleep spindles and their significance for declarative memory consolidation. *Sleep*, *27*(8), 1479–1485. https://doi.org/10.1093/sleep/27.7.1479

Scullin, M. K., & Bliwise, D. L. (2015). Sleep, cognition, and normal aging: Integrating a half century of multidisciplinary research. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science*, *10*(1), 97–137. https://doi.org/10.1177/1745691614556680

Sirota, A., Csicsvari, J., Buhl, D., & Buzsaki, G. (2003). Communication between neocortex and hippocampus during sleep in rodents. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(4), 2065–2069. https://doi.org/10.1073/pnas.0437938100

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience*, *6*(3), 309–315. https://doi.org/10.1038/nn1008

Spiegelhalder, K., Baglioni, C., Regen, W., Kyle, S. D., Nissen, C., Hennig, J., … Riemann, D. (2016). Brain reactivity and selective attention to sleep-related words in patients with chronic insomnia. *Behavioral Sleep Medicine*, *1–15*, https://doi.org/10.1080/15402002.2016.1253014

Spiegelhalder, K., Regen, W., Baglioni, C., Klöppel, S., Abdulkadir, A., Hennig, J., … Feige, B. (2013). Insomnia does not appear to be associated with substantial structural brain changes. *Sleep*, *36*(5), 731–737. https://doi.org/10.5665/sleep.2638

Spiegelhalder, K., Regen, W., Prem, M., Baglioni, C., Nissen, C., Feige, B., … Riemann, D. (2014). Reduced anterior internal capsule white matter integrity in primary insomnia. *Human Brain Mapping*, *35*(7), 3431–3438. https://doi.org/10.1002/hbm.22412

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(24), 13,515–13,522. https://doi.org/10.1073/pnas.93.24.13515

Suzuki, W. A., & Amaral, D. G. (2004). Functional neuroanatomy of the medial temporal lobe memory system. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *40*(1), 220–222. https://doi.org/10.1016/S0010-9452(08)70958-4

Takehara, K., Kawahara, S., & Kirino, Y. (2003). Time-dependent reorganization of the brain components underlying memory retention in trace eyeblink conditioning. *The Journal of Neuroscience*, *23*(30), 9897–9905. https://doi.org/10.1523/JNEUROSCI.23-30-09897.2003

Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Medicine Reviews*, *10*(1), 49–62. https://doi.org/10.1016/j.smrv.2005.05.002

Van Cauter, E., Leproult, R., & Plat, L. (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA*, *284*(7), 861–868. https://doi.org/10.1001/jama.284.7.861

Vyazovskiy, V. V., Walton, M. E., Peirson, S. N., & Bannerman, D. M. (2017). Sleep homeostasis, habits and habituation. *Current Opinion in Neurobiology*, *44*, 202–211. https://doi.org/10.1016/j.conb.2017.05.002

Witter, M. P., & Amaral, D. G. (1991). Entorhinal cortex of the monkey: V. Projections to the dentate gyrus, hippocampus, and subicular complex. *The Journal of Comparative Neurology*, *307*(3), 437–459. https://doi.org/10.1002/cne.903070308

Yang, G., Lai, C. S. W., Cichon, J., Ma, L., Li, W., & Gan, W.-B. (2014). Sleep promotes branch-specific formation of dendritic spines after learning. *Science (New York, N.Y.)*, *344*(6188), 1173–1178. https://doi.org/10.1126/science.1249098

Yaple, Z. A., Stevens, W. D., & Arsalidou, M. (2019). Meta-analyses of the n-back working memory task: FMRI evidence of age-related changes in prefrontal cortex involvement across the adult lifespan. *NeuroImage*, *196*, 16–31. https://doi.org/10.1016/j.neuroimage.2019.03.074

Yonelinas, A. P., Ranganath, C., Ekstrom, A. D., & Wiltgen, B. J. (2019). A contextual binding theory of episodic memory: Systems consolidation reconsidered. *Nature Reviews Neuroscience*, *20*(6), 364–375. https://doi.org/10.1038/s41583-019-0150-4

How to cite this article: Frase L, Regen W, Kass S, et al. Hippocampal and medial prefrontal cortical volume is associated with overnight declarative memory consolidation independent of specific sleep oscillations. *J Sleep Res*. 2020;29:e13062. https://doi.org/10.1111/jsr.13062