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Research Project 1: Cognitive and Neural Dynamics of Memory Across the Lifespan (ConMem)

The overarching objective of the *ConMem* project is to provide mechanistic explanations for developmental changes and interindividual differences in various aspects and functions of memory, with an emphasis on episodic and working memory. The project proceeds on the assumption that lifespan changes in memory functioning can be mapped onto the interacting contributions of two components, one associative and the other strategic. The associative component of memory refers to mechanisms that bind different aspects of an event into a cohesive memory representation and can be linked to medio-temporal areas (especially the hippocampus, HC) as well as posterior association areas. The strategic component refers to attentional and control processes that aid and regulate memory functions and is mainly supported by prefrontal and parietal regions. Interactions among maturational, experience-dependent, and senescent forces shape the relative contributions of associative and strategic processes during memory encoding, consolidation, and retrieval.

The heuristic value of this framework for understanding lifespan age differences in episodic and working memory has been empirically validated in a series of behavioral, functional imaging (fMRI), and electroencephalographic (EEG) studies (e.g., Fandakova, Sander, Werkle-Bergner, & Shing, 2014; Sander, Lindenberger, & Werkle-Bergner, 2012; Shing, Werkle-Bergner, Brehmer, Müller, Li, & Lindenberger, 2010).

Age Differences in the Interplay Between Associative and Strategic Components: Modulation by Memory Strength at Encoding, Consolidation, and Retrieval

Not all mnemonic events are equal. Some are encountered only once, but are vividly remembered throughout life. By contrast, other events occur repeatedly without leaving any recoverable trace. Do aging-related changes in prefrontal and medio-temporal regions weaken memory traces formed in old age? Do younger and older adults differentially rely on associative and strategic processes when forming new memories? Do mechanisms contributing to memory consolidation during sleep differ by age?

To address these questions, we designed the *MERLIN Study*, which allows us to track the mnemonic strength of single events within a given person (for details, see Figure 5). The study consisted of a multisession protocol including behavioral, EEG, and MRI assessments, as well as ambulatory polysomnographic sleep monitoring in half of the

sample. It was conducted from July 2013 to July 2015. Based on the data from this study, we are currently investigating whether age differences in the elaboration of learned scene-word pairs contribute to age differences in episodic memory performance. Preliminary results demonstrate that during initial encoding, decreases in rhythmic neural alpha activity (~10 Hz) gradually track differences in memory strength, suggesting that prolonged alpha desynchronization during encoding enables deeper semantic elaboration on individual items. Younger and older adults show qualitatively similar effect patterns, suggesting that successful encoding depends on comparable neural mechanisms across the entire adult age range. Age-associated decrements in memory performance most likely result from a decreased propensity to reliably implement similar sets of mechanisms.

Sleeping after learning benefits memory, but with advancing adult age, both sleep and memory performance tend to deteriorate. By assessing memory strength at the item level within each study participant, we seek to disentangle the effects of reduced overnight forgetting from active enhancement of initially labile memory traces (Dissertation Beate E. Mühlroth). First analyses conducted in collaboration with Björn Rasch (University of Fribourg, Switzerland) show that overnight memory enhancement was of similar magnitude in both age groups, whereas forgetting was more pronounced in older adults. Despite

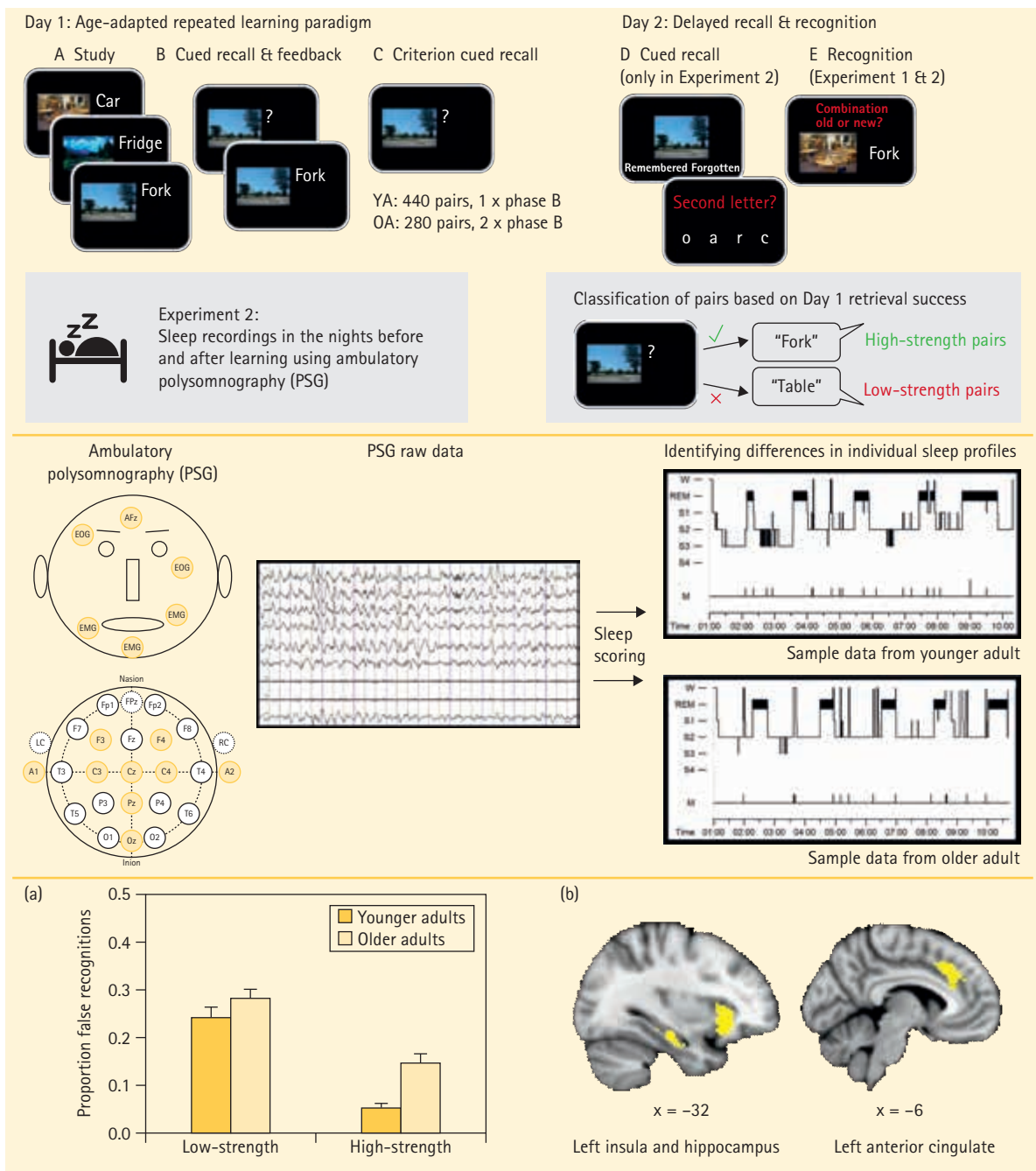


Figure 5. MERLIN Study design. Upper panel: Participants studied scene–word pairs using an imagery-based memory technique (Day 1). After first presentation, each image served as a cue for participants to recall the associated word. Regardless of recall accuracy, the correct word was presented again, allowing further associative learning. A final cued-recall task without feedback (Day 1, C) served to classify the items as high-versus low-strength pairs for a recognition test on Day 2 (Experiment 1). Learning was monitored with EEG and retrieval was assessed with fMRI. In a new sample, we used the same paradigm, with delayed cued recall instead of recognition, and monitored sleep in the nights before and after learning (Experiment 2). Middle panel: Ambulatory polysomnography (PSG) allows monitoring of neurophysiological sleep patterns at home. Manual scoring of sleep stages revealed less time spent in deep sleep and more fragmented sleep in older than in younger adults. Lower panel: Initial analyses show increased proportions of false recognitions in older adults, specifically for high-strength scene–word pairs. Apparently, they experienced greater difficulties in identifying new combinations of overlearned material. This effect was associated with altered neural activity in insular cortex, hippocampus, and anterior cingulate.

altered sleep architecture in older adults, there were no age differences in the association between sleep physiology and memory performance. Slow wave activity and the occurrence of sleep spindles were related to overnight forgetting in both age groups. Older adults are more likely than younger adults to form partially or entirely false memories of past episodes. In collaboration with Roberto Cabeza (Duke University, USA), we sought to delineate the neural correlates of this particular pronounced age difference. While there were no age differences in false memory for low-strength pairs, older adults were also more likely to falsely endorse high-strength pairs. False recognition engaged cingulo-opercular regions. Activity in these regions increased for low-strength pairs in younger, but not older, adults, indicating age-related deficits in retrieval monitoring. We found no age differences in HC activity, which was higher for correct recognition of high-strength pairs. Higher cingulo-opercular and HC activity predicted lower false memory rates in younger and older adults, suggesting that binding and monitoring mechanisms contribute to false memory complementarily.

HC Subfield Contributions to Memory Development

Adaptive learning systems need to meet two conflicting goals: detecting regularities in the world through generalization versus remembering specific events through disambiguation—functions implemented in the neural circuits of the HC. Animal studies suggest that HC subfields reorganize during maturation. Studying this reorganization in the human HC is technically challenging. As a result, the ontogenetic timing of HC maturation is controversial and the contribution to generalization and specification in cognitive development remains elusive. By using high-resolution in-vivo MRI data from children (6–14 years) and younger adults, we were able to identify a multivariate profile of age-related differences in intra-HC structures and to show that HC maturity as captured by this pattern is associated with age differences in the differential encoding of unique memory representations (see Figure 6). The uneven time course of HC subfield maturation identified in this study provides a mechanistic explanation for the observation that generalization precedes specification in memory development during childhood.

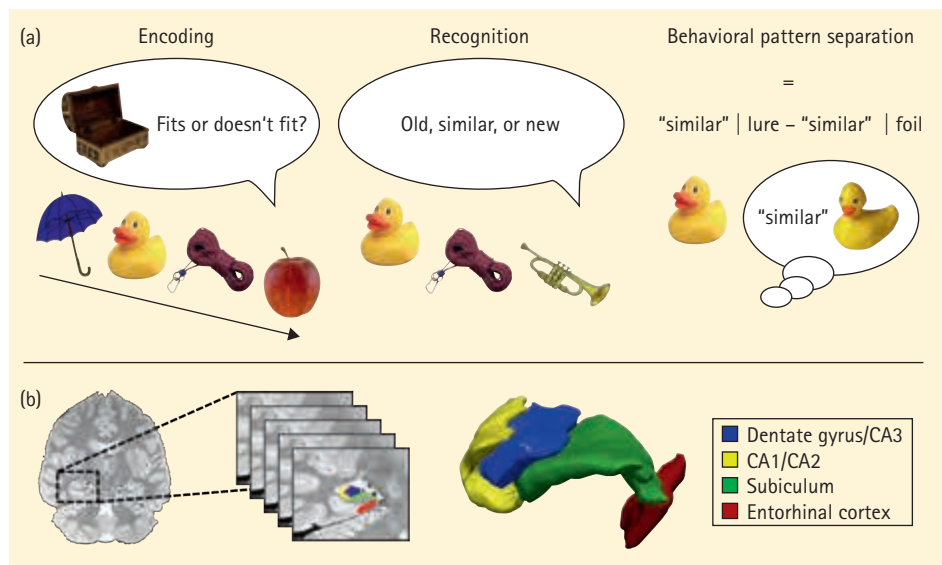


Figure 6. High-resolution structural MR images were acquired to study the contributions of maturational changes in hippocampal subregions to memory development. Trained raters manually identified boundaries between subfields. By combining subfield boundaries along the long axis of the HC, volumes were estimated based on three-dimensional models (shown on the right for the four traced subregions).

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Age Differences in the Influence of Prior Knowledge on Memory

Prior knowledge influences memory functioning (Dissertation Garvin Brod). We showed that knowledge improves memory by facilitating binding in the HC and enhancing its communication with the association cortices (Brod, Lindenberger, Wagner, & Shing, 2016). To disentangle knowledge accessibility from availability, we developed a paradigm that induces equal amounts of artificial knowledge in younger adults and children. We showed that the medial versus lateral prefrontal cortices support successful retrieval of information that is congruent versus incongruent with prior knowledge, respectively (Brod, Lindenberger, Werkle-Bergner, & Shing, 2015). Furthermore, children aged 8 to 12 years showed less medial prefrontal, but similar HC activation as younger adults when retrieving information successfully (Brod, Lindenberger, & Shing, 2016). This is in line with the two-component model of episodic memory development (Shing et al., 2010) proposing a developmental shift from HC-bound processing to increasing recruitment of prefrontal cortex in the service of memory.

Age Differences in the Interplay of Attention and Memory

Memory is tightly modulated by attention. However, the contributions of age differences in attention to memory are not well understood. The modulation of attention is linked to the functionality of the noradrenergic system as well as rhythmic neural activity in the alpha frequency range. To reveal their interplay and alterations with advancing age, we conducted a multimodal assessment (Dissertation Martin J. Dahl) of the structural and functional integrity of the central noradrenergic system (via neuromelanin-sensitive

MRI and pupillometry respectively) and of rhythmic neural activity (via simultaneous EEG). Our ultimate aim is to derive a mechanistic understanding of age-related declines in attention by revealing the interplay between the noradrenergic system and rhythmic neural activity within persons. This study is conducted in collaboration with Mara Mather (University of Southern California, USA).

Extending the Toolbox of Developmental Memory Research

Cognitive neuroscience aims to establish general laws that validly describe the multiple mappings between neural processes and behavior for any individual. The heterogeneity of these mappings within and across individuals poses methodological and conceptual problems, which are exacerbated by lifespan changes in neural resources and behavioral repertoires.

So far, between-person differences are often treated as "noise" that can be suppressed by averaging across persons. However, if individuals deviate from the "mean model" in significant ways, inferences derived from group studies may be misguided. As a principled alternative, we attempt to reliably identify neural and behavioral processing parameters at the within-person level. To this end, we explored the potential of massively repeated assessments (Dissertation Thomas H. Grandy) in conjunction with advanced statistical pattern recognition techniques (see Figure 7; cf. Karch, Sander, von Oertzen, Brandmaier, & Werkle-Bergner, 2015) to estimate person-specific parameters of processing dynamics as a viable and sound basis for generalizations across persons. This line of research is pursued in close collaboration with the *Formal Methods* project (see pp. 172–174).

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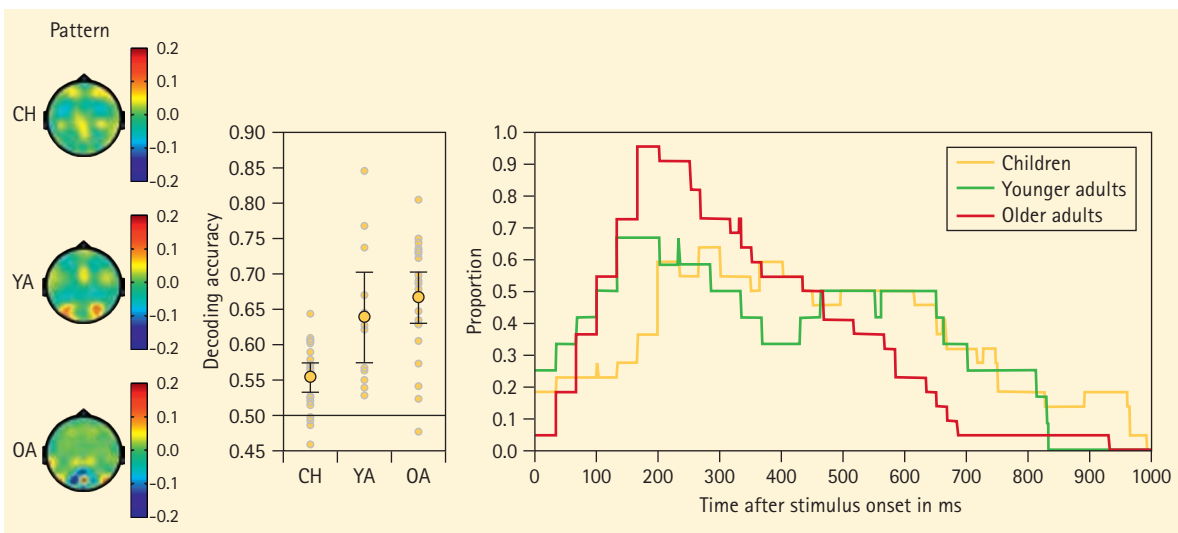


Figure 7. The current focus of spatial attention can be decoded with good precision from rhythmic neural EEG activity in the alpha frequency range (~10 Hz) in children, younger, and older adults. The sources of neural activity used for classification differ across age groups, as illustrated in the topographical distributions on the left. Decoding accuracy is lowest in children, but comparably high in younger and older adults, possibly suggesting higher consistency of task-based neural patterns in adults (middle graph). Inspection of the onset time points and the duration of time frames related to each participant's best classification accuracy reveals differences in the temporal emergence of discriminatory neural activity (graph to the right). High decoding accuracy for children and adults can be achieved across the entire poststimulus period. In older adults, activity specific to attentional focus is mainly found early on after stimulus onset, most likely reflecting a greater reliance on bottom-up processing (adapted from Karch, Sander, von Oertzen, Brandmeier, & Werkle-Bergner, 2015).

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Minerva Group (led by Yee Lee Shing)

Delineating Environmental Effects on Brain and Cognitive Development

The overarching goal of this group is to better understand the mechanisms through which environmental factors, such as school entry and stress-related social disadvantage, may affect neural and behavioral development. The *HippoKID Study* longitudinally followed children born close to the cut-off date for school entry who subsequently did or did not enter school that year. Schoolchildren displayed larger behavioral improvements in cognitive control than kindergarteners and also showed increased activation in posterior parietal cortex, a region important for sustained attention, while performing an inhibitory control task (Brod, Bunge, & Shing, 2017). In contrast, longitudinally observed improvements in episodic memory did not differ reliably between the two groups, suggesting that formal school entry primarily promotes brain mechanisms that help children to focus on cognitively demanding tasks. The ongoing longitudinal *Jacobs Study* aims to elucidate the roles of glucocorticoid and inflammation signaling in mediating the effects of stress on neural and behavioral development while assessing moderators at multiple levels, including (epi-)genetic dispositions (Dissertation Laurel Raffington).

Box 1.

Minerva Group (led by Myriam C. Sander)

Age Differences in Memory Representations

Established in 2016, this research group aims at understanding how aging affects memory representations and performance. Memories are encoded in distributed patterns of neural activity that are reactivated during later recall. To promote accurate retrieval, patterns representing different memories should differ from one another, whereas patterns representing several instances of the same memory should be similar to each other. To render memories durable, newly encoded patterns are spontaneously reactivated and strengthened during rest and sleep periods. The group will investigate how normal aging affects the distinctiveness and similarity of memory representations during memory formation and retrieval (Dissertation Verena R. Sommer). A related line of research will target age differences in the spontaneous reactivation of memories during rest.

Box 2.

Research Project 2: Mechanisms and Sequential Progression of Plasticity

This project addresses the questions of *whether and how* plasticity contributes to adult development. Special attention is given to the relationship between neural and behavioral manifestations of plasticity. Simone Kühn was the main principal investigator of this project from 2013. She was awarded a Heisenberg Professorship (W3) at the University Medical Center Hamburg-Eppendorf (UKE), where she is continuing her work from 2017 onward. In October 2016, Yana Fandakova and Elisabeth Wenger became the co-heads of this project.

The human brain has a significant capacity to adapt to changing environmental demands by altering its function and structure (see Lövdén, Wenger, Mårtensson, Lindenberger, & Bäckman, 2013). The central goals of this project are to delineate the *mechanisms and sequential progression* of behavioral and neural plasticity across the lifespan. The guiding propositions of the project are based on the assumption that plasticity is induced by a mismatch between environmental demands and an individual's current behavioral and neural resources (see Figure 4, p. 145). The project is interested in plastic changes across the lifespan, induced by mismatches in either direction: It examines situations in which current demands exceed supply (e.g., cognitive interventions) as well as situations in which supply exceeds current demands (e.g., sensory deprivation). Training studies targeting specific brain regions and circuits that hypothetically support particular skills are central to the project's research agenda. In addition, the project also examines plasticity in real-life contexts that are likely to induce a mismatch between demand and capacity. Furthermore, examining individuals who are experts in particular skills offers yet another window on the consequences and correlates of plasticity. In the following, we provide a selective summary of completed studies, ongoing work, and future plans.

Skilled Motor Performance

Skilled motor performance provides a rich testing ground for exploration of the mechanisms and progression of plasticity. We acquired up to 18 structural magnetic resonance (MR) images over a 7-week period while 15 right-handed participants practiced left-hand writing and drawing (Wenger et al., 2017). After 4 weeks, we observed increases in gray matter in both left and right primary

motor cortices relative to a control group; another 3 weeks later, these differences were no longer reliable (see Figure 8). Time-series analyses showed that gray matter in both primary motor cortices expanded during the first 4 weeks and then partially renormalized, in particular in the right hemisphere, in the presence of continued practice and increasing task proficiency. The regions of observed structural change are in close vicinity to anatomical hand knobs that are easily discernible on anatomical MR images and also lie within regions of functional activation maps for left- and right-hand finger tapping and left- and right-hand writing inside the scanner.

Spatial Navigation

Following up on a series of studies investigating the influence of spatial navigation training on brain structure, we have reported gray matter increases in the right prefrontal cortex, the right hippocampal formation, and in both hemispheres of the cerebellum after daily playing of a commercially available video game in which participants had to navigate an avatar through a 3D world (Kühn, Gleich, Lorenz, Lindenberger, & Gallinat, 2014). An ongoing study examines scientists who are spending 15 months at the Neumayer Station of the Centre of German Research in Antarctica. Before the scientists leave for their extended stay in an environment that is generally devoid of spatial cues, we assess their spatial abilities and acquire high-resolution structural images of the hippocampus. MR imaging assessment is repeated after the scientists return from Antarctica to examine whether the spatially poor environment in Antarctica is associated with declines in spatial abilities and related brain structures, and whether these declines are reversible. Data acquisition of two cohorts of participants is now

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