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Age-related impairment of semantic integration into long-term memory is related to theta-alpha and low beta oscillations

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Abstract

Long-term memory encoding is impaired in healthy aging but the underlying mechanisms in humans remain unclear. Here, we tested whether this relates to failures in associating information with previous memories to build multi-item representations. To gain insight into age-related differences in such neural mechanisms during online encoding, we employed the temporal precision of electroencephalography to examine how semantic integration during encoding is affected by healthy aging. As expected, we found that congruent matches improved subsequent recognition memory in younger adults (i.e. congruency effect) but this effect was reduced in the elderly. At the neural level, congruence caused changes in neural activity within ~1500 ms after stimulus presentation, and there were widespread differences in ERPs and alpha-beta oscillations (8-30 Hz), which are known to support semantic processing. Importantly, these ERP differences predicted increases in memory performance, especially for congruent items. Finally, age-related differences in memory were accompanied by an early positive ERP and a later decrease in theta-alpha and low beta power (5-13 Hz), during encoding, which were greater in the younger group. Our findings provide evidence that age-related memory impairments can be explained by deficits in online semantic integration, depending on theta-alpha and low beta oscillations.

Key words: aging, brain oscillations, congruence, EEG, semantic memory

Significance statement

Memory impairments are a hallmark of healthy aging, but the underlying neural mechanisms in humans still remain unclear. We investigated how age-related memory deficits relate to failures during online encoding in associating information with previous memories. The results provide direct evidence that age-related memory impairments can be explained by deficits in online semantic integration within ~1500 ms after stimulus presentation, depending on theta-alpha and low beta neural oscillations (5-13 Hz). As such, our work gives new insights into the functional role of theta-alpha and low beta oscillations as well as into the physiological basis of memory impairments during healthy aging.

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Introduction

The decline of long-term memory is a hallmark of healthy aging (e.g. Hedden & Gabrieli, 2004). One understudied explanation is based on the associative-binding hypothesis (Naveh-Benjamin, 2000), which highlights the importance of association processes for successful multi-item memory formation (Craik and Byrd, 1982; Chalfonte and Johnson, 1996; Bayen et al., 2000; Castel and Craik, 2003; Old and Naveh-Benjamin, 2008). While evidence suggests age-related encoding deficits for integrated representations (Kilb and Naveh-Benjamin, 2007), the underlying neural mechanisms remain unclear.

Memories including stimuli and associated information are a key aspect of recollection, as opposed to familiarity (Diana et al., 2007; Eichenbaum et al., 2007). Different parts of the medial temporal lobe are involved (Diana et al., 2007) and recollection is more strongly affected by age (Nyberg et al., 2012). Furthermore, declarative memory performance is enhanced when additional information helps form an integrated unit, especially with congruent information (Schulman, 1974; Craik and Tulving, 1975; Hall and Geis, 1980; Kapur et al., 1994; Tse et al., 2007, 2011). Associating contextual information and previous knowledge from semantic memory into well-integrated units is thus critical for successful encoding.

Post-stimulus ERP differences around 200-600 ms, typically maximal at centro-parietal electrodes (N400), reflect how stimulus-driven activity enters into synchrony with a broad network shaped by recent and long-term experiences (Kutas and Federmeier, 2011). The state of semantic memory encountered by stimuli is modulated by factors that affect earlier input or the configuration of activity in memory, thus determining memory integration (Federmeier and Laszlo, 2009). How semantic congruence modulates the encoding of integrated representations is reflected by an early post-stimulus positive ERP (Packard et al., 2016; Sans-Dublanc et al., 2017; Varga and Bauer, 2017). Age-related decreases in ERPs associated with semantic congruence reflect an age-related deterioration in integration mechanisms (Kutas and Iragui, 1998; Wlotko et al., 2010; Huang et al., 2012) causing declines in encoding (Friedman et al., 1996; Glisky et al., 2001; Logan et al., 2002; Daselaar et al., 2003; Kamp and Zimmer, 2015).

Beta oscillations support the maintenance of events necessary for integrated memory encoding (Morton and Polyn, 2017). In addition, alpha-beta (8-30 Hz) oscillations underlie encoding, possibly reflecting an increase in information (Hanslmayr et al., 2012; Hanslmayr and Staudigl, 2014), or controlled access to matching information in semantic memory (Klimesch, 2012). In general terms, theta (4-8 Hz) and alpha (8-13 Hz) oscillations closely relate to memory performance (Klimesch, 1999), and age-related changes lead to memory deficiencies (Lithfous et al., 2015). Theta-alpha oscillations support the binding of information across large-scale networks (Fuentemilla et al., 2014; Herweg et al., 2016). Finally, theta oscillations are involved in integrative encoding (Sans-Dublanc et al., 2017), and may mediate the positive semantic congruence effect for episodic memories and explain age-related declines (Crespo-Garcia et al., 2010, 2012; Atienza et al., 2011).

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Here, we investigated the neural mechanisms involved in the age-related decline of the ability to encode integrated representations. We used EEG to track online dynamics, in younger and older adults, while highlighting differences in encoding mechanisms by manipulating the congruence matching of the event with a previous semantic cue. Because integrative encoding is sensible to semantic congruence, age-related decline was expected to be especially apparent during congruent memory encoding. Early differences in post-stimulus ERPs and theta, alpha and possibly beta oscillations during the online encoding of the event were expected to reflect the age-related decline in memory performance. We implemented an adapted word list paradigm from a previous study (Packard et al., 2016), in which a strong memory enhancement was found for congruent words, with a corresponding early appearing ERP during encoding. Participants were presented with a series of word pairs: the first word was a semantic category designed to preactivate specific semantic memory networks. The second word was an item either congruent or incongruent with the previous category. Subjects classified the second word as either congruent or incongruent with the first and were tested shortly afterwards with a recognition test.

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Materials and Methods

Participants

Thirty young participants (ages 19-33 years, mean 23.87; SD 3.53, 14 males) and twenty-eight healthy elderly participants (ages 50-79 years, mean 62.55; SD 7.02, 13 males) were recruited for the behavioral experiment (experiment 1). Subsequently, twenty-three young participants (ages 18-28 years, mean 20.95; SD 3.23, 11 males) and twenty-five healthy elderly participants (ages 52-79 years, mean 63.21; SD 5.82, 11 males) were recruited for the EEG experiment (experiment 2). Participants were right-handed, had normal or corrected-to-normal vision (including color-vision) and reported no history of neurological or psychiatric disorders, or current medical problems (excluding blood pressure). All elderly participants scored a 23 or higher (mean 26.45 SD 0.94) on the Montreal Cognitive Assessment (MoCA, version 24). This study and the protocol were carried out in accordance with the recommendations and approval of the local ethics committee (University of Lübeck). Each subject understood the protocol and gave written informed consent in accordance with the Declaration of Helsinki.

Materials

Experimental stimuli consisted of 72 categorical 6 word lists (Packard et al., 2016) translated into German, selected from category norms (Battig and Montague, 1969; Yoon et al., 2004; Kim and Cabeza, 2007a). Each list consisted of the 6 most typical instances (e.g., cow, pig, horse, chicken, sheep, and goat) of a natural/artificial category (e.g., farm animal). All of the 396 typical instances, belonging to the 72 semantic categories, were presented in separate encoding trials, each time preceded by the corresponding category (semantic cue). Additionally, semantically unrelated words were used as control words (new words) in the test phase.

Behavioral procedures

We implemented an adaptation of an experimental paradigm used in a previous EEG study (Packard et al., 2017) itself adapted from previous paradigms (Roediger and McDermott, 1995; Kim and Cabeza, 2007a, 2007b). In the paradigm used here, participants preactivate specific semantic memory networks before words are presented. Thus, the cueing of a semantic network favors the incorporation of the associated word item into a context with congruent or incongruent semantic unfolding. The study phase consisted of the presentation of 396 separate one word encoding trials, presented mixed in random order. Participants were informed that, after this first phase, there would be a recognition memory test. They observed the screen from a distance of 50 cm on a display with a diagonal of 62 cm. Arial letter type, 36 letter size was used.

Each trial started with the appearance of a fixation cross on the screen for a random duration of 2000–3000 ms. Subsequently, a category name in blue appeared on a white background for 1500 ms. After the cue

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disappeared, a fixation cross appeared for 2000 ms. Participants were then sequentially shown the subsequent word in green for 1000 ms. In the congruent condition, the subsequent word belonged to the semantic category (Craik and Tulving, 1975), for example, 'colors' followed by 'blue'; or 'furniture' followed by 'desk'. In the incongruent condition, the category name did not correspond to the subsequent word, for example 'planets' followed by 'cottage'; or 'continents' followed by 'oxygen'. While the second word was shown, the participants pressed a button on the mouse indicating whether the word was congruent (left click) or incongruent (right click) with the semantic category indicated at the beginning of the trial. Participants were instructed to respond as quickly and correctly as possible.

There were 216 congruent-list trials and 216 incongruent-list trials. Together, the study phase lasted 50 min. At the end of this phase, subjects were presented with a distraction task in which they solved simple arithmetical problems (additions and subtractions). The distraction task ensured the participants would not rehearse the words they had previously seen. The distraction task lasted 5 min, which together with the explanations for it and the subsequent recognition test made for a total time interval of 10 min between encoding and the subsequent test. Considering that the retention interval between encoding and test was only 10 min, the paradigm was thus designed to capture only the encoding component and not the consolidation-dependent processes underlying the semantic congruence (schema) effect.

Included in the recognition test were a total of 396 Old-word (all items presented at encoding) and 396 New-word trials. The trials were presented in a pseudorandom order for each participant, thus directly avoiding any possible confounds due to order during the test. Words in the Old and New categories were predetermined and the same for all participants. Each of the 792 trials started with a fixation cross in the screen center (1500 ms). All words in the recognition phase were displayed in the middle of the screen, in green and same font and size as the study phase, each for 4000 ms. After each word, subjects responded by pressing one of 4 keys according to whether the word was judged to be "sure old," "unsure old," "unsure new," or "sure new." The scale graduations were color-coded on the keyboard. Participants were instructed to respond within 4000 ms. Every 50 trials the participants could take a short break. The test phase had a duration of 60 min approx.

Statistical analyses of memory results

ANOVAs (IBM SPPS Statistics 22), with encoding condition (two levels: Congruent vs Incongruent) as a within-subject factor was performed on the rate of responses. For all analyses, α was set at 0.05. To estimate effect sizes, we used η^2 and Cohen's *d* as appropriate. In the case of a participant judging a word sequence during encoding differently than we had predesigned, the sequence was not included. Participants subjective congruence ratings almost always coincided with our experimental design (94 %). We ran one-sample t tests [accuracy = hit rate/(hit rate + false alarm rate)] (Urgolites et al., 2015) to test whether hit rates for each category (congruent, incongruent) for all groups were greater than chance (i.e., 0.50, see **Table 1**). Given that elderly subjects are more vulnerable to making high-confidence errors (Dodson et al., 2007; Chua et al., 2009; Shing et al., 2009), we specifically ran the tests including only high-confidence responses.

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EEG analysis – experiment 2

During encoding, electroencephalographic (EEG) activity was acquired with an Easy Cap system by BrainProducts with 32 standard active electrodes. For detecting vertical and horizontal eye movement (VEOG / HEOG), 4 electrodes were used. Impedances were maintained under 20 kΩ. FCz served as reference and AFz as ground electrode. The sampling rate was at 500 Hz with online high-pass (0.1 Hz) and low-pass (240 Hz) filters. EEGLAB (version 13; Delorme and Makeig, 2004) and customized MATLAB version 2016b (The MathWorks; RRID:SCR_006826) tools were used for preprocessing the EEG data offline. First, data were high-pass (0.5 Hz) and low-pass (35 Hz) filtered. Second, all trials of the encoding phase were epoched and down sampled to 250 Hz. Subsequently, major atypical artifacts, trials with amplifier saturation, and bad channels were visually identified. Blinks and eye movement artifacts were removed with independent component analysis (ICA; Delorme and Makeig, 2004). Finally, bad channels were interpolated (maximum one single channel for each subject). Oz was selected to re-reference the data, as re-referencing to average can mask the effects of EEG differences with a broad distribution across the scalp (Luck, 2005), such as we expected following previous experiments (Packard et al., 2016).

EEG trials with a shift exceeding 100 μV were rejected offline. There were two separate conditions, 'Congruent' (109-182 trials per subject; mean 148.29), and 'Incongruent' (97-181 trials per subject; mean 145.38). Three young subjects and one elderly subject were excluded from the analysis due to excessively noisy data or being a low performing outlier. Fieldtrip (Oostenveld et al., 2010) and customized MATLAB scripts were used for statistical data analysis. Here, ERPs during the encoding were studied by extracting event-locked EEG epochs of 1600 ms, ending 1500 ms after stimulus onset, with the 100 ms prior to stimulus onset used for the baseline.

To detect reliable differences between the ERPs during encoding, the conditions were contrasted using Fieldtrip via a two-tailed non-parametric cluster-based permutation test (Maris and Oostenveld, 2007). All time points between 50 ms and 1500 ms at 27 scalp electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, O2) were included in the test. Time points before 50 ms were too early to be considered relevant for the test. For all contrasts, a *t* test was performed for each sample (channel, frequency, time). For each permutation, all t scores corresponding to uncorrected *p* values of 0.05 were formed into clusters. The sum of the t scores in each cluster is the 'mass' of that cluster and the most extreme cluster mass in each of the sets of tests was recorded and used to estimate the distribution of the null hypothesis. The Monte Carlo estimate was calculated by running random permutations of the condition labels (n = 1000) and comparing the cluster statistics found in the real data with that found in the random data. The p-value is thus obtained with the proportion of cluster statistics in the random data exceeding that in the real data. Clusters were formed from significant samples ($p < 0.05$), considering only effects with minimum three significant neighboring channels based on triangulation.

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For the time-frequency analysis, we extracted event-locked EEG epochs of 4500 ms starting at 2000 ms before the presentation of the first word of the word list. Time-frequency decompositions were conducted from 2 Hz to 30 Hz, from 1000 ms before stimulus onset to 1500 ms after stimulus onset, using convolution on the single-trial time series with complex Morlet wavelets (4 cycles), with steps of 8 ms in the time and 0.22 Hz in the frequency domain. For each condition, power was averaged across trials. A 300 ms baseline correction was applied (from 500 ms before stimulus onset to 200 ms before stimulus onset). Non-parametric cluster-based permutation tests (Maris and Oostenveld, 2007), as described above, were conducted on the time-frequency from 50 ms to 1500 ms after word onset, from 2 Hz to 30 Hz.

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Results

Behavioral findings

Experiment 1

Main effects of congruence, and age, and a congruence by age interaction, for high-confidence CHR

The proportions of high-confidence 'Sure' responses during the recognition phase were analyzed (see Figure 1A). Again, a 2x2 ANOVA with the factors congruence and age revealed a significant main effect of congruence ($F_{(1,56)}$ = 515.45, p < 0.001, η_p^2 = 0.90), driven by higher corrected hit rates for congruent words (mean 0.64, SEM 0.02), than for incongruent words (mean 0.41, SEM 0.02). There was also a significant main effect of age ($F_{(1,56)}$ = 4.72, p = 0.034, η_p^2 = 0.08), with higher corrected hit rates for younger (mean 0.60, SEM 0.02), than for elderly subjects (mean 0.53, SEM 0.03). Importantly, a significant congruence by age interaction effect was also revealed ($F_{(1,56)}$ = 4.73, p = 0.034, η_p^2 = 0.08). Post-hoc t-tests showed that young subjects had higher congruent corrected hit-rates ($t_{(56)}$ = 2.63, p = 0.011, Cohen's d = 0.69). In contrast, there were no significant differences between incongruent hit rates between young and elderly subjects (p = .133).

Main effect of congruence for RT

For participants' reaction times during the encoding phase, we found a main effect of congruence ($F_{(1,56)}$ = 44.04, p < 0.001, η_p^2 = 0.44), participants were slower at identifying incongruent words (see Table 2). However, age did not reach significance level ($F_{(1,56)}$ = 2.29, p = 0.136, η_p^2 = 0.04), and there was no significant congruence by age interaction ($F_{(1,56)}$ = 0.62, p = 0.435, η_p^2 = 0.01).

Experiment 2

Main effect of congruence for high-confidence CHR

In experiment 2, the proportions of high-confidence 'Sure' responses during the recognition phase were analyzed, again, in a 2x2 ANOVA (see Figure 1B). This analysis only showed a significant main effect for congruence ($F_{(1,46)}$ = 292.01, p < 0.001, η_p^2 = 0.86) with higher corrected hit rates for congruent words (mean 0.57, SEM 0.02), than for incongruent words (mean 0.34, SEM 0.03). In contrast to the behavioral experiment (Experiment 1), there was no main effect of age ($F_{(1,46)}$ = 0.075, p = 0.785, η_p^2 < 0.01), and no congruence by age interaction effect ($F_{(1,46)}$ = 1.39, p = 0.244, η_p^2 = 0.03).

Main effect of congruence for RT

For participants' reaction times during the encoding phase, there was a main effect of congruence ($F_{(1,46)}$ = 22.42, p < 0.001, η_p^2 = 0.33), participants were slower at identifying incongruent words (see Table 2). However, age did not quite reach significance level ($F_{(1,46)}$ = 3.59, p = 0.06, η_p^2 = 0.07), and there was no significant congruence by age interaction ($F_{(1,46)}$ = 1.02, p = 0.319, η_p^2 = 0.02). This result on reaction times replicated the results of the behavioral experiment and is in line with the recognition memory performance (i.e. no age effect and no interaction).

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Analysis of both experiments

Main effect of congruence, experiment group, and a congruence by age interaction, for high-confidence CHR

A separate 2x2x2 ANOVA on high-confidence 'Sure' responses during the recognition phase, with congruence, age group, and experimental group as factors, including all the participants from both experiments, revealed a significant main effect of congruence ($F_{(1,102)} = 772.28$, $p < 0.001$, $\eta_p^2 = 0.88$); a marginal effect of age ($F_{(1,102)} = 3.00$, $p = 0.087$, $\eta_p^2 = 0.029$); and a main effect of experiment ($F_{(1,102)} = 7.39$, $p = 0.008$, $\eta_p^2 = 0.068$), with lower corrected hit rates in the EEG group (see Figure 1C). Importantly, there was a significant congruence by age interaction effect ($F_{(1,102)} = 5.24$, $p = 0.024$, $\eta_p^2 < 0.05$). This interaction was driven by a stronger congruence effect in the younger subjects as compared to the elderly. Specifically, post-hoc t-tests showed the young subjects had higher congruent high-confidence corrected hit-rates ($t_{(104)} = 2.47$, $p = 0.015$, Cohen's $d = 0.48$). In contrast, there were no significant differences between incongruent high-confidence hit rates between young and elderly subjects ($p = .261$). Finally, there were no other interactions between EEG group and age or congruence (all $p > 0.170$).

Main effect of congruence, and age, for RT

There was a main effect of congruence for participants' reaction times ($F_{(1,102)} = 63.37$, $p < 0.001$, $\eta_p^2 = 0.38$), participants were slower at identifying incongruent words (see Table 2). There was also a significant main effect of age ($F_{(1,102)} = 5.72$, $p = 0.019$, $\eta_p^2 = 0.05$), younger subjects were faster, but there was no significant congruence by age interaction ($F_{(1,102)} = 1.55$, $p = 0.216$, $\eta_p^2 = 0.02$). There was no significant main effect of EEG group ($F_{(1,102)} = 0.67$, $p = 0.796$, $\eta_p^2 = 0.1$), and no other interactions between EEG group and age or congruence (all $p > 0.129$).

EEG findings

ERPs

Cluster Analysis

Main effect of congruence, and a congruence by age interaction

A Monte Carlo cluster-based permutation test was performed on the data of young and elderly grouped together (see Table 3), from 50 ms to 1500 ms after word onset, which revealed a positive cluster due to congruence during encoding (congruent vs incongruent). Next, the effect of congruence between young and elderly was contrasted in the same way (congruent minus incongruent in young subjects vs congruent minus incongruent in elderly subjects), and significant differences in a positive cluster were found with a broad central topography (see Figure 2). As such, this activity pattern resembles the behavioral effects.

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Time-Frequency

Cluster Analysis

Main effect of congruence, and a congruence by age interaction

A Monte Carlo cluster-based permutation test was run on the time-frequency data of young and elderly grouped together (see Table 3), from 50 ms to 1500 ms after word onset, and from 2 to 30 Hz. It revealed significant differences due to congruence (congruent vs incongruent) in a negative cluster, with a broad central topography, approximately from 2-26 Hz at 50-1400 ms after stimulus onset (see Figure 3). In a next step, the differential effect of congruence between young and elderly was contrasted in the same way (congruent minus incongruent in young subjects vs congruent minus incongruent in elderly subjects). This analysis revealed significant differences (see Figure 4) in a negative cluster, with a broad central topography, approximately from 5-14 Hz at 700-1100 ms after stimulus onset. Again, this activity pattern mirrors the behavioral effect.

Behavioral EEG correlations

To investigate whether the advantage observed for congruent memories could be predicted from the neural correlates associated to the congruent condition, covering the entire time range of the congruence ERP cluster, from 320 ms to 1176 ms after word onset, a partial correlation test was run (see Figure 5). The effect of age on the relationship was controlled. The first variable in the correlation was the behavioral advantage for congruent memories (congruent high-confidence corrected hit rate minus incongruent high-confidence corrected hit rate). The second variable was the neural correlate associated to the congruent condition (Congruent ERP minus Incongruent ERP) measured at the central and parietal electrodes (C3, Cz, C4, CP5, CP1, CP2, CP6, P3, Pz, P4) that were found in the ERP cluster associated to congruence (Congruent ERP minus Incongruent ERP). A significant correlation was revealed ($r = .34$, $p = .017$). The greater the difference between the ERP in the congruent condition versus the incongruent condition across the central and parietal electrodes, the greater the difference between congruent high-confidence CHR and incongruent high-confidence CHR, across the participants from both age groups. When we tested for the same correlation across the fronto-central electrodes, it did not reach significance level ($p = 0.091$). There was no such relationship for the time-frequency data.

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Discussion

We investigated the underlying mechanisms of semantic integration of novel information into long-term memory. Our results demonstrate that semantic congruence drives long-term memory, but this effect is less pronounced in the elderly subjects. At the neural level, this observation was paralleled by age-related differences in post-stimulus neural activity, including large differences in ERP amplitude (see Figure 2) and differences in the relative power of brain oscillations in the theta-alpha and low beta range (see Figures 3-4). Importantly, ERP differences associated to congruent semantic matches across central and parietal electrodes predicted the increases in memory performance for congruent items across participants from both age groups (see Figure 5). Thus, our results show age-related deficits in semantic integration into long-term memory and they provide evidence for a role of ERPs and theta-alpha and low beta oscillations as underlying neural mechanisms.

Brain oscillations provide insight into semantic processes carried out during encoding (Hanslmayr and Staudigl, 2014). Alpha and beta power decreases during encoding, as in our study, may reflect successful encoding possibly due to their relation to semantic integration, which increases subsequent memory (Craik, 2002). At the neural level, such desynchronization may be associated to an increase of information processing capability within local cell assemblies (Hanslmayr et al., 2012). Beta oscillations have also been shown to be related to the maintenance of information about recent events that facilitates integrating inputs into a larger representation in memory (Morton and Polyn, 2017). More specifically, alpha-band oscillations have been posited to reflect the key process of selective access to long-term knowledge stores which allows the semantic orientation (Klimesch, 2012) that is necessary to form semantic matches. Our results suggest the elderly may have difficulties with such cognitive mechanisms and this impairs their memory performance.

Theta oscillations play a key role in the encoding and retrieval of episodic memories (Fell and Axmacher, 2011; Eckart and Bunzeck, 2013; Fuentemilla et al., 2014; Hasselmo and Stern, 2014; Herweg et al., 2016; Sans-Dublanc et al., 2017). In our study, theta power decreases were associated with processing congruent items, further suggesting a functional role of theta in semantic integration into long-term memory. While this is, generally speaking, in line with previous work, the direction of the effect is opposite to what has been reported recently (Crespo-Garcia et al., 2012). More precisely, Crespo-Garcia et al. (2012) could show increased theta power for semantically related face-location association, which, similar to our findings, changed depending on age. While there are several differences between both study designs (including stimulus material and task), this opposite pattern in theta activity is compatible with the view that neural oscillations during encoding depend on perceptual and cognitive processes of the encoding task and their relation to the subsequent memory test (Hanslmayr and Staudigl, 2014).

Changes in theta-alpha and low beta oscillations, which we observed over frontal brain regions (Figure 3), might also reflect inhibitory processes during semantic integration. Specifically, the “schema-linked interactions

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between medial prefrontal and temporal regions" (SLIMM) framework (van Kesteren 2012) suggests that the medial prefrontal cortex detects congruency with already existing neocortical information and, in this case, inhibits the medial temporal lobe which leads to more efficient cortical learning. Indeed, congruent items were associated with lower power as compared to incongruent items and this effect was reduced in the elderly (Figure 4) who, supposedly, have structurally and functionally impaired prefrontal cortices (Hedden and Gabrieli, 2004). Clearly, neural oscillations may not necessarily originate within the prefrontal cortex; therefore, future studies may address this more directly, for instance, by using combined EEG/fMRI, which would also allow to quantify structural changes in the prefrontal cortex and medial temporal lobe.

Finally, we would like to point out that, comparable to our findings, previous memory studies did not find differential effects for the theta and (low) alpha band questioning their functional dissociation during long-term memory processes (Herweg et al., 2016). While this could also represent a spill-over between neighboring frequency bands (due to the inherent limitations of time-frequency measurements), future studies will need to further examine this open question.

As expected and already described above, the congruence effect for high-confidence memory responses declined with age. However, this interaction was only significant across both experiments, and in the behavioral group by itself. In other words, in the EEG group by itself, such age-related differences in memory performance were not apparent. This may be due to the sample size (as supported by the analysis across experiment 1 and 2), or, alternatively, could relate to interindividual differences in the underlying mechanisms of encoding congruent information. Indeed, our correlation analysis shows that the congruence effect (i.e. improved memory) varies as a function of ERP congruence differences (see Figure 5). Interestingly, this correlation was significant across young and elderly subjects suggesting one underlying mechanism of congruence encoding that may continuously change with age and/or other associated factors such as learning strategies or structural brain integrity. However, this hypothesis needs to be addressed in a longitudinal study or a design that includes a more equally distributed age range across the life-span.

Our results support the idea that the elderly do not benefit as much from congruency as younger people, which is compatible with other studies emphasizing that congruence can aid elderly bind items together (Naveh-Benjamin et al., 2005; Patterson et al., 2009; Badham et al., 2012). Note however that there is a difference in the encoding task: whereas here the subjects engaged in a semantic encoding task in which they judged the congruence of the words (deep encoding), in these previous experiments the subjects did not. Indeed, the benefits of semantic congruence are known to be related to deep encoding processes involving semantic associations (Schulman, 1974; Craik and Tulving, 1975). As such, our results agree with the idea that age-related memory deficits are pronounced in tasks that require the use or creation of associations (Naveh-Benjamin, 2000), and that the congruent condition is (in younger subjects) associated with stronger memory benefits.

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We observed faster reaction times for the accurate classification of congruent words as compared to incongruent words (see Table 2). This effect appeared consistently across both age groups and is in line with previous studies (Neely et al., 1989). It can be explained with models assuming that top-down connections allow high-level contextual expectancies to affect perception by preparing the visual system before the stimulus even arrives, i.e., a pre-selection of possible congruent words in semantic memory (Graboi and Lisman, 2003). This suggests that incongruent stimuli are more difficult to process than congruent stimuli, which argues against the otherwise possible explanation that the congruent memory increase was due to additional effort or difficulty during encoding.

Semantic processing associated to congruent matching during encoding per se may lead to better memories (Craik, 2002; Tibon et al., 2017). However, there is increasing support for a basic congruence dependent neural mechanism associated to the integration of memories into long-term knowledge structures or schemas (Tse et al., 2011; van Kesteren et al., 2012, 2014; Buuren et al., 2014; Spalding et al., 2015; Gilboa and Marlatte, 2017; Liu et al., 2017; Robin and Moscovitch, 2017; van der Linden et al., 2017). According to this framework, the semantic congruence matching during online encoding may be an initial step in such a general schema-dependent process of memory integration which entails interactions between the medial temporal lobe and the prefrontal cortex that favor an efficient retention and a faster consolidation of congruent events. Schema-related memory theories also nicely complement theories which emphasize the anticipatory, constructive nature of cognition and memory (Engel et al., 2001; Bar, 2007, 2009). Recently, the idea of cognition as a constructive, active, and selective process has received increasing support and attention (Engel et al., 2001; Graboi and Lisman, 2003; Bar, 2007). According to this view, incoming information is linked to representations in memory that pre-activate associations, thus forming predictions and selectively facilitating cognition. Therefore, general knowledge stored in neural networks plays an important role in guiding the selection of the inputs that are meaningful according to goals; moreover, the process of generating predictions and searching for matches in the environment helps explain how the brain can make such efficient and fast computations while processing ongoing stimuli. The relevance of such theories in the field of memory is directly supported by our data showing that congruence drives subsequent long-term memory.

Taken together, the beneficial effect of semantic congruence on long-term memory is less pronounced in the elderly. An early positive ERP and a later decrease in theta-alpha and low beta power during online encoding accompanied these age-related differences suggesting a close link. Therefore, memory impairments during healthy aging can be explained by deficits in online semantic integration, which depends on neural oscillations within low to mid frequency bands.

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Figures

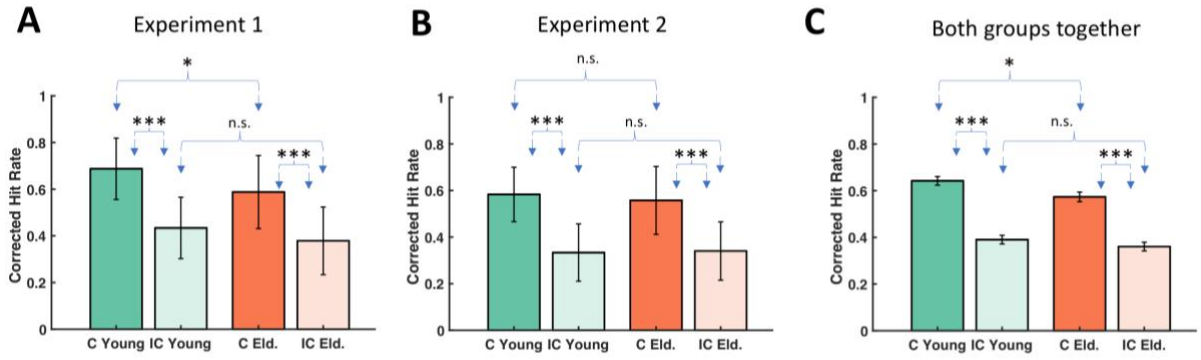

Figure 1. (A) Corrected Hit Rates for Experiment 1. All conditions were above chance level. There was a main effect of congruence, a main effect of age, and a congruence by age interaction. (B) Corrected Hit Rates for Experiment 2 responses. All conditions were above chance level. There was a main effect of congruence, but the effect of age and the congruence by age interaction were not significant. (C) Corrected Hit Rates for the both experiments together. All conditions were above chance level. There was a main effect of congruence, and a congruence by age interaction. The effect of age was not significant. *p < 0.05. *** *p* < 0.001. Error bars indicate SEM.

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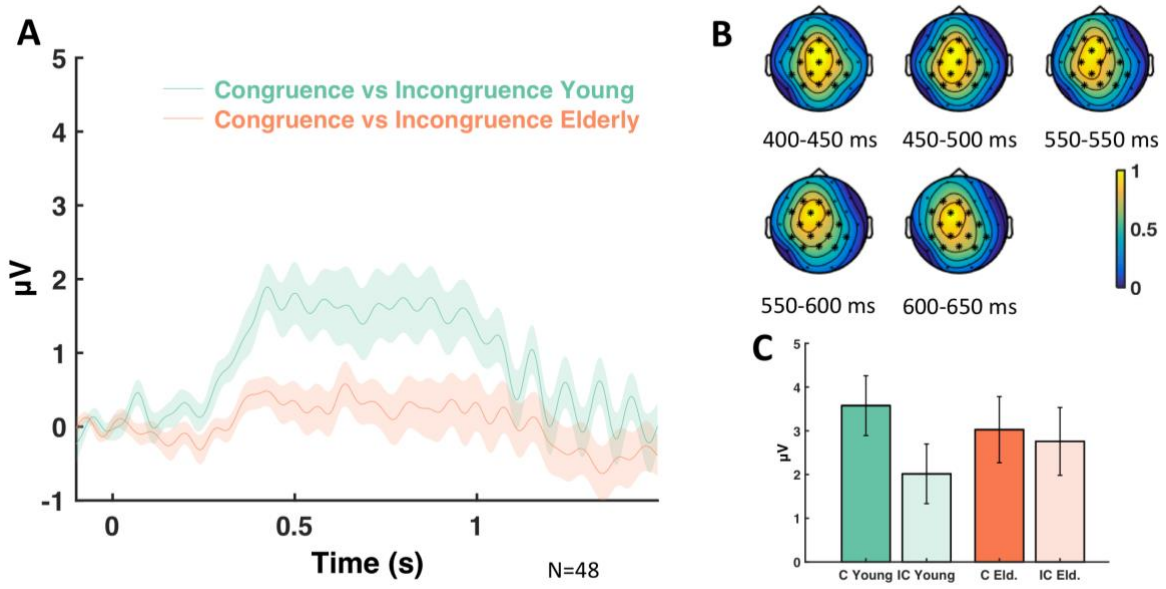

Figure 2. Congruence by Age ERP interaction. (A) Mean amplitude of the congruence by age ERP interaction across the significant electrodes found in the cluster. The time window of the significant differences detected in the cluster was from 404 to 604 ms. The difference wave of the congruent minus the incongruent condition in the young group was contrasted against the same difference wave in the elderly group, in the cluster analysis. For the figure, the mean was calculated from the grand averages across the 15 electrodes (F3, Fz, FC5, FC1, FC2, C3, Cz, C4, CP5, CP1, CP2, CP6, P3, Pz, P4) of the cluster. (B) ERP Topoplots (mean amplitude in μV) of the significant cluster of the congruence by age interaction. Electrodes where significant differences were detected corresponding to the interaction are highlighted with asterisks. The difference wave of the congruent minus the incongruent condition in the young group was contrasted with the same difference wave in the elderly group in the cluster analysis. (C) Barplot showing the mean amplitude across the electrodes of the significant cluster of the congruence by age interaction, from 404 to 604 ms, with the congruent (c) and incongruent condition (ic) shown for the groups of young and elderly (eld.) adults.

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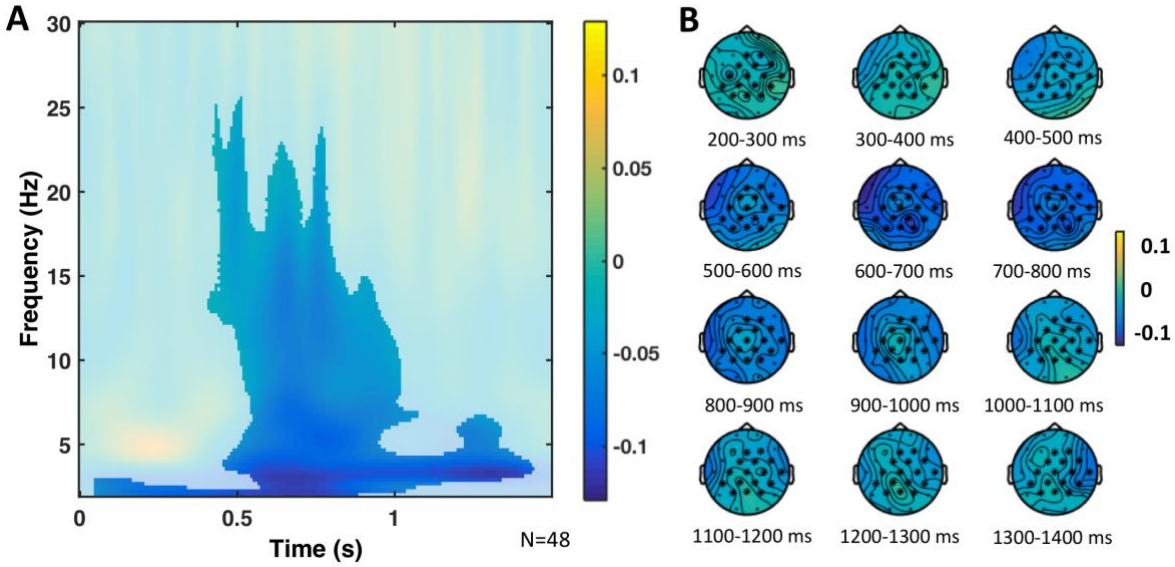

Figure 3. Congruence TF effect. (A) Relative power change of the congruence time-frequency effect across the significant electrodes found in the cluster. The significant time window was from 50 ms to 1440 ms, and the significant frequency window was from 2 Hz to 25.56 Hz. The difference between the congruent minus the incongruent condition was contrasted in the cluster analysis. For the figure, the mean was calculated from the grand averages across the 19 electrodes (F3, Fz, F4, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P3, Pz, P4) of the cluster. (B) TF power topoplots of the significant cluster of the congruence effect, in the significant time-frequency window. Electrodes with significant differences corresponding to the effect are highlighted with asterisks.

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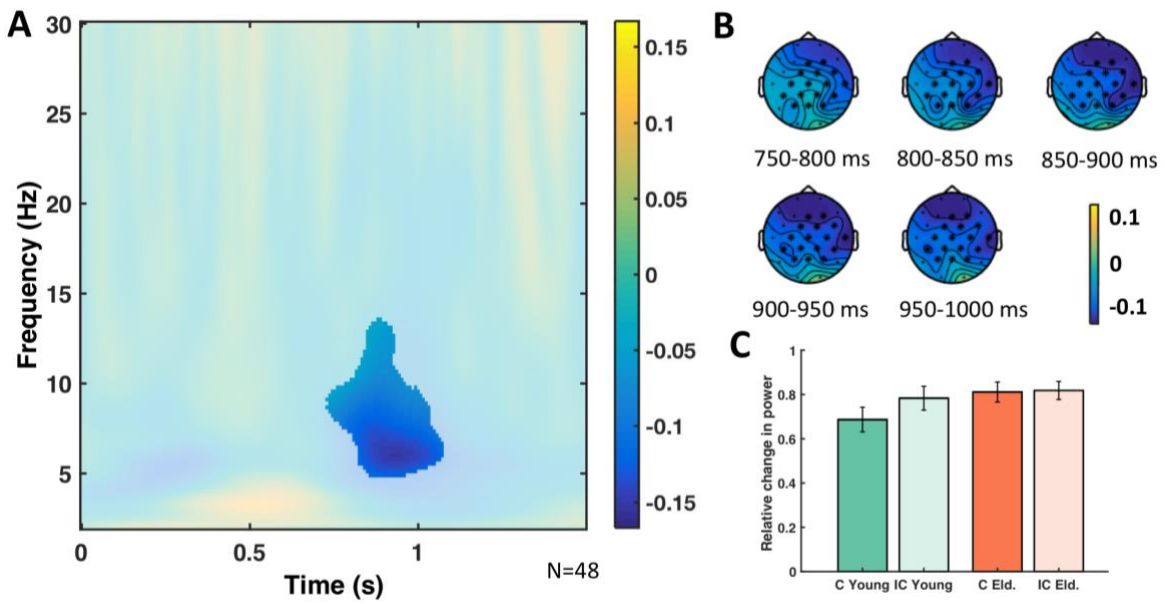

Figure 4. Congruence by Age TF interaction. (A) Relative power change of the congruence by age time-frequency interaction across the significant electrodes found in the cluster. The significant time window was from 728 ms to 1072 ms, and the significant frequency window was from 4.89 Hz to 13.56 Hz. The difference in relative power of the congruent minus the incongruent condition in the young group was contrasted against the same difference in the elderly group, in the cluster analysis. For the figure, the mean was calculated from the grand averages across the 19 electrodes (F3, Fz, F4, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P3, Pz, P4) of the cluster. (B) TF power topoplots of the significant cluster of the congruence by age interaction, in the significant time-frequency window. Electrodes with significant differences corresponding to the interactions are highlighted with asterisks. (C) Barplot showing the relative power change across the electrodes of the significant cluster of the congruence by age interaction, in the significant time-frequency window, with the congruent (c) and incongruent condition (ic) shown for the groups of young and elderly (eld.) adults.

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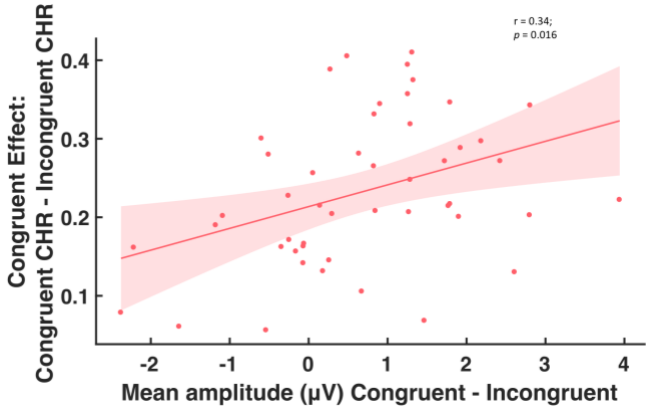

Figure 5. Inter-individual correlation between the ERP difference wave (mean amplitude in µV) of the congruent condition minus the incongruent condition, averaging across the central and parietal electrodes of the cluster (C3, Cz, C4, CP5, CP1, CP2, CP6, P3, Pz, P4), with the difference resulting from congruent high-confidence CHR minus incongruent high-confidence CHR, across participants from both age groups controlling for age. The ERP congruent minus incongruent difference wave predicted the difference in congruent memory performance across individuals in both groups controlling for age (r =.34, p=.016). The line shows the fit of a generalized linear model to the data, with the 95% confidence bounds displayed.

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Tables

Place after the behavioral memory results section

Table 1

Recognition accuracy data

		Congruent High Confidence	Incongruent High Confidence
Behavioral Group	Young	0.96 (0.002)	0.93 (0.002)
	Elderly	0.94 (0.002)	0.91 (0.002)
EEG Group	Young	0.95 (0.002)	0.92 (0.002)
	Elderly	0.92 (0.003)	0.89 (0.003)

Note: Mean (SEM) accuracy as calculated according with the following formula: (Hit Rate / (Hit Rate + False-Alarm Rate)). Accuracy is indicated for both groups separately for the congruent and incongruent conditions, both when including all responses and when including only the high-confidence responses during the memory test. Single-sample t tests showed that accuracy for each of the conditions was higher than chance (>0.50). In other words, subjects were able to distinguish old words from new words (all $p < 0.001$).

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Place after the reaction time results section

Table 2

Reaction times for the semantic matching encoding task

		Congruent	Incongruent
Behavioral Group	Young	845.14 (7.56)	899.80 (8.75)
	Elderly	931.69 (7.72)	1001.03 (8.15)
EEG Group	Young	855.04 (10.30)	888.15(10.67)
	Elderly	964.75 (7.02)	1015.76 (7.83)

Note: Mean (SEM) reaction times in ms. Here we included only trials in which the participants correctly classified the word pairs. The anova showed a main effect of congruence ($p < 0.001$), participants were slower to classify incongruent words than congruent words.

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Table 3

Place after the EEG results section

Significant Clusters

Cluster	Duration	Frequency range	Electrodes	p
Congruence contrast: positive ERP	320-1176 ms	-	Fz F4 FC1 FC2 FC6 C3 Cz C4 T8 CP1 CP2 CP6 Pz P4	0.002
Congruence by age interaction: positive ERP	404-604 ms	-	F3 Fz FC5 FC1 FC2 C3 Cz C4 CP5 CP1 CP2 CP6 P3 Pz P4	0.012
Congruence contrast: relative power decrease (TF)	50-1440 ms	2-25.56 Hz	F3 Fz F4 FC5 FC1 FC2 FC6 T7 C3 Cz C4 T8 CP5 CP1 CP2 CP6 P3 Pz P4	0.002
Congruence by age interaction: relative power decrease (TF)	728-1072 ms	4.89-13.56 Hz	F3 Fz F4 FC5 FC1 FC2 FC6 T7 C3 Cz C4 T8 CP5 CP1 CP2 CP6 P3 Pz P4	0.030

Note: Contrasts for each cluster are indicated as detected by the two-tailed non-parametric cluster-based permutation tests. ERP and TF clusters are presented. Congruence contrasts (congruent minus incongruent) and congruence by age interaction contrasts (Congruence contrast in young group minus congruence contrast in elderly group) are shown. The duration in ms and the list of electrodes which were detected in the cluster are shown for each contrast, together with the significance level.