# Oscillatory Mechanisms of Successful Memory Formation in Younger and Older Adults Are Related to Structural Integrity

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**Abstract**

We studied oscillatory mechanisms of successful memory formation in 47 younger and 52 older adults in an intentional associative memory task with cued recall. While older adults showed reduced memory performance, we found subsequent memory effects (SME) in alpha/beta and theta frequency bands in both age groups. Using logistic mixed effect models, we then investigated whether interindividual differences in structural integrity of memory regions that were functionally linked to oscillatory dynamics in previous studies (Hanslmayr et al., 2011) could account for interindividual differences in the strength of the SME. Structural integrity of inferior frontal gyrus (IFG) and hippocampus (HC) was reduced in older adults. SME in the alpha/beta band were indeed modulated by the cortical thickness of inferior frontal gyrus (IFG), in line with its hypothesized role for deep semantic elaboration. Importantly, this structure–function relationship did not differ by age group. However, older adults were more frequently represented among the participants with low cortical thickness and consequently weaker SME in the alpha band. Thus, our results suggest that differences in the structural integrity of the IFG are the basis not only for interindividual, but also for age differences in memory formation.

*Keywords:* oscillations, episodic memory, alpha, theta, inferior frontal gyrus, hippocampus, aging

## Introduction

Episodic memory, the ability to remember episodes with their spatial and temporal details and context (Tulving, 2002) declines with age. The sources of its decline are multifaceted and reflect age-related differences in retrieval (Fandakova et al., 2018), sleep-dependent consolidation (Muehlroth et al., 2018) as well as forgetting (Fandakova et al., 2019). Most crucially, the way information is encoded differs with age (Craik & Rose, 2012), particularly with regard to the binding of associative information (Naveh-Benjamin, 2000). Age differences in the quality of memory representations are persistent and have downstream consequences for later stages of memory processing like consolidation and retrieval (see Fandakova et al., 2018). However, whether age-related changes in brain integrity of memory regions affect the mechanisms of memory formation in older adults is still unclear.

Mechanisms of successful memory formation can be studied with the *subsequent memory paradigm* (Paller & Wagner, 2002; Werkle-Bergner, Müller, Li, & Lindenberger, 2006). This approach makes use of the fact that not all encoded information can later be remembered. Comparing the neural dynamics in trials that will subsequently be remembered against those that will subsequently be not-remembered reveals the neural underpinnings of successful memory formation. Functional magnetic resonance imaging (fMRI) studies using this paradigm have provided convincing evidence for the contribution and interaction of medio-temporal (MTL) and prefrontal cortical (PFC) regions to successful memory formation (e.g., Reber et al., 2002; Wagner et al., 1998). In particular, the MTL, and more specifically the hippocampus (HC), is regarded as crucial for binding pieces of information into a coherent memory representation, whereas PFC regions serve the selection and elaboration of encoded information (Miller & Cohen, 2001; Simons & Spiers, 2003). Within the PFC, prominent roles have been attributed to the left inferior frontal gyrus (IFG) for memory formation of semantic information and to the right IFG for memory formation of pictorial information Paller & Wagner, 2002).

Thus, episodic memory formation crucially depends on interactions between regions of the PFC and regions of the MTL (Simons & Spiers, 2003). A mechanism for efficient representation and communication in broad neural networks is rhythmic neural activity (Fries, 2005; Parish, Hanslmayr, & Bowman, 2018; von der Malsburg, 1995). In particular, increases in oscillatory theta power and decreases in alpha/beta power support successful encoding of episodes (Hanslmayr & Staudigl, 2014). On a cognitive level, alpha/beta oscillations seem to reflect elaborative encoding processes (Hanslmayr, Staudigl, & Fellner, 2012), whereas theta oscillations may serve associative binding of information (Clouter, Shapiro, & Hanslmayr, 2017). This picture is completed by a study that simultaneously assessed SME in electroencephalography (EEG) and fMRI, and identified the IFG as the source region of SME in the alpha/beta band, and the hippocampus as the source region of SME in the theta band (Hanslmayr et al., 2011).

While several studies have compared SME in younger and older adults using fMRI (for a meta-analysis of 18 studies, see Maillet & Rajah, 2014), surprisingly little is known about age differences in oscillatory neural mechanisms of episodic memory formation (Werkle-Bergner et al., 2006, but see Strunk & Duarte, 2018). Here, we therefore examined to what extent patterns of oscillatory neural activity related to memory formation are altered in older adults as compared to younger adults, with regard to SME in the theta and alpha band. Furthermore, to the best of our knowledge, the relation between structural integrity of key regions of memory functions and oscillatory mechanisms of memory formation has not been investigated. We hypothesized that while theta and alpha power modulations (i.e., subsequent memory effects) explain accuracy on a trial-by-trial level, differences in MTL and PFC structure may be related to between-person differences in accuracy. As SME in the alpha band are thought to reflect elaborative processing of information, we hypothesized that SME in that range depend on the structural integrity of the IFG, which has been previously *functionally* related to subsequent memory (Hanslmayr et al., 2011). Second, as SME in the theta band are thought to reflect interactions between the HC and PFC (Klimesch, 1999; Nyhus & Curran, 2010) and have previously been localized to the HC (Hanslmayr et al.,

2011), we hypothesized that the degree of theta power modulation depends on the structural integrity of the HC. Importantly, since both MTL and PFC show pronounced structural and functional decline in normal aging (Raz et al., 2005; Shing et al., 2010; West, 1996), we expected large between-person differences in structural integrity in an age-comparative setting to be particularly conducive to delineate these structure–function relationships. We hypothesized that a reduced structural integrity of HC and PFC in older adults would be accompanied by smaller SME in theta and alpha frequency bands in this age group.

We used repeated cued-recall tests with feedback to track learning of a large set of scene–word pairs in younger and older adults. Specifically, younger and older adults were instructed to study and try to remember scene–word pairs by building an integrated image of the pair (cf. Fandakova et al., 2018; Muehlroth et al., 2018). Prior to study, all participants were instructed in an imagery strategy that has been shown to increase associative memory in younger and older adults effectively (Brehmer, Li, Müller, von Oertzen, & Lindenberger, 2007; Shing, Werkle-Bergner, Li, & Lindenberger, 2008). In contrast to most other studies examining SME in older adults (for review, see Maillet & Rajah, 2014) we used cued verbal recall instead of a recognition procedure to test memory. While correct responses in a cued-recall task depend on remembering the specific scene–word binding, performance on recognition tasks may also, at least partially, be supported by additional processes such as the overall familiarity of the presented scenes and words (Yonelinas, 2002). Since age differences in the SME may be overshadowed by age differences in the speed and limits of learning, we opted for a task design that would eliminate or at least reduce age differences in memory performance, and allow us to track the learning history of individual items (see Fig. 1). We therefore used different numbers of trials and different numbers of learning and recall cycles for younger and older adults (see Method for the details). We simultaneously recorded EEG while participants encoded and recalled scene–word pairs. In addition, we used structural MR to assess IFG cortical thickness and HC volume. We examined the role of within-person power modulations and between-person differences in structure for the prediction of single trial accuracy, modelling them simultaneously in a logistic mixed effects

model. We hypothesized that oscillatory mechanisms of memory formation depend on the structural integrity of HC and IFG, which are affected by advancing age, leading to less successful encoding in older compared to younger adults.

## Method

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., 2018, for the effects of age and memory quality on false memory retrieval and Muehlroth et al., 2018, for the effects of sleep on memory retrieval). At the core of the experimental design was an associative scene–word pair memory paradigm, consisting of a learning session on the first day (Day 1) and a delayed recognition or delayed cued-recall task approximately 24 hours later (Day 2) (see Figure 1 for a depiction of the study procedure of Day 1). Structural MRI (sMRI) and fMRI data were collected during and after delayed recall or recognition on Day 2. In a part of the sample, sleep was also monitored at participants' homes using ambulatory polysomnography (PSG). As the current study focusses on age differences in encoding (Day 1), neither fMRI nor PSG data are included in the present report (see Fandakova et al., 2018; Muehlroth et al., 2018, respectively). We included sMRI data to test our hypothesis that structural integrity of the HC (i.e., HC volume) and IFG (i.e., cortical thickness) may be related to oscillatory SME in theta and alpha frequencies.

### Participants

Participants from two samples (cf. Fandakova et al., 2018; Muehlroth et al., 2018) assessed at different time points were jointly analyzed in the present analyses as the learning procedure on Day 1 was identical between the samples. In total, (partial) data from 141 participants (61 younger and 80 older adults) were available. Due to technical failures or extreme artifacts, EEG data were only available for 113 participants (50 younger and 63 older adults). This sample was used for the determination of time-frequency clusters with SME on the grand-average EEG data.

In the EEG sample, 3 younger and 11 older adults did not provide full MRI data sets (T1 and/or T2 missing or containing strong motion artefacts). The effective final sample in the main analyses comprised 47 younger adults ($M_{age}$ (SD) = 24.12 (2.53), range 19.12–27.87 years), and 52 older adults ($M_{age}$ (SD) = 70.18 (2.72), range 63.78–75.75 years). Performance of the final sample did not differ from the EEG-only sample. All participants were assessed on marker tests of verbal knowledge (Spot-a-Word, cf. Lehrl, 1977) and perceptual speed (digit symbol substitution test, cf. Wechsler, 1955) and showed age typical performance (younger adults: $M_{Digit\ Symbol}$ (SD) = 69.12 (10.77), $M_{Spot\text{-}a\text{-}word}$(SD) = 23.32 (3.17), older adults: $M_{Digit\ Symbol}$ (SD) = 50.73 (10.64), $M_{Spot\text{-}a\text{-}word}$(SD) = 29.12 (3.16), . The ethics committee of the Deutsche Gesellschaft für Psychologie (DGP) approved the study.

Experimental Paradigm

A subsequent memory paradigm (Paller & Wagner, 2002) was used to compare neural oscillations related to later remembered versus later not-remembered items. Initially, participants were instructed to memorize randomly paired scene–word stimuli using an imagery strategy. Participants were strongly encouraged to generate integrated images of the pairs that were vivid and creative. Examples were discussed in detail until the strategy was well understood. During the experiment, scene–word pairs were presented for 4 seconds, with the scene on the left and the word on the right of the screen. During this initial presentation, participants used a four-point imaginability scale to indicate how well they were able to form an integrated image of the scene and word. In subsequent blocks, the scenes served as cues and participants had to verbally recall the associated word. Verbal responses were digitally recorded. Recall time was not constrained. The accuracy of the answers was coded online by the experimenter. Independent of recall accuracy, the correct word was shown again together with the scene (for 3 seconds), fostering further learning of the pair. Then participants completed a final cued-recall task without feedback. Importantly, to adjust task difficulty between the two age groups, younger adults learned 440 pairs, whereas older adults learned 280 pairs. Older adults also completed an additional cued-recall/restudy cycle

before the final test. While younger adults were able to learn a number of scene–word pairs that would allow for subsequent memory analysis of the initial study phase, older adults' initial performance was too low for such an analysis (but see Sommer et al., 2019, for an alternative age-comparative analysis of the initial study phase). Therefore, the subsequent memory analysis of the EEG data in both age groups is focused on the last restudy phase before the final test. Pairs recalled correctly prior to this last encoding phase were omitted from the analysis.

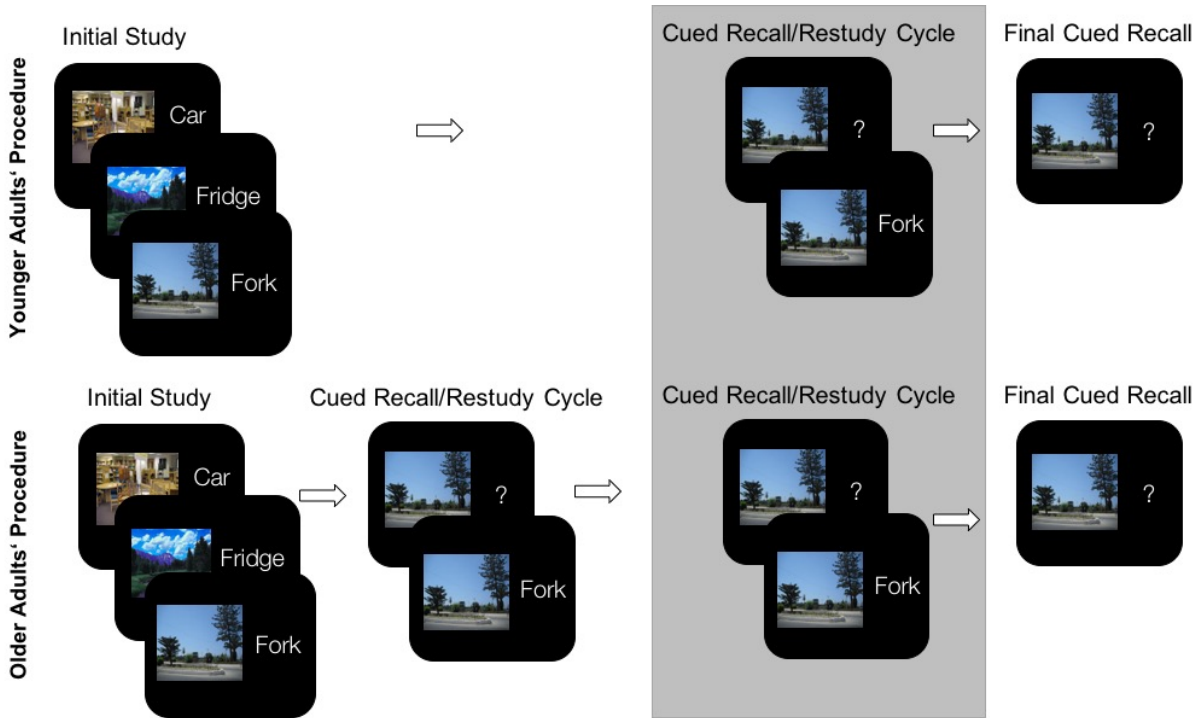


Figure 1. Memory Paradigm (cf. Fandakova et al., 2018; Muehlroth et al., 2018). (A) During initial study, participants were instructed to remember 440 scene–word pairs (younger adults) or 280 scene–word pairs (older adults). (B) During the cued recall/restudy phase, the scene was presented as a cue to recall the corresponding word. Irrespective of recall accuracy, the original pair was presented again to allow for restudy. The whole cued recall/restudy cycle was performed once in younger adults and twice in older adults. (C) During final recall, scenes again served as cues to recall the corresponding word, but no occasion for restudy was provided. Subsequent memory analysis was done on the last cued restudy of the scene–word pairs before final cued recall (marked by the grey background).

During the experimental procedure, participants were seated comfortably in a dimly lit room that was electromagnetically and acoustically shielded. The EEG measurement started with a 6-minute relaxation phase (resting EEG), followed by the task. Between blocks, participants were allowed to take breaks and leave the cabin.

Stimuli

Stimuli are described in detail in Fandakova et al. (2018). Briefly, we selected 580 picture stimuli, half of them depicting indoor scenes and the other half depicting outdoor scenes. In addition, 580 concrete nouns with 2 phonetic syllables and a word length of 4–8 letters were selected from the CELEX database of the Max Planck Institute for Psycholinguistics (http://celex.mpi.nl/). Pictures and words were randomly paired to form stimuli for the presentation during the experiment.

Analysis of Behavioral Data

Behavioral data was analysed usin R 3.5.2 (R Development Core Team, 2018). Raincloud plots were used for illustration of the data (Allen et al., 2018).

*Overall learning success*: Overall learning success was calculated as the proportion of correctly recalled items out of all presented items (i.e.. 440 for younger adults and 280 for older adults*)* and was compared between age groups using the Wilcoxon rank sum test since assumptions of normality were violated.

*Learning gain in the last restudy phase:* To keep the behavioral analysis in line with the subsequent memory analysis, our main behavioral measure of interest was the *learning gain in the last restudy phase*. We therefore computed the learning gain as the percentage of items correctly recalled in the final cued recall out of those pairs that were not previously recalled in earlier recall cycles. Differences in learning gains were compared between age groups using the Wilcoxon rank sum test.

*Imagery ratings:* Participants rated the imaginability of each scene–word pair during the initial study phase. Unfortunately, these imagery ratings contained many missing trials, mostly because of a technical programming mistake. Post-hoc inspection of our data revealed that participants often seem to have run out of time for the imagery rating and given their rating too late for registration or even during the next trial. This led to missing data in the following trial since only one response was registered per trial. We therefore excluded trials with missing responses or reaction times below 500 ms from the analysis. The number of trials included in the analysis was *M (SD)* = 227.32 (68.59) in the younger and *M (SD)* = 135.04 (59.85) in the older adults.

To investigate whether adults of both age groups were able to modulate their imagery ratings according to subsequent memory success, we compared imagery ratings for later recalled and not-remembered trials within each age group using Wilcoxon signed-rank tests. We then tested whether age groups differed in the modulation of the imagery ratings by comparing individual difference values (remembered minus not-remembered pairs) between age groups using the Wilcoxon rank sum test.

Acquisition and structural MR analyses

Whole-brain MRI data were acquired on a Siemens Magnetom 3T TimTrio machine. 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 from each participant. Cortical thickness was estimated using Freesurfer 5.1.0 following the Freesurfer standard image analysis processing pipeline as described on (http://surfer.nmr.mgh.harvard.edu/). This pipeline generates assessments of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). Parcellation of the cerebral cortex into units with respect to gyral and sulcal structure was performed using the Desikan-Atlas (Desikan et al., 2006). Cortical thickness per subject was extracted for pars triangularis, pars orbitalis, and pars opercularis separately for the left and the right hemisphere. To capture the structural integrity of the IFG

for a given person, we computed the sum of cortical thickness of these six regions (i.e., collapsing across hemispheres).

Since the automatic procedures pipeline in Freesurfer has been shown to selectively overestimate hippocampal volume in younger adults and to thereby bias age comparisons (Wenger et al., 2014), we acquired images of the MTL using a high-resolution, T2-weighted 2D turbo-spin echo (TSE) sequence, oriented perpendicularly to the long axis of the hippocampus (in-plane resolution: 0.4 mm x 0.4 mm, slice thickness: 2 mm, 31 slices, image matrix: 384 x 384, TR: 8150 ms, TE: 50 ms, flip angle: 120°) that was optimized for hippocampal subfield volume estimation (cf. Keresztes et al., 2017; Shing et al., 2011). Total volume of the hippocampal body was estimated as the sum of HC subfields including CA1, dentate gyrus, and subiculum and corrected for intracranial volume. The subfields were segmented using a semi-automated procedure with a custom-built hippocampal subfield atlas (both the procedure and the atlas described in Bender et al. (2018) using ASHS (Automatic Segmentation of Hippocampal Subfields; Yushkevich et al., 2015). Since we had no specific hypothesis how HC subfields would relate to SME in theta frequencies, we took the sum of left and right HC total volume of all subfields, thus the total HC body, as a measure of HC structural integrity. Differences in structural integrity were compared between age groups using independent sample t-tests.

EEG Recording and Preprocessing

EEG was recorded continuously with BrainVision amplifiers (BrainVision Products GmbH, Gilching, Germany) from 61 Ag/Ag-Cl electrodes embedded in an elastic cap. Three additional electrodes were placed at the outer canthi and below the left eye to monitor eye movements. During recording, all electrodes were referenced to the right mastoid electrode, while the left mastoid electrode was recorded as an additional channel. The EEG was recorded with a band-pass of 0.1 to 250 Hz and digitized with a sampling rate of 1000 Hz. During preparation, electrode impedances were kept below 5 kΩ.

EEG data preprocessing was performed with the Fieldtrip software package (developed at the F. C. Donders Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands; http://fieldtrip.fcdonders.nl/) supplemented by custom-made MATLAB code (The MathWorks Inc., Natick, MA, USA). An independent-component analysis (ICA) was used to correct for eye blink and cardio artifacts (Jung et al., 2000). Independent components representing artifactual sources were automatically detected, visually checked, and removed from the data. For analyses, the EEG was demeaned, re-referenced to mathematically linked mastoids, band-pass filtered (0.2–100 Hz; fourth order Butterworth) and downsampled to 250 Hz. Automatic artifact correction was performed for remaining artifacts following the FASTER procedure (Nolan, Whelan, & Reilly, 2010). Excluded channels were interpolated with spherical splines (Perrin, Pernier, Bertrand, & Echallier, 1989).

Data epochs were selected from the last cued recall/restudy cycle. Four-second data epochs were extracted from -1 s to 3 s with respect to the onset of scene–word presentation during the last restudy phase. Time-frequency representations (TFRs) within the frequency range of interest (2–20 Hz) were derived from a short-time Fourier analysis with Hanning tapers with a fixed width of 500 ms, resulting in frequency steps of 2 Hz. Single-trial power was log-transformed. Only *subsequently* remembered or not-remembered trials were included in the analysis. Trials that were successfully remembered prior to the final cued recall/restudy cycle were omitted from the analysis. The number of trials included was *M(SD)* = 290.04 (43.00) for younger adults and *M(SD)* = 183.48 (39.14) for older adults.

Analysis of Oscillatory Activity at the Group Level

First, trials remembered and trials not-remembered during the final cued recall were averaged for each subject. We then determined time-frequency clusters on the grand-average level (collapsed across age groups) that showed reliable differences between subsequently remembered and not-remembered trials. We therefore used dependent-sample t-tests on all electrodes across the whole trial length (from stimulus onset to 3 s). The threshold for electrodes to be included in a cluster was set to $p = .05$ and clusters were

defined as a minimum of two neighboring electrodes showing reliable differences in activity. We controlled for multiple comparisons using non-parametric cluster-based permutation tests (Maris and Oostenveld, 2007). The permutation null-distribution for the resulting t-values was determined by randomly switching the condition labels 1000 times and recomputing the t-tests. Note that we excluded one younger and two older adults' data with final recall accuracy below 10% or above 90% from this part of the analysis in order not to bias the results via participants with highly unbalanced trial numbers across conditions. However, these participants were only excluded for the determination of the clusters of interest, but included in the subsequent data modelling as our mixed effects model with a random subject factor was able to account for differences in trial numbers. To explain the next steps, we need to foreshadow the results of this analysis: The cluster-based permutation statistics yielded two significant ($p < .025$) clusters of electrodes that were considered as regions of interest in subsequent analyses (see Figure 2). The early cluster had a maximum around 500–800ms and was predominantly found in the theta frequency range (4–6 Hz). The later cluster had a maximum around 1000–2000ms and encompassed alpha and beta frequencies (8–20 Hz). To ease comprehension, we will refer to the earlier cluster as the SME in the theta band and to the later cluster as the SME in the alpha/beta frequency band.

Single-Trial Statistical Analysis

To further investigate the behavioral relevance of modulations in theta and alpha/beta frequencies at the individual level, we extracted single-trial log-transformed power for each participant from the two time-frequency-electrode clusters determined in the first step and averaged across time- and frequency points within the cluster. Single-trial power was then used in a mixed-effects logistic regression (i.e., a generalized linear mixed-effects model, GLMM; Quené & van den Bergh, 2008) to predict single-trial accuracy (correct/incorrect, i.e., a binomially distributed response). Alpha/beta power and theta power (both continuous predictors) were z-scored within subjects across trials and centered around the mean of the individual before analysis in order to facilitate the interpretation of parameter estimates.

Between-subject differences were included as random effects. In order to understand the source of between-person differences in the trial dynamics of alpha and theta power, we included measures of structural integrity for regions of interest, namely cortical thickness of the IFG and HC volume as a between-person fixed effect (continuous predictor, z-scored across the whole sample of younger and older adults). Alpha power modulations have previously been related to the IFG, whereas theta power modulations have been linked to the HC (Hanslmayr et al., 2011). We therefore allowed IFG cortical thickness to interact with single trial alpha power and HC volume to interact with single trial theta power. As we were interested in age differences in SME as well as structure–function relationships, we included age group as a fixed effect and allowed for its interaction.

**(Equation) accuracy ~ alpha x IFG x age + theta x HC x age + (1| subject)**

We used maximum likelihood with an Adaptive Gauss-Hermite Quadrature (nAGQ = 10) to estimate model parameters as implemented in the lme4 package (Bates et al., 2015) in R 3.5.2 (R Development Core Team, 2018). We report model parameter estimates with standard errors, z-values, and p-values in Table 1.

## Results

Age Differences in Behavior

*Age Differences in Overall Learning Success:* In the final recall test on 440 scene–word pairs for younger and 280 scene–word pairs for older adults, young adults showed higher memory performance than did older adults (*M (SD)* = 0.57 (0.20) vs. *M (SD)* = 0.44 (0.22), *W* = 1608, *p* = 0.00*).* However, given the large number of study pairs, performance was in a good range and close to the mean level performance of 0.5 in both age groups, thus providing a sufficient number of trials for subsequent memory analyses.

*Age Differences in Learning Gain in the Last Restudy Phase:* In the current study we focussed on the successful learning of scene–word pairs in the last restudy phase. Therefore, we only chose pairs that had not been learned during previous study phases, but were acquired during the last restudy phase (as indicated by successful recall during the final cued recall). We compared them to pairs that were not recalled at any point during the learning procedure. The learning gain in the last restudy phase was higher in younger (*M(SD)* = 0.51 (0.19) than in older adults (*M(SD)* = 0.33 (0.18), *W* = 1791, *p*= 0.000). Thus, while young adults recalled about 50 % of the pairs they did not remember in the previous recall phase, older adults gained less from the restudy phase, despite having an additional opportunity to strengthen their mental image of each pair.

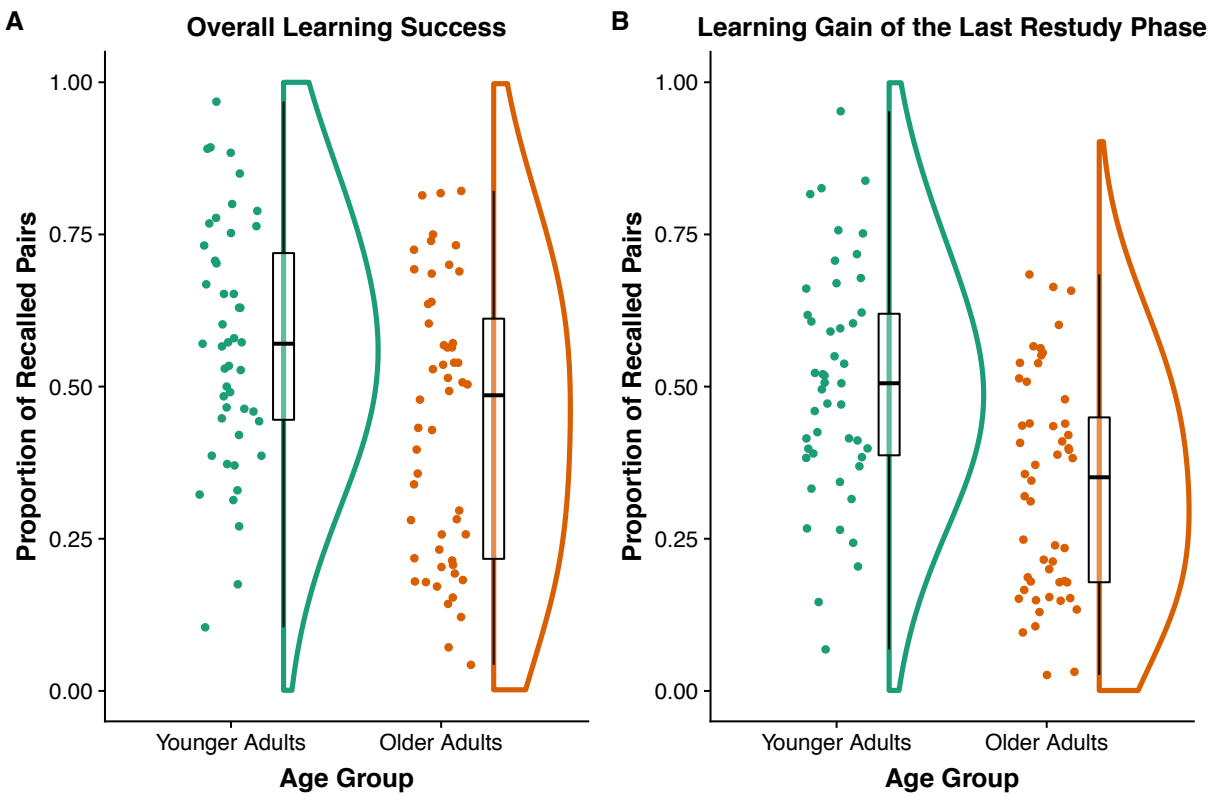


Figure 2. Participants repeatedly studied and recalled scene–word pairs. A. This panel shows their overall learning success as a proportion of recalled pairs at the end of the experiment. Younger adults are shown in green and older adults in red. Points represent individual participants, boxplots (median, first, and third quantiles) and violin plots illustrate the sample density. Mean performance levels are close to 0.5 for both age groups with large differences between participants. B. Learning gain of the last restudy phase (i.e., the proportion of recalled pairs in the final recall out of those pairs that had not been successfully remembered in any previous recall phase). Younger adults showed larger gains from restudy than older adults. This behavioral measure was taken as the basis for the subsequent memory analysis.

*Age Differences in Imagery Ratings*

To investigate whether older and younger adults differed in their subjective experience as to how well they were able to use the imagery strategy and whether ratings were modulated by subsequent memory, we compared imagery ratings for remembered and not-remembered pairs in younger and older adults (see Figure 3). Both age groups showed a

significant effect of subsequent memory on the imagery ratings with higher levels of ratings for subsequently remembered pairs (younger adults: remembered pairs *M (SD)* = 2.38 (.34) vs not-remembered pairs *M (SD)* = 2.05 (.32), *V* = 0, *p* = .00; older adults: remembered pairs *M (SD)* = 2.27 (.53) vs. not-remembered pairs *M (SD)* = 2.06 (.46), *V* = 246, *p* = .00). However, comparing the size of the modulation (computed as difference in mean ratings for remembered minus not-remembered trials), younger adults showed stronger modulations than did older adults (younger adults: *M (SD)* = .34 (.16) vs. older adults *M (SD)* = .21 (.38), *W* = 1792, *p* = .00).

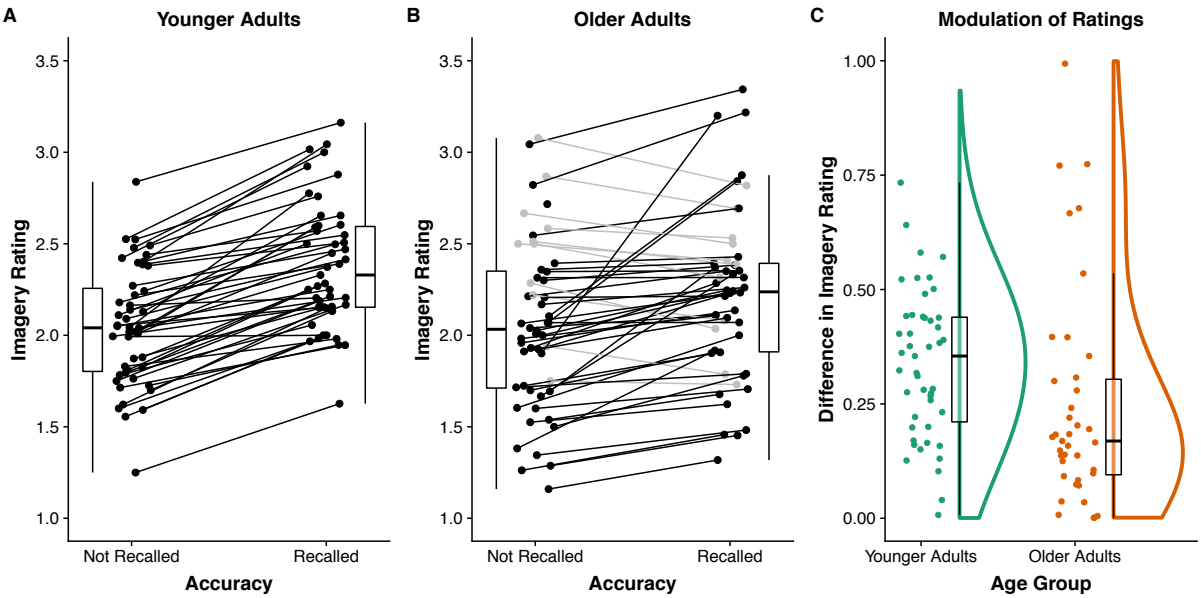


Figure 3. Both younger (A) and older adults' (B) subjective judgement of the quality of the imagery and elaboration process during encoding varies in accordance to later memory performance (A and B). Individual participants are represented by dots, paired measures are connected by lines. Participants displaying an effect in the expected direction (i.e., higher ratings for later remembered than for not-remembered pairs) are depicted in black, whereas participants with opposite patterns or no difference are depicted in gray. While the effect was present in all but one younger adult, a larger subsample of older adults did not show the effect. C. Comparing both samples, the modulatory effect was indeed stronger in younger than in older adults.

Age Differences in Measures of Structural Integrity

Overall, as shown in Figure 4, older adults showed lower (z-normed across the sample) IFG cortical thickness (*M (SD)* = -.92 (0.67)) than did younger adults (*M (SD)* = 0.67 (.65), $t(97) = 11.98$, $p = 0.00$). Hippocampal body volume (z-normed across the sample) was also reduced in older adults (*M (SD)* = -.40 (0.92)) relative to younger adults, (*M (SD)* = 0.32 (0.96), $t(97) = 3.78$, $p = 0.00$).

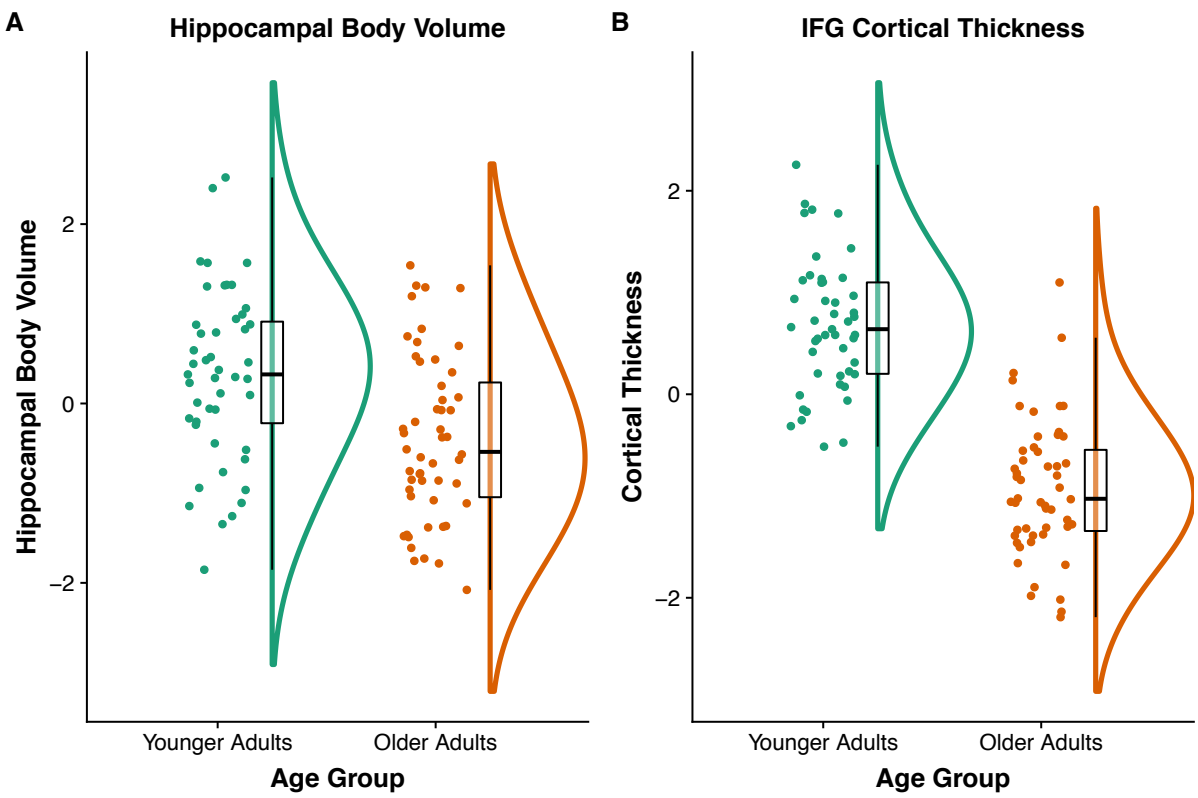


Figure 4. Hippocampal body volume (A) and cortical thickness of inferior frontal gyrus (IFG) (B) shown for each participant (indicated by individual points) together with boxplots and sample density, separated by age group. Older adults (red) show lower IFG cortical thickness and lower hippocampal volume than do younger adults (green).

Age Differences in EEG SME Effects

*Results of cluster-permutation corrected SME analysis on EEG data (averaged on the subject level)*

Trials that were remembered and trials that were not remembered during the final cued recall were averaged for each subject. To increase power to detect SME and to derive clusters that are similarly representative for the SME of all participants independent of their age group, grand averages were created by collapsing across age groups. Grand averages were used to determine time-frequency clusters that showed reliable differences between remembered and not-remembered trials on the group level. The cluster-based permutation tests yielded two significant ($p < .025$) clusters of electrodes (see Figure 5): One early cluster ($p = .01$) with a maximum around 500–800 ms that was predominantly found in low frequencies (2–6 Hz), and one later cluster ($p = .00$) with a maximum around 1000–2000ms encompassing alpha and beta frequencies (8–20 Hz). For ease of comprehension, we refer to the earlier cluster as SME in the theta band and to the later cluster as SME in the alpha/beta frequency band. Both effects displayed a very broad topography. The theta cluster displayed a mid-frontal maximum and the alpha/beta cluster, a centro-posterior maximum.

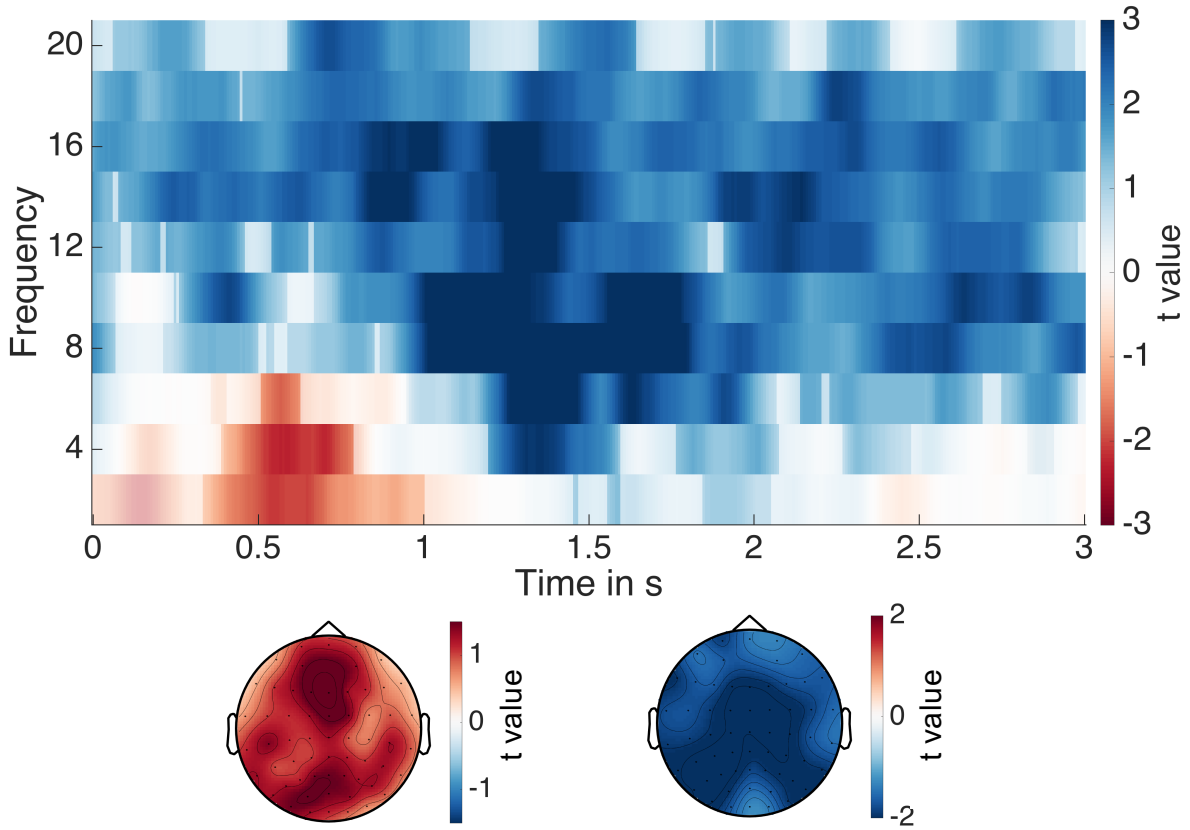


Figure 5. T-values for the comparison of subsequently remembered versus subsequently not-remembered pairs, averaged across electrodes and displayed with their respective

topographical distribution. Semi-transparent time-frequency samples are not part of any of the significant clusters. The data were collapsed across participants of both age groups for the derivation of the clusters.

*Single-Trial Statistical Analysis of EEG SME Effects*

To derive a deeper understanding of the theta and alpha/beta power SME, we extracted single-trial log-transformed power for each participant from both time-frequency-electrode clusters determined in the first step. The SME of the log-transformed and within-person z-transformed theta and alpha/beta power are shown in Figure 6. The effect was present in most participants (indicated by black lines).

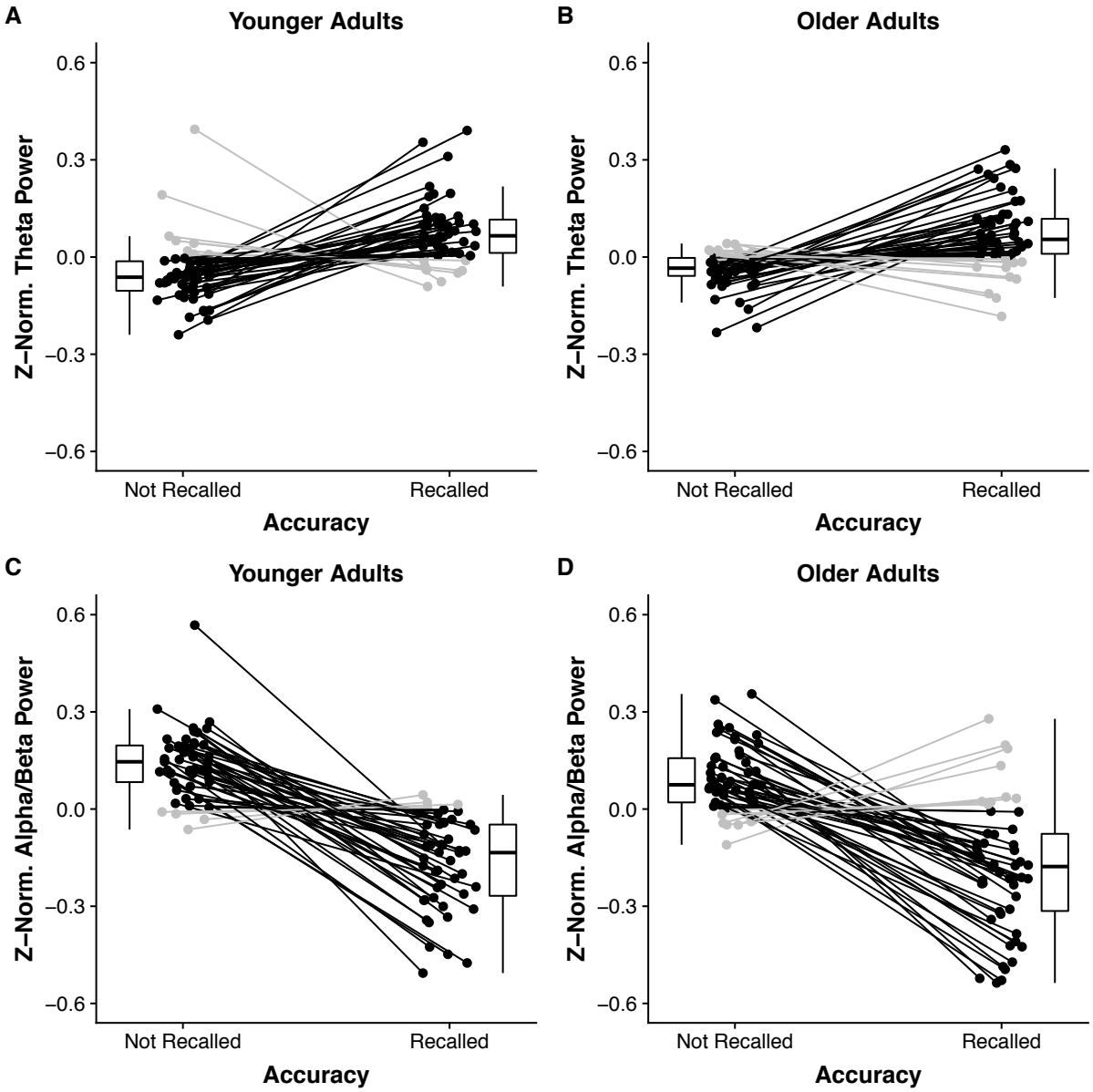


Figure 6. Within-subject modulation of theta power in younger and older (A and B, respectively) and of alpha/beta power (C and D) in accordance with subsequent memory. Within-subject z-normalized power was averaged for each participant separately for accurate and inaccurate trials. To display the within-subject effect, data points of individual participants are connected with lines. Participants displaying an effect in the expected direction (i.e, higher power for remembered than not-remembered pairs in theta frequency, and lower power for remembered than not-remembered pairs in alpha/beta frequencies) are depicted in black, whereas participants with opposite patterns or no difference are shown in gray. It is clearly visible that the expected SME were present in most participants in both age groups.

We entered single trial theta and alpha/beta power in a mixed-effects logistic regression to predict single-trial accuracy (correct / incorrect) together with measures of structural integrity of the two brain regions that have previously been related to oscillatory mechanisms of memory formation in the theta and alpha/beta frequency, namely HC and IFG. Thus, we added cortical thickness of IFG and HC body volume as between-person factors and allowed them to interact with the alpha and theta SME, respectively. Finally, we asked whether oscillatory SME and structure-function relationships would differ between age groups. We therefore included age group as an additional predictor in our model, allowing for interactions with all other predictors. The model had a conditional $R^2$ = 0.27, thus, our predictors accounted for 27 % of the variance in single-trial accuracy. All parameter estimates can be found in Table 1.

**Table 1: Parameter Estimates for the Mixed-Effects Model Including EEG-SME, Age Group and Measures of Structural Integrity as Predictors of Single-Trial Accuracy**

| | ESTIMATE | STD. ERROR | Z VALUE | PR(>\|Z\|) |
|---|---|---|---|---|
| (INTERCEPT) | 0.09 | 0.20 | 0.44 | 0.66 |
| **ALPHA** | **-0.28** | **0.03** | **-10.69** | **0.00** |
| IFG | -0.03 | 0.21 | -0.16 | 0.88 |
| **AGE=OA** | **-0.98** | **0.30** | **-3.21** | **0.00** |
| **THETA** | **0.16** | **0.02** | **8.03** | **0.00** |
| HC | -0.13 | 0.14 | -0.89 | 0.37 |
| **ALPHA:IFG** | **-0.07** | **0.03** | **-2.28** | **0.02** |
| ALPHA:AGE=OA | -0.06 | 0.05 | -1.14 | 0.25 |
| IFG:AGE=OA | -0.09 | 0.30 | -0.30 | 0.77 |
| THETA:HC | -0.03 | 0.02 | -1.60 | 0.11 |
| OA:THETA | -0.02 | 0.03 | -0.71 | 0.48 |
| OA:HC | 0.32 | 0.21 | 1.55 | 0.12 |
| ALPHA:IFG:AGE=OA | 0.03 | 0.05 | 0.60 | 0.55 |
| AGE=OA:THETA:HC | 0.04 | 0.03 | 1.29 | 0.20 |

Note. IFG = inferior frontal gyrus, HC = hippocampus, OA = older adults. Significant effects ($p$ < .05) are printed in boldface.

Single trial alpha/beta and theta power were robustly linked to performance (both $p$ = .00), with higher theta power and lower alpha/beta power yielding a higher likelihood for correct recall. Importantly, although age group as a fixed effect was a strong predictor of performance ($p$ = .00), consistent with the behavioral results reported above, age did not interact with any of the other predictors. These results suggest that SME in alpha/beta and theta power were similar across age groups. To further illustrate the similarity between younger and older adults with regard to these within-subjects power modulations, we displayed the predicted probabilities separately for younger and older adults in Figure 7.

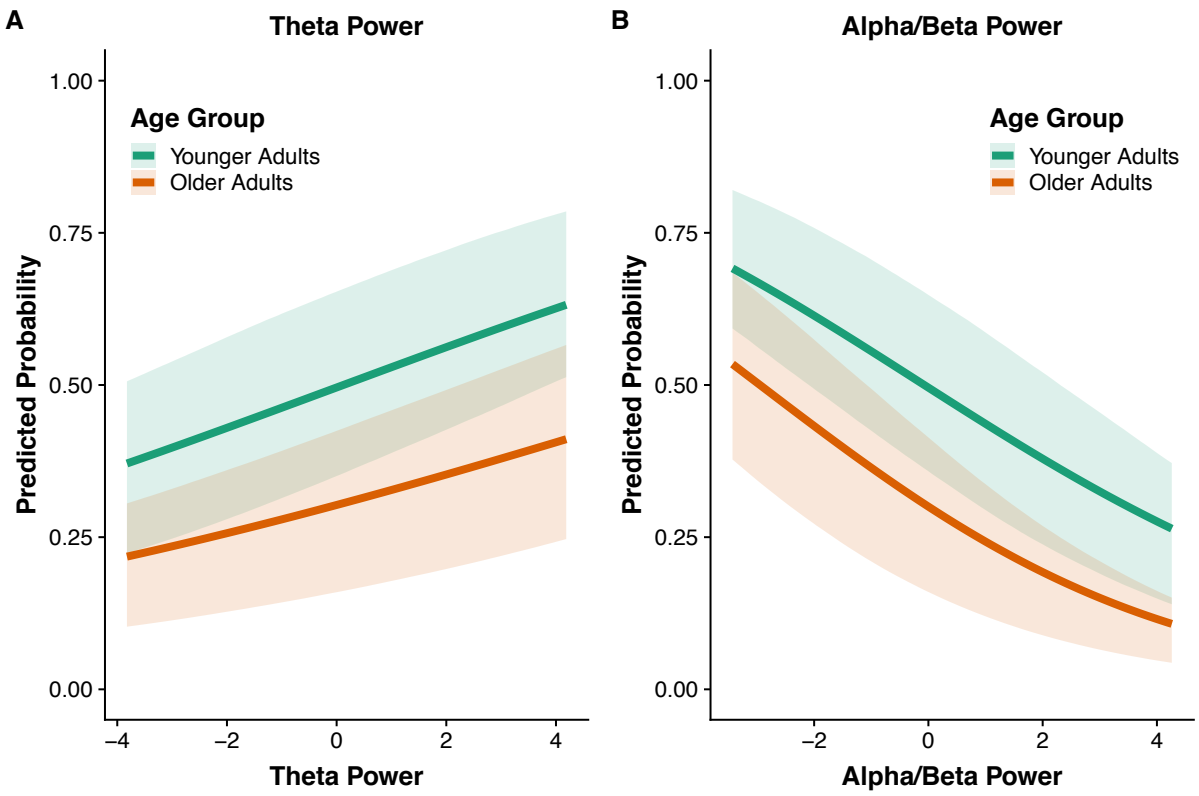


Figure 7. Main effects of theta (A) and alpha/beta (B) power on the predicted probability of recall. While the mixed-effects model showed a main effect of age group, there were no interactions with alpha/beta or theta power. Nevertheless, we display the predicted probabilities separated by age group to illustrate this point.

HC volume neither predicted accuracy ($p$ = .37) nor showed significant interactions with theta power ($p$ = .11). However, the effect of alpha power on the probability of

successful recall was modulated by IFG cortical thickness ($p$ = .02). Accordingly, for participants with lower cortical thickness, modulations in alpha power less reliably predicted subsequent memory performance (see Figure 8). Importantly, this structure–function relationship did not differ by age group ($p$ = .55), underscoring that general mechanisms of memory formation as well as the factors underlying interindividual differences in memory performance remain unchanged in older adults. Nevertheless, given the above reported age differences in structural integrity of the IFG, most participants of the lower quantiles happen to be older adults and thus have a higher probability for a less reliable relation between alpha power modulations and subsequent memory performance (as displayed in Figure 8).

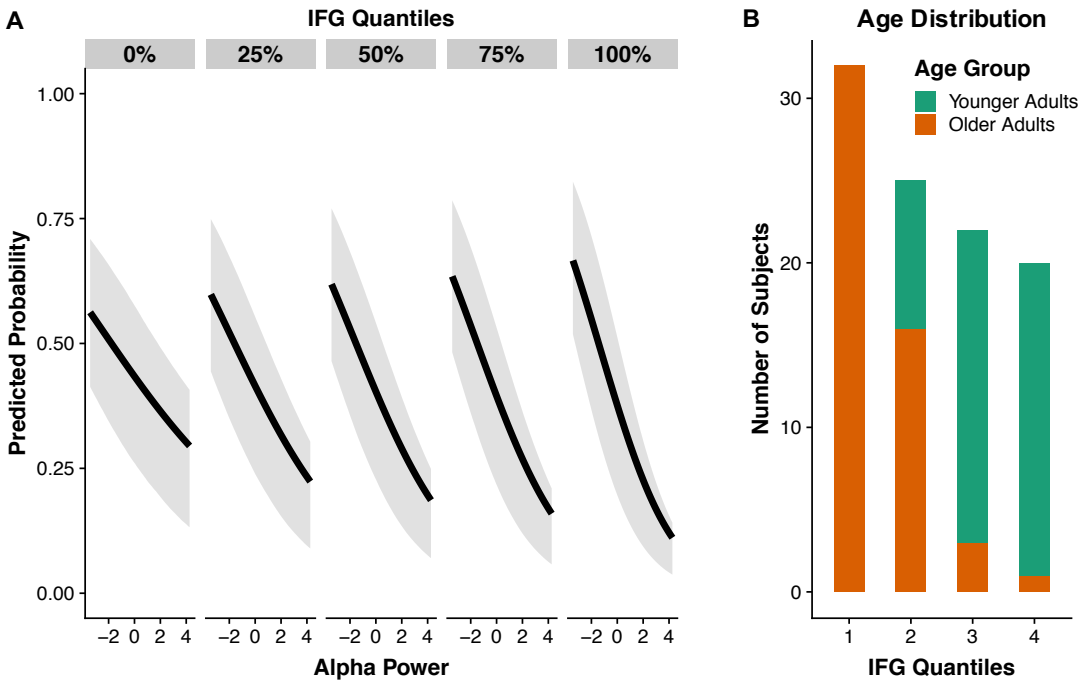


Figure 8. A. The effect of alpha power on predicted probability of successful recall is modulated by IFG cortical thickness, as shown by displaying predicted probabilities of varying alpha power for different IFG quantiles. For participants with lower cortical thickness, modulations in alpha power less reliably predicted subsequent memory performance. B. Distribution of older and younger adults across different levels of structural integrity of the inferior frontal gyrus (IFG) (represented by quantiles).

## Discussion

We set out to investigate SME in oscillatory activity in young and older adults and their relation to between-person differences in structural integrity of key brain regions for memory formation.

We found that single-trial alpha/beta and theta power were reliable predictors of memory success or failure in a cued-recall task in both younger and older adults, indicating that general mechanisms of memory formation do not change with age. We then examined whether differences in the structural integrity of the IFG, a brain region closely linked to elaborative processes during encoding, and the HC, a brain region relevant for the binding of information into a coherent memory representation, could explain between-person differences in oscillatory mechanisms of memory formation in the alpha/beta and theta band, respectively. We found that cortical thickness of the IFG was related to SME in the alpha/beta band. For participants with a greater cortical thickness of the IFG, a difference in alpha power was a better predictor of subsequent memory performance than for participants with lower cortical thickness. In contrast to our hypothesis, we did not observe effects of HC volume on oscillatory dynamics in the theta band. Importantly, while we observed overall age differences in memory accuracy as well as in the structural integrity of the IFG and the HC, we did not find an age-differential effect for the observed structure–function relationship between alpha power and cortical thickness of the IFG. However, older adults were more frequently represented among the participants with low cortical thickness and consequently weaker SME in the alpha band. Thus, our results suggest that differences in the structural integrity of the IFG are the basis not only for interindividual, but also for age differences in memory formation.

### Contributions of structural integrity to oscillatory mechanisms of successful memory formation

Episodic memory formation is tightly linked to interactions between MTL regions that bind incoming information into coherent representations and PFC regions that select and

elaborate these representations (Shing et al., 2010; Simons & Spiers, 2003). These two systems show opposing oscillatory behavior – synchronization in the theta band mediates binding (Staudigl & Hanslmayr, 2013) whereas desynchronization in the alpha band supports successful memory elaboration (Hanslmayr, Staresina, & Bowman, 2016).

We observed reliable SME in the theta band with increased power for scene–word pairs that were later successfully remembered compared to those that were not remembered. Our finding is in line with studies using intracranial recordings that found theta power increases during successful encoding in the HC (Lin et al., 2017; for similar results see also Lega, Jacobs, & Kahana, 2012; Sederberg, Kahana, Howard, Donner, & Madsen, 2003). Similarly, SME in the theta band were previously observed in young adults with their source being located to the HC (Hanslmayr et al., 2011). These findings support the idea that the HC plays a critical role for episodic memory formation via the integration of multiple features into coherent memory traces. This assumption was further underlined by a recent magnetoencephalography (MEG) study (Staudigl & Hanslmayr, 2013) that found theta–gamma coupling in the MTL during item–context binding in episodic memory. Based on these previous findings, we therefore hypothesized that interindividual differences in the structural integrity of the HC modulate SME in the theta band. However, we did not find strong evidence for this assumption. Since our conclusions are based on EEG scalp recordings, it is possible that the observed effects in the theta frequency do not directly capture HC activity, but rather reflect HC-frontal interactions during encoding (for review, see Klimesch, 1999; Nyhus & Curran, 2010). It is therefore possible that HC volume alone is not a good predictor for (EEG-) theta power modulations.

In contrast to the observed *increases* in power in the theta frequency range, we observed reliable alpha/beta power *reductions* for scene–word pairs that were successfully remembered as compared to those that were not remembered. Reduced alpha power for items later remembered has previously been found in in EEG studies using young adult samples (Fellner, Bäuml, & Hanslmayr, 2013; Noh, Herzmann, Curran, & De Sa, 2014). The observation of reduced alpha power for successful memory formation is in line with recent

theoretical accounts (Hanslmayr, Staresina, & Bowman, 2016; Hanslmayr et al., 2012) suggesting that information processing capacity can be increased within local cell assemblies via a decrease in local synchronization. Thus, long time windows of desynchronization in the alpha/beta frequency range may indicate prolonged elaborative encoding that in turn facilitates episodic memory success. In our study, participants were instructed to use an imagery strategy during encoding that indeed aimed to foster such deep elaboration of the presented scene–word pair. In line with electrophysiological SME, imagery ratings also differed according to subsequent accuracy: Recalled pairs received higher imagery ratings in both age groups, underlining that deep elaboration is crucial for memory formation (Craik & Lockhart, 1972; Craik & Rose, 2012). This assumption is further supported by our finding that the structural integrity of the IFG modulated the contribution of alpha power to successful memory performance. While a previous EEG-MRI study demonstrated that beta power decreases correlated with increases in the BOLD signal in the left IFG on a trial-by-trial basis (Hanslmayr et al., 2011), our study is the first to show that *structural* integrity of this region is crucial for the modulatory effects of alpha power on successful memory formation.

No age-related changes in neural mechanisms of memory formation?

Importantly, we found that in older adults, similarly to younger adults, successful memory encoding was accompanied by reliable modulations of theta and alpha/beta power. Put differently, SME were not modulated by age, despite overall age differences in performance, indicating that the general mechanisms of memory formation do not differ between age groups. In addition, the observed structure–function relationship between IFG and alpha with its effect on memory performance did not differ by age group, despite overall age differences in cortical thickness of the IFG.

Our results are in line with previous fMRI studies (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2016; De Chastelaine, Wang, Minton, Muftuler, & Rugg, 2011; Shing, Brehmer, Heekeren, Bäckman, & Lindenberger, 2016) that observed robust SME in the IFG and the HC in both younger and older adults. Similarly, a recent meta-analysis of the subsequent memory paradigm in age-comparative settings (Maillet & Rajah, 2014) came to

the conclusion that MTL and IFG are among those brain regions that show age-invariant patterns of SME, at least with regard to fMRI.

To the best of our knowledge, there is only one unpublished study that investigated oscillatory SME in younger and older adults (Strunk & Duarte, 2018). Similar to our results, they found SME in alpha/beta and theta frequency that did not differ by age group. Importantly, in contrast to their study, which used recognition memory, we used cued recall to test successful memory formation. This procedure has clear advantages over recognition tasks in which hits that were committed with high confidence are frequently contrasted with low confidence hits collapsed together with misses (Strunk & Duarte, 2018). Whereas recalling an associate in a cued recall task is a clear indication of recollection, hits in recognition tasks do not only rely on recollection, but also on familiarity, which is only partly taken into account by counting low-confidence hits as forgotten. Furthermore, the reliance on confidence ratings can be particularly problematic in age-comparative settings, as metacognitive differences between younger and older adults may affect the subsequent memory analysis (e.g., older adults appear to commit false alarms with high confidence, see Fandakova, Shing, & Lindenberger, 2013; Shing, Werkle-Bergner, Li, & Lindenberger, 2009). In addition, in our study, participants were instructed to use an imagery strategy that explicitly aimed to foster associative and elaborative processing. Indeed, like younger adults, older adults' subjective judgement of elaboration success also varied with subsequent memory performance. By using an intentional encoding task that fostered elaborative processing, we thus may indeed have successfully induced effective encoding strategies to improve episodic memory performance in older adults, which then manifest as age-invariant mechanisms of memory formation.

At the same time, as expected, older adults' memory performance was overall significantly lower than younger adults' performance. How can age-invariant mechanisms of memory formation be reconciled with the well-known general age differences in memory performance? First, it is notable that there were reliable age differences in structural integrity in IFG and HC, in line with previous reports on differences in volume and cortical thickness in

these brain regions (Raz & Rodrigue, 2006). Structural age-related changes in these regions have previously been linked to episodic memory performance and are seen to underlie functional activation differences between younger and older adults (for a review, see Nyberg, 2017). Our results support this view by revealing the contribution of structural integrity of the IFG to interindividual differences in memory formation, independent of age. In addition, we observed a modulatory effect of the IFG for SME in the alpha/beta band, indicating an age-invariant structure–function relationship. However, the participants with low cortical thickness were mostly older adults and consequently, power modulations in the alpha/beta band were also less predictive for subsequent memory performance in these older adults. An altered slope of the alpha power function is in line with the prominent hypothesis of an overall noisier system in older adults (Li, 2000) that has far-reaching consequences for performance (Garrett et al., 2013).

To conclude, our results support the assumption that oscillatory mechanisms of successful memory formation do not generally change with age. At the same time age-related differences in structural brain integrity contribute to the decline of episodic memory performance in older adults. Our findings support the notion that the maintenance of structural integrity goes hand in hand with the maintenance of youth-like mechanisms of memory formation in older adults (Fandakova, Lindenberger, & Shing, 2015; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012; Nyberg & Pudas, 2019).

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