Effects of Age Differences in Memory Formation on Neural Mechanisms of Consolidation and Retrieval

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Abstract

Episodic memory decline is a hallmark of cognitive aging and a multifaceted phenomenon. We review studies that target age differences across different memory processing stages, i.e., from encoding to retrieval. The available evidence suggests that age differences during memory formation may affect the quality of memory representations in an age-graded manner with downstream consequences for later processing stages. We argue that low memory quality in combination with age-related neural decline of key regions of the episodic memory network puts older adults in a double jeopardy situation that finally results in broader memory impairments in older compared to younger adults.

Introduction

Our ability to vividly re-experience past events is one of the most fundamental human abilities. However, during the course of aging, *episodic memory*, the ability to remember episodes with their spatial and temporal details [1], steadily declines [2–4], whereas the likelihood to remember episodes that are (partially) false increases [5]. To pinpoint the neural mechanisms underlying the decline in episodic memory in old adulthood while precisely delineating their contribution to cognitive component processes is therefore a major endeavour of the cognitive neuroscience of aging [6,7]. The goal of this review is to discuss age-related changes in neural processes within the episodic memory network that give rise to age-related changes in the ability to recall events from the past.

Episodic memory relies on a widely distributed network of brain regions, with the central parts being the mediotemporal lobe (MTL) including the hippocampus, perirhinal cortex, entorhinal cortex, and parahippocampal cortex [8,9], and the prefrontal cortex (PFC) [10,11] as well as regions such as the posterior cingulate, lateral temporal and parietal cortices [12,13]. Within the core episodic memory network, the most prominent role is certainly taken by the hippocampus which is involved in the rapid *formation and recall of associations* among stimuli, or between stimuli and their context [8,9,14]. A complementary role is taken by the PFC that subserves rather domain-general executive functions [15] and supports monitoring and control processes during encoding and retrieval in particular [11,16]. Importantly, these key players of the episodic memory network undergo strong senescent changes during aging. With regard to the PFC, marked gray matter reductions [17,18] and changes in prefrontal white matter [19,20] have been reported in cross-sectional and longitudinal studies (for recent reviews, see [21,22]). Similarly, gray matter reductions occur within the MTL [21], with particularly strong decline observed in the hippocampus and the entorhinal cortex [18,22]. Together with changes in functional [23] and structural [24] connectivity and declines in central neurotransmitter systems [25–28], age-related structural changes are thought to affect the functionality of brain regions that have been shown to be involved in successful memory in young adults, with detrimental consequences for memory performance in old age [7,29–32].

Traditional cognitive theories [33–35] conceive memory as a product of three sequential processing stages: *encoding*, *consolidation*, and *retrieval*. Encoding can be defined as the process of memory formation by which incoming inputs from the external world are transformed into an internal representation of that information. Consolidation refers to processes (mostly occurring during sleep) that result in the persistence of information over time (often in a more generalized form including a loss of information detail, [38,39]. Retrieval is the attempt to access information that was acquired previously. Thus, episodic memory performance relies on the ability to successfully form detailed, bound representations of content and contextual information, transform these representations into a lasting format, and later access, evaluate, and use these memory representations to guide behavior [38,39].

Here, we argue that among these stages, encoding may play a particularly important role for memory abilities and their age-related changes. Any differences at encoding can produce downstream consequences for later processing stages. In the extreme case, this notion is intuitively obvious: An event that was not (sufficiently) encoded in the first place cannot result in an internal representation that will be consolidated or even retrieved. By contrast, attentively studying personally relevant information will most likely result in a detailed mnemonic representation with a high likelihood for consolidation and later retrieval. In any natural situation, we can safely assume that encoding depth varies from moment to moment, producing mnemonic representations with a wide range of quality [34,35,40,41], even in younger adults. Age-related changes affecting encoding processes may increase the proportion of memories of low quality. Since memory quality has consequences for ensuing processing stages, age-related changes in encoding may thus explain a large part of age differences in episodic memory performance.

In the following we provide a focused review of how age-related alterations in memory encoding (see [42]) produce differences in memory quality that affect later stages of memory processing such as consolidation and retrieval. Illustratively, we will focus on a series of studies conducted by our lab (the so-called MERLIN studies = **M**emory **E**ncoding and **R**etrieval across the **Li**fespa**n** studies) that aimed at comprehensively describing age differences at all stages of memory processing [5,43–47], (see also [48] for an extension of this approach to childhood). At the core of the MERLIN studies was an age-adapted associative picture–word memory task (Figure 1).

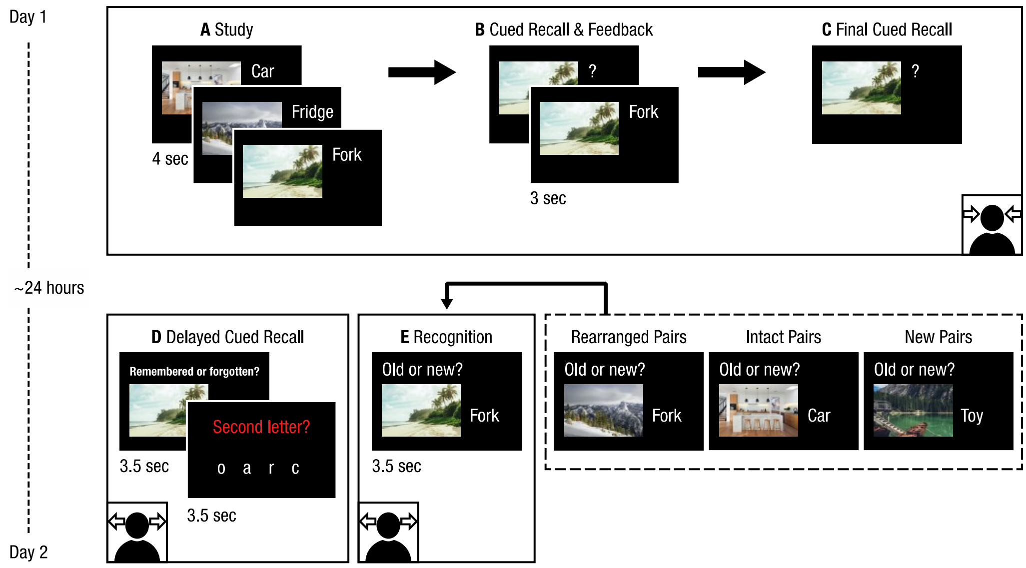

Figure 1. Experimental paradigm. A. In the study phase, participants were asked to associate 440 (young adults) or 280 (older adults) scenes and words using an imagery strategy. Cued recall was used to test memory performance. B. During the cued recall and feedback phase, the scene was presented as a cue to verbally recall the associated word. Subsequently, the original pair was presented again for restudy. The cued recall and feedback phase was carried out once for younger and twice for older adults. C. During final recall, no feedback was provided. Scene-word pairs were sorted into high or low memory quality based on recall performance in phase C [43]. In the studies by Muehlroth et al. [45] and Sommer et al. [47], high quality pairs were further distinguished into high and intermediate quality dependent on whether they were successfully recalled in phase B or not. Memory performance was tested approximately 24 hours later either with a delayed cued recall task (D) or with a recognition task (E). D. During delayed cued recall, participants were presented with the scenes only and had to indicate if they still remembered the associated word. Afterwards, they had to select the corresponding second letter of the word to verify their true memory of the associate. E. In the recognition task, participants were presented with intact, rearranged, and new pairs, and instructed to decide if the corresponding pair was old (i.e., studied on Day 1) or new (not studied on Day 1). Intact and rearranged pairs varied in memory quality to test effects of memory quality on recognition.

Specifically, on their first visit to our lab, younger and older adults were instructed to intentionally encode memories by associating scene pictures with words using an imagery strategy . Given well-known age differences in the speed and limits of learning between younger and older adults, we adapted the task difficulty between age groups. Specifically, older adults studied fewer picture–word pairs than younger adults. While both age groups performed several rounds of learning and retrieval of the picture–word pairs, older adults were provided with an additional learning round. This procedure allowed us to trace the mnemonic fate of single items within a given individual. We later capitalized on the item-level information from the learning phase to determine the *memory quality* for single picture–word pairs for each individual participant: We reasoned that pairs that were successfully acquired during learning, such that when cued with a scene picture, participants were able to verbally recall the associated word, are items of *high quality*. In contrast, *low-quality* items are pairs to which participants were exposed several times, but did not succeed in forming and retrieving a bound memory representation. Thus, low-quality items included pairs that were not recalled until the end of the learning session of day one. In some analyses, we further distinguished the high-quality items into those that were learned early during the procedure and those that were only acquired after repeated learning, the latter representing *intermediate-quality* items. Defining memory quality based on the learning history allowed us to exploit person-specific item-level information to investigate effects of memory quality on later stages of cognitive and neural processes. Note that from an experimental perspective, other procedures have also been used in order to vary memory quality, e.g. by comparing deep versus shallow encoding instructions [34], situations with full versus divided attention [49], varying numbers of repetitions during learning [50,51], and many more. However, these previous procedures require aggregation across items of a given condition. By contrast, determining memory quality based on the learning history provided person-specific information about single mnemonic items.

During the learning phase of Day 1 of our MERLIN studies, we measured our participants' electroencephalographic (EEG) responses, allowing us to observe differences and commonalities between age groups in the neurophysiological mechanisms underlying this initial acquisition phase of information. We will elaborate on these findings in section 1. To investigate age differences in consolidation, we monitored our participants' sleep with ambulatory polysomnography (PSG) during the night before and immediately following the learning phase. We will present the findings in section 2. Finally, to investigate neural age differences during retrieval, we probed younger and older adults' memory of the picture–word pairs learned 24 hours earlier on Day 2 with a recognition task and a cued recall task using functional magnetic resonance imaging (fMRI; section 3). We will elaborate on this in the section “age-differences in memory retrieval”. In the conclusion part, two main findings that emerged across studies will be discussed: The role of age-related changes in neural structures for the functioning of memory processes as well as the contribution of age differences in memory quality to memory performance.

Section 1: Age differences during encoding

Without any doubt, younger and older adults’ memory already differs at encoding, i.e., during the processing of incoming information (see [42], for a review). Neural mechanisms of memory formation can be studied with so-called subsequent memory paradigms [52,53]. Here, neural activity during encoding of those trials that are later remember is contrasted with neural activity during trials that are later not remembered (maybe even forgotten), thereby revealing the neural mechanisms of successful versus unsuccessful memory formation.

Using this approach, fMRI has revealed reliable subsequent memory effects (SMEs) in key regions of the episodic memory network, in particular, in the MTL and PFC [54–56]. Electroencephalographic studies have complemented these findings by demonstrating SMEs in event-related potentials [e.g. 57–59], intra-cranial recordings [60], and oscillatory activity, in particular within the alpha/beta (~ 8–30 Hz), theta (~ 4–8 Hz) and gamma (> 40 Hz) frequency ranges (for a review, see [61]). Thus, SMEs can be leveraged to investigate whether aging already affects mnemonic processing at encoding.

Adopting a subsequent memory approach, we studied oscillatory mechanisms of memory formation in the associative memory paradigm described above [46]. Specifically, we examined whether age differences in the structural integrity of core memory regions, notably inferior frontal gyrus (IFG), a region that has been shown to be involved in the elaboration of the incoming information during encoding [62,63], and hippocampus, could account for between-person differences in the strength of oscillatory SMEs. Neural oscillations reflect the coordinated firing patterns of neurons in local and global networks [64–68]. In previous studies, precisely timed neural interactions have emerged as being crucial for accurate memory formation, stabilization, and reactivation [69–72]. Using the MERLIN procedure as described above, younger and older adults were asked to intentionally encode picture–word pairs repeatedly using an imagery strategy. Despite our age-adaptive procedure, age group differences in performance were present even in terms of proportion of recalled pairs, with younger adults outperforming older adults. Oscillatory power of the trials of the last learning round was then analyzed with regard to whether recall was successful or not. We observed highly similar mechanisms of successful memory formation in older and younger adults (Figure 2). In both age groups power increases in the theta band were accompanied by power decreases in the alpha/beta range (Figure 2a). These effects have been shown to indicate associative binding and elaboration mechanisms in young adults [61,70,73–75]. However, we also found that the strength of the oscillatory subsequent memory effect was modulated by the structural integrity of brain regions that are part of the core episodic network. More specifically, lower structural integrity in the IFG was accompanied by smaller SMEs in the alpha/beta frequency bands (Figure 2c). While this structure–function relationship did not generally differ between age groups, it is important to note that those participants with low IFG integrity were mostly older (Figure 2b). These results suggest that older adults, in particular those with low IFG integrity and reduced SMEs in the alpha/beta band, tend to form memory representations that have undergone less deep elaboration during encoding and may contain fewer details as a consequence. Alternatively, in line with studies pointing to an inhibitory function of both the IFG [76,77] and alpha oscillations [78], reduced SME in those participants with reduced IFG integrity might also indicate a less flexible adjustment of inhibitory processes to task demands. In other words, while the general mechanisms that underlie successful memory formation appear not to change across adulthood, the *probability* to successfully engage memory formation operations does seem to deteriorate as well as the level of detail or specificity of memories (see also [79,80]).

Recent advances in neuroimaging analysis techniques allow one to characterize memories with regard to their informational content, ultimately improving investigations of the detail of memories. Representational pattern analysis (RSA) is a multivariate analysis technique that describes neural activation patterns distinguishing stimuli in terms of their similarity or distance in geometric space [81,82]. Perceptually or semantically similar stimuli are generally represented closer to each other in geometric space. Thus, RSA can be used to ask whether informational content of specific memories is represented in the same way in younger and older adults [83], and allow to investigate the neural underpinnings of age differences in memory specificity.

Relying on RSA of spatio-temporal EEG frequency patterns that reflect the neural representation of information in rhythmic neural activity across time, we therefore asked whether the similarity of these patterns differed between younger and older adults during encoding [47]. In particular, we hypothesized that older adults form less detailed representations than younger adults. Indeed, we observed age differences in representational similarity during the encoding of picture–word pairs. Older adults generally showed more similar, thus less distinct activation patterns than younger adults, in line with the assumption that memories become more similar and less specific as we age [83–85]. Interestingly, the relation to memory performance also showed an age-differential effect: In older adults, higher representational similarity in early stages of processing was related to successful subsequent memory, whereas in younger adults, lower similarity during later stages of encoding was related to a higher recall probability. These results are in line with the assumption that older adults are less able to form precise and detailed memory representations compared to younger adults [79,86,87]. As a consequence, they rely more on encoding of the general gist of stimuli [2,88] as reflected in the positive relation between increased similarity and memory performance. In contrast, young adults form memory representations that entail more details and are distinct from each other as reflected in increased dissimilarity during later phases of encoding.

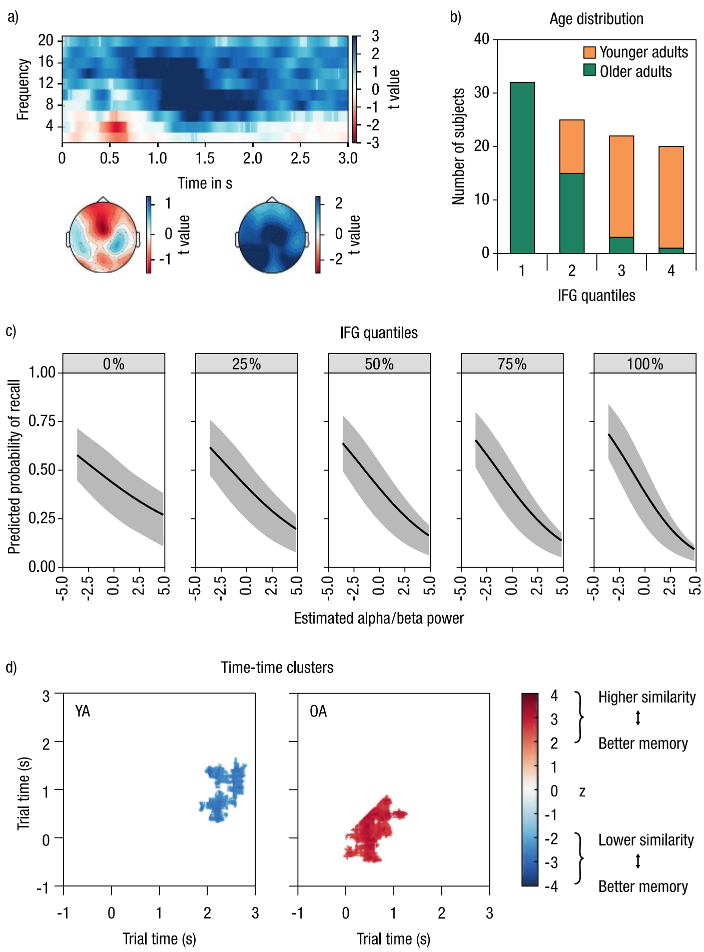

Figure 2. Age differences during encoding. A. Across age groups, recall success is reflected in an early power increase in the theta band, and a broad decrease in alpha/beta power. The comparison of subsequently remembered versus not-remembered pairs is represented as t-values in time and frequency along with their respective topographical distribution. B. Age distribution of younger and older adults with regard to structural integrity of the inferior frontal gyrus (IFG). Older adults mostly belong to the lower two quantiles, younger adults dominate the upper two quantiles. C. Subsequent memory effects in alpha/beta power differ by IFG quantiles as indicated by differences in slopes when displaying predicted

probabilities of recall of varying alpha/beta power for different IFG quantiles. D. In older adults (OA, righthand panel), better memory is related to higher similarity early in a trial, whereas in younger adults (YA, lefthand panel), lower similarity between items later in the trial benefits performance. Time-time clusters revealing the respective relationship are displayed separately for younger and older adults. Figure 2 a-c adapted from [46]. Figure d adapted from [47].

In sum, the available evidence suggests that age differences between younger and older adults already emerge during encoding, and that the age differences may result in memories of different quality: Older adults' memories are generally less specific and detailed and individual representations may be more similar to each other. At the same time, it is necessary to stress that some older adults are still able to form high-quality memories, depending on external factors such as the encoding conditions (e.g., the number of learning repetitions) and individual factors such as neural integrity of brain regions within the core memory network [7,89,90]. Taken together, the quality of encoded memories differs between age groups on average, but also varies from trial to trial within a person. Thus, it becomes important to examine how inter- and intraindividual differences in memory quality resulting from encoding impact memory consolidation (section 2) and memory retrieval (section 3).

Section 2: Age differences during memory consolidation

Consolidation refers to the transformation of transient memory representations, initially strongly supported by the hippocampus, into long-lasting representations in neocortical regions [37,91–93]. This so-called system-level consolidation is dependent on rhythmic neural events during sleep. Specifically, slow oscillations (SO) and sleep spindles (SP) [94–97] as well as their precise coupling [97–99] are assumed to drive consolidation.

With increasing age, sleep changes with regard to its architecture (i.e., the stability and succession of sleep phases) and physiology. Typically, sleep in older adults becomes lighter and more fragile. At the same time, fatigue and daytime napping become more prevalent (for a review, see [99]). Most crucially, cardinal neural sleep rhythms, specifically slow oscillations and spindles, decrease in amplitude and frequency of occurrence with increasing age [100,101]. While daytime fatigue may have detrimental effects on acquiring new memories, altered sleep physiology may distort the necessary neural processes for memory stabilization.

Importantly, sleep-dependent memory consolidation does not affect all encoded memories similarly [102–105] and the reliance on consolidation processes for successful memory stabilization may differ for memories of varying quality. On the one hand, sleep may stabilize previously successfully encoded memories. On the other hand, it may also enhance the availability of initially poor memories beyond a pre-sleep learning level [103,106]. The available evidence so far leans towards a role of sleep mainly in memory maintenance. Behaviorally observed memory gains, by contrast, appear less reliant on sleep [40,107,108].

If sleep-dependent consolidation mainly serves the stabilization of mnemonic contents, it may be particularly relevant for the maintenance of memories of intermediate quality, i.e., when encoding was successful, but not very detailed. Accordingly, it has been shown that these memories are prioritized during sleep-dependent consolidation over mnemonic contents of high quality for which subsequent consolidation processes are largely redundant [104,109,110].

As discussed above, aging differentially affects encoding. Accordingly, also the distribution of memory quality across items is likely shifted in older compared to younger adults. Hence, proper assessment of age differences in sleep-dependent memory consolidation requires consideration of the quality of encoded memories. By tracing the fate of individual memory contents [40,107] in the MERLIN studies, Muehlroth and colleagues [45] found that the effects of aging on memory maintenance were indeed most pronounced when the acquired memory representations were of lower quality.

Besides age differences in memory quality, changes in brain structure can also impair sleep-dependent consolidation in older adults. For example, Muehlroth et al. [44] investigated age-related changes in the coupling of SO with slow and fast SP. They tested whether differences in structural integrity of source regions of SO and SP generation were related to the loss of precision in SO–SP coupling and memory consolidation. To that end, they monitored the sleep of the MERLIN participants using ambulatory polysomnography (PSG) and assessed structural brain integrity by voxel-based morphometry (VBM) of structural magnetic resonance images (MRI). Comparing the PSG recordings of younger and older adults, Muehlroth et al. [44] identified age-related differences in the coordination of SO and SP. Specifically, the characteristic SO–SP coupling in young adults was marked by a strong increase in SP coupled to the SO peak, predominantly for fast spindles. By contrast, the coupling was shifted towards lower SP frequencies with a wider spread around the SO peak in older adults, indicating a reduced precision in SO–SP coupling [111].

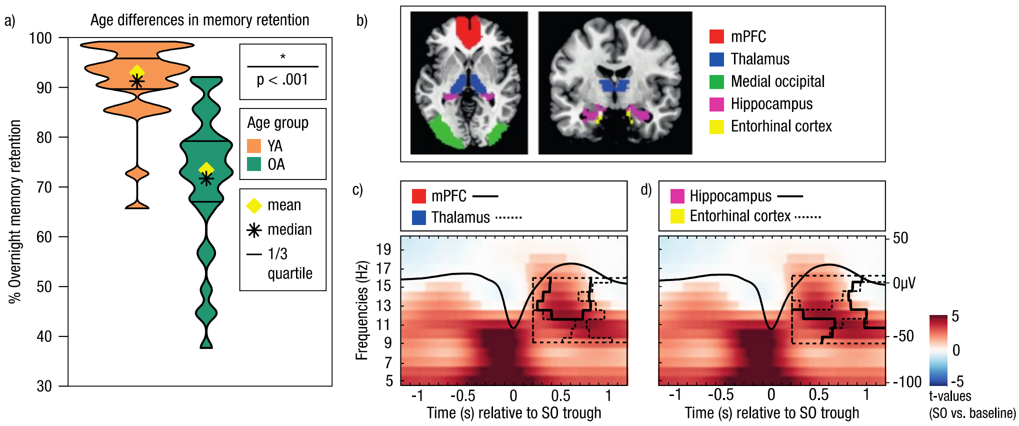

Figure 3. Age differences during sleep-dependent consolidation. A. Overnight memory retention indicates the percentage of correctly recalled items during delayed recall (on Day2) relative to all items that were correctly retrieved during immediate recall (on Day1) before sleep. Overnight memory retention is significantly reduced in older adults. B. Voxel-based morphometry was used to determine the individual level of structural integrity of brain-regions of interest (ROI masks overlaid in color). C. Higher structural integrity of source regions of slow oscillations (SO) and sleep spindles (SP) is related to increased spindle activity at the peak of the SO. Positive correlations are outlined by solid (mPFC) and dashed black lines (thalamus). For illustration purposes, a SO is overlaid on time-frequency profiles (in t-score units). The reference window for the correlation analysis is outlined with the dashed black line. D. Higher structural integrity in core regions of the episodic memory network (hippocampus, entorhinal cortex) is positively correlated with global power increases during the SO up-state. Adapted from [44] .

Crucially, the precision of SO–SP coupling was related to overnight memory retention. Interestingly, older adults with higher structural integrity (i.e., larger brain volume) in source regions of SO and SP (i.e., medial PFC and thalamus) showed a more youth-like pattern of SO–SP coupling, indicating that structural integrity of these brain regions plays an important role in the coordination of SO and SP [97].

Thus, like our observations with regard to age differences during encoding, these results suggest that age-related impairments in the processes supporting memory consolidation display large interindividual differences that are related to the structural integrity of core memory regions. Accordingly, older adults with few signs of structural decline also seem to show less changes in functional memory processes [89,90].

Together, these findings suggest that age differences in memory quality as a result of altered encoding combined with person-specific factors like brain integrity influence the success or failure of memory consolidation processes in older adults.

Section 3: Age differences during memory retrieval

In this final section we elaborate on the effects of age differences in memory quality on memory retrieval processes. Explicit memory retrieval refers to the successful recovery of a previously acquired memory trace and can be tested with a *recognition task* or a *cued recall task*. In a *cued recall task*, participants are presented with one part of the learned stimulus, typically a pair, and are asked to retrieve the associated part. In the case of the MERLIN studies, participants saw the picture and were asked to recall the associated word. This task is usually more difficult and reveals larger age group differences than *recognition tasks* [112]. In old/new recognition tasks, participants' memory is probed by presenting "old" stimuli from the encoding phase intermixed with "new" , previously unseen stimuli. A particular variation of old/new recognition tasks is often used when testing associative memory: Since stimuli are pairs in associative tasks, they can be presented during test either in the identical pairing as during encoding or in a “rearranged” pairing, which means that although both elements of the pair have been seen before, they were part of different pairs. In the latter case, the exact combination is “new” and has not been encountered before. Therefore, participants would have to judge such a pair as “new” , and not as “old” , and then correctly reject it. This kind of paradigm aims particularly at the specificity and detail of memories since reliance on familiarity, the feeling that one has seen parts of the pair before, is not sufficient for successful performance. Correct rejection of rearranged information is particularly difficult for older adults and is behaviorally reflected in higher false alarm rates [113,114], that is, a greater propensity to wrongly endorse rearranged pairs as old compared to younger adults.

Higher levels of false alarms in older adults may result from the interaction of lower quality memory representations and age-related deficits in the ability to monitor retrieval outcomes in order to reject misleading information [86,115]. Monitoring processes are engaged to evaluate retrieved memories in the context of current goals and task demands [116]. They are particularly important to avoid errors when retrieved memories are very similar to each other or highly familiar, as is the case for rearranged pairs [117–119]. On the neural level, close interactions between fronto-parietal and cingulo-opercular regions support retrieval monitoring processes. The cingulo-opercular network plays an important role in the monitoring of ongoing performance [120,121] and in the initiation of control and evaluation processes supported by fronto-parietal regions [122–124]. Thus, these brain networks are crucial for successful memory retrieval because they ensure that the right memory is recovered in sufficient detail when needed. While demands on monitoring processes are lower when a high-quality distinct memory is retrieved, fronto-parietal and cingulo-opercular activity is expected to increase when the quality of the retrieved memory is relatively low. Thus, the selective recruitment of fronto-parietal and cingulo-opercular regions with varying memory quality represents a hallmark of efficient retrieval monitoring. At the same time, advancing age is associated with declines in the structural integrity of regions in the cingulo-opercular network [125] as well as in the lateral PFC and the parietal lobes [18]. Additionally, major tracts connecting those regions, such as the superior longitudinal fasciculus are also compromised in older adults [126]. In parallel to these structural changes, older adults display reduced activity in fronto-parietal and cingulo-opercular regions when correctly rejecting highly familiar information such as rearranged pairs [127,128]. Based on these age-related deficits in retrieval monitoring we sought to examine how they are modulated by the quality of newly established mnemonic representations.

We thus probed younger and older adults' memory in the scanner with a recognition task on picture–word pairs learned 24 hours earlier using fMRI [43]. Participants saw new picture–words pairs that were intermixed with intact pairs (i.e., pairs that were identical to those presented during the learning phase), or rearranged ones (i.e., pairs for which both the picture and the word were familiar to the participants, but not their combination). Importantly, based on the participant-specific recall history of Day 1, we were able to construct individualized recognition tasks that included balanced numbers of high- and low-quality pairs. Thus, by referring to successful versus unsuccessful retrieval on the previous day as an indicator of memory quality, we were able to test how memories of different quality modulate activity in brain regions that have been found to be involved in successful recall-to-reject and monitoring processes in younger and older adults. On the behavioral level, memory quality influenced overall recognition performance in both groups with a lower probability of correct recognition for low- compared to high-quality memories. However, regarding rearranged pairs, older adults committed more false alarms than younger adults, and this age group difference was even larger for high quality memories (see [5]).

On the neural level, we again observed commonalities and differences between age groups (Figure 4): Mnemonic quality modulated younger and older adults' brain activity in the anterior hippocampus as well as medial and lateral PFC similarly. Higher activation in these regions for correct rejection of high-quality rearranged pairs than of low-quality information rearranged pairs seems to reflect the more detailed and successful reinstatement of mnemonic information in the case of high-quality memories [129]. At the same time, young adults recruited brain regions that are associated with post-retrieval monitoring, including cingulo-opercular regions, more when mnemonic quality was low and errors were likely, and less when they were able to rely on high-quality representations. However, older adults did not show such a quality-dependent activation in these regions. Notably, the modulation of activation in these regions was negatively related to the proportion of false alarms, suggesting that quality-dependent recruitment of these regions was highly relevant for memory performance.

In sum, our results provide evidence for the modulatory effect of memory quality on retrieval processes. Similar to the effect of memory quality on consolidation, older adults may thus be in a double-jeopardy situation during retrieval if memory quality is low due to additional deficits in the recruitment of monitoring and control processes.

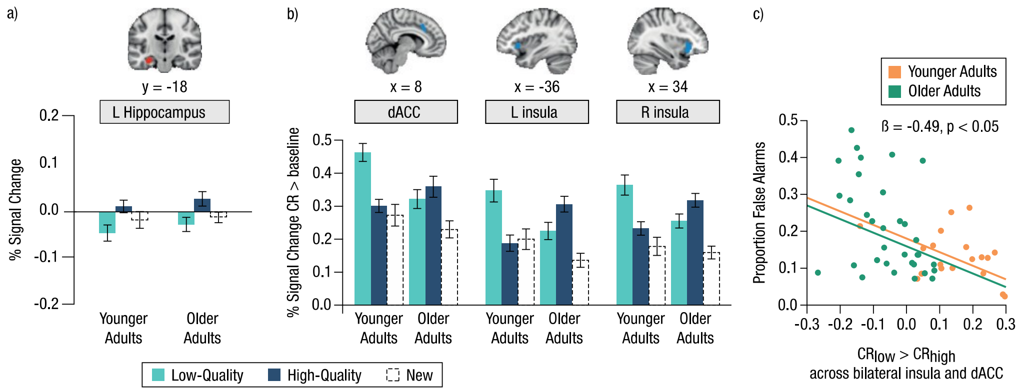

Figure 4. Age differences during retrieval. A. Example of age-invariant effects of memory quality on the engagement of core regions of the episodic memory network. Both younger and older adults show higher percentages of signal change in the left (L) hippocampus during the correct rejection of high-quality versus low-quality pairs, indicating the retrieval of relevant mnemonic details to reject rearranged pairs. B. In contrast, age differences were observed in monitoring and control regions, with larger effects of memory quality on the recruitment of dorsal anterior cingulate (dACC) and insula in younger than older adults. C. Greater activity differences between correct rejections (CR) for low- and high-quality pairs were related to fewer false alarms. Adapted from [45].

Discussion

Reviewing evidence across several studies, we show that episodic memory decline during aging is a multifaceted phenomenon that results from impaired processing at different cognitive stages, spanning the full range from encoding to retrieval. We find that differences in memory quality play an important role for memory consolidation and retrieval such that memories of low quality pose a greater challenge to the episodic memory network. As a consequence, the structural and functional integrity of the regions that are recruited during a specific cognitive stage determine whether this challenge is successfully met or not, and predict interindividual differences in memory performance.

With regard to memory formation, while we observed generally similar mechanisms of memory encoding in younger and older adults in cases of successful memory (see also [80,130]), older adults more often formed memories that are of lower quality than those of younger adults. For example, we found that both age groups showed reliable oscillatory subsequent memory effects. At the same time, the scale of alpha/beta desynchronization was related to the cortical thickness of the IFG, an important region for elaboration processes [54,62,63], which was significantly lower in older adults [46]. Thus, it seems that impaired structural integrity of key regions of the core episodic memory network alters the precise recruitment and efficiency of memory formation processes. As a consequence, despite similar encoding mechanisms, the quality of encoded memory representations may differ between younger and older adults and impact later cognitive stages such as consolidation and retrieval.

Differences in the quality of memory representations between younger and older adults are implicated as a key source of differences in behavior by age group. Influential theories of cognitive aging have suggested that neural dedifferentiation (i.e., a loss of representational specificity [83,131]) underlies cognitive decline in old adulthood [84,132]. For example, univariate fMRI studies focusing on content-specific activation in category-selective regions of the ventral visual cortex have consistently shown that these are less selective, with less differentiated activation patterns for stimuli of different categories such as faces and houses, in older compared to younger adults ([133], see also [134,135]). Importantly, interindividual differences in neural dedifferentation are related to memory performance [136,137], such that participants with higher levels of neural dedifferentiation showed lower memory performance (for a recent review, see [82]). Complementary evidence is accumulating from studies using multivariate approaches such as neural pattern analysis [138,139]. Accordingly, in a recent study [136] we observed age group differences in neural specificity during encoding not only on the level of category information, but even on the item level, providing further evidence for the crucial contribution of specific, high-quality memories for memory performance. Strikingly, age differences on the item level were located in occipital regions, thus early in the visual processing hierarchy, in line with earlier observations of a close connection between age differences in perception and cognition [140,141].

Computational models suggest that neural dedifferentiation is caused by age-related changes in neurotransmitter availability, in particular to deficient dopaminergic modulation [84,132,142]. Li and colleagues [83,131] conceptualized the age-related attenuation of dopaminergic modulation as an alteration of the activation function of units in a neural network, leading a reduced fidelity of neural information processing and reductions in the distinctiveness of representations. Evidence of reliable individual differences in the presence of D2/D3 dopamine receptors in occipital cortex [143] supports the idea that their availability in early sensory regions could play an important role in neural dedifferentation. Interestingly, recent studies also demonstrated a relationship between a decline of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and neural distinctiveness. Combining magnetic resonance spectroscopy (MRS) to measure GABA with fMRI, Chamberlain et al. [144] found that older adults had lower GABA levels (see also [145]) and less distinct activation patterns in the ventral visual cortex. Furthermore, individual differences in GABA levels predicted individual differences in distinctiveness (see [145], for similar results with regard to the discrimination of auditory stimuli and GABA levels in the auditory cortex). Reduced inhibition by GABAergic interneurons might impair the resolution of conflict between neural representations and result in less distinct representations [144,146].

In sum, accumulating evidence supports the proposition that age differences in structural integrity, functionality, and neurotransmitter availability already alter neural mechanisms of memory encoding at early stages of the processing hierarchy with downstream consequences for ensuing consolidation and retrieval of memory representations. Age differences in memory encoding may thus explain a large part of episodic memory decline [42,147]. Having to deal with more gist-like [47,88,148] and less specific [136,137] memory representations increases the challenge for older adults' episodic memory network that can hardly be counteracted at later stages of processing [149]. In line with this assumption, our results highlight that age differences in prefrontally mediated monitoring and control processes contribute to age-related memory decline [3,115], particularly, when an item's memory quality is low.

With standard paradigms it is difficult to experimentally distinguish between effects of memory quality due to differences in encoding and age-related processing differences at later stages. The experimental design developed for the MERLIN studies tracked the fate of single items within each participant, thereby allowing us to separate these effects.

Our findings further emphasize that age differences in structural and functional integrity do not only impact the ability to form high-quality memories with rich details. Rather, we can demonstrate that impaired structural integrity in memory-specific networks puts an additional burden on all processing stages, from encoding to consolidation and retrieval. This observation is generally in line with the so-called "brain maintenance" hypothesis, which suggests that the level of an older person's cognitive capabilities is related to the degree of maintained neural integrity, including structure, function, and neurochemistry [6,7,89,90].

The formation and maintenance of highly specific memories has been shown to depend on successful pattern separation processes in the hippocampus [150,151]. Yet, the hippocampus is disproportionately atrophied in old age [18] and that shrinkage is clearly related to episodic memory decline in longitudinal studies [31,152]. Unsurprisingly, impaired pattern separation processes, linked to structural alterations in hippocampal subfields, have been shown to drive age differences in memory performance in humans [153,154] as well as in animal models [85]. Accordingly, with regard to episodic memory functioning, hippocampal maintenance [155] may be crucial for the formation of high-quality memories and the key determinant of episodic memory functioning in old age [90].

At the same time, age-related changes of the brain are widespread, even if they do not affect all regions to the same degree (for a recent review, see [156]). Whether neural decline is a general or specific phenomenon is still a matter of debate (see [89], for a discussion); however, there is evidence that changes within functional neural networks are indeed often correlated among each other. For example, longitudinal evidence has shown that 5-year changes in prefrontal white matter and hippocampus volume show high correlations, whereas lower change-change correlations were observed for other regions [18]. Thus, interdependencies in structural change in PFC and MTL support the notion that age-related impairments in memory quality and controlled retrieval processes [3,7,86,113,115] might often occur in parallel and impact memory performance in aging.

Conclusion

In sum, we have reviewed evidence that while general mechanisms of memory formation may not differ between younger and older adults, age-related structural changes in the episodic memory network, and particularly in key regions such as the hippocampus and PFC, may nonetheless result in a reduced quality of older adults' memories. We have further argued that variations in memory quality have downstream consequences for subsequent cognitive stages like consolidation and retrieval. Accordingly, memories of low quality pose a general challenge to the episodic memory network such that their processing requires an increase in activation/upregulation within brain regions that are central to the cognitive process at hand. At the same time, structural decline in those brain regions that support consolidation and retrieval such as cingulo-opercular regions, medial PFC, and the thalamus, then puts older adults in a double-jeopardy situation during the processing of low-quality memories, resulting in a decline in episodic memory performance in old adulthood.

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