Center for Lifespan Psychology

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Research Project 1: Lifespan Rhythms of Memory and Cognition (RHYME)

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This project investigates lifespan changes in attention, working memory, and episodic memory at structural, functional, and behavioral levels of analysis, with an emphasis on age differences in the coordination of oscillatory brain activity. It combines experimental with longitudinal research designs and uses multimodal data from a wide range of neuroimaging methods. During the reporting period, the project's research activities were centered around four interrelated themes.

Aging Cognition, Neuromodulation, and Rhythmic Neural Activity

In their daily lives, individuals constantly experience a wide range of feelings, thoughts, and sensations. To permit goal-directed behavior and sustain cognitive development, some of these signals need to be enhanced whereas others need to be suppressed. At the neural level, this selection operation is implemented by a network of frontoparietal cortical regions, interconnected via the thalamus. Processing in this network is orchestrated through temporally synchronized activation patterns. Neuromodulators are of key importance in this process, as they regulate the efficacy of synaptic transmission. We hypothesize that senescent changes in the precision with which neuromodulators are released from brainstem nuclei might affect the functionality of selective processing, rendering selection more difficult with advancing adult age.

In a series of studies (Dissertation Martin J. Dahl) conducted in collaboration with Mara Mather from the University of Southern California, USA, we have probed the interaction between age-associated differences in the integrity and functionality of the central noradrenergic system and rhythmic neural activity in the alpha frequency range (~10 Hz). Structurally, we focused on the locus coeruleus (LC), a small brainstem nucleus that serves as the main source of norepinephrine (NE) in the brain. In the past, the LC's small size and location deep in the brain have prevented noninvasive studies of its integrity and functionality. Hence, in a first study (Dahl, Mather et al., 2019), we developed a semiautomatic method to derive individualized estimates of structural LC integrity from high-resolution neuromelanin-sensitive magnetic resonance images (MRI; see Figure 5). Applying these methods in samples of younger and older adults from the Berlin Aging Study II (see also pp. 138 ff.), we found that LC integrity correlated positively with individual differences in learning and memory across age groups and within the group of older adults. Analyses across the rostro-caudal extent of the LC revealed spatially confined and functionally relevant age differences in LC integrity. Critically, older adults who showed more youth-like intensity ratios in rostral, hippocampus (HC)-projecting LC segments also showed higher levels of memory performance. An LC probability map derived from this study is freely available to the neuroscience community to facilitate comparability of studies.

Memory is tightly modulated by attention, but the contribution of adult age differences in attention to memory is not well understood. To reveal the interplay between the functionality of the NE system and rhythmic neural activity in the alpha frequency range that modulates attention, we used neuromelanin-sensitive MRI, pupillometry, and electroencephalography (EEG) to relate the structural and functional integrity of the central NE system to rhythmic neural activity in the context of a demanding auditory selective attention task. Recently, we used the same task to reveal a partial reorganization of attention-related rhythmic neural responses (Dahl, Ilg et al., 2019). We combined the auditory attention task with a fear-conditioning manipulation to manipulate NE release on a trial-by-trial level. During conditioning trials, we noted a reliable arousal response reflected in larger pupil responses and stronger desynchronization of rhythmic neural alpha activity for trials with the reinforced conditioned stimulus (CS+) compared to non-reinforced (CS–) trials. Critically, presentation of fear-conditioned stimuli during the auditory

Key References

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Link to LC Map
www.mpib-berlin.mpg.de/lc-map

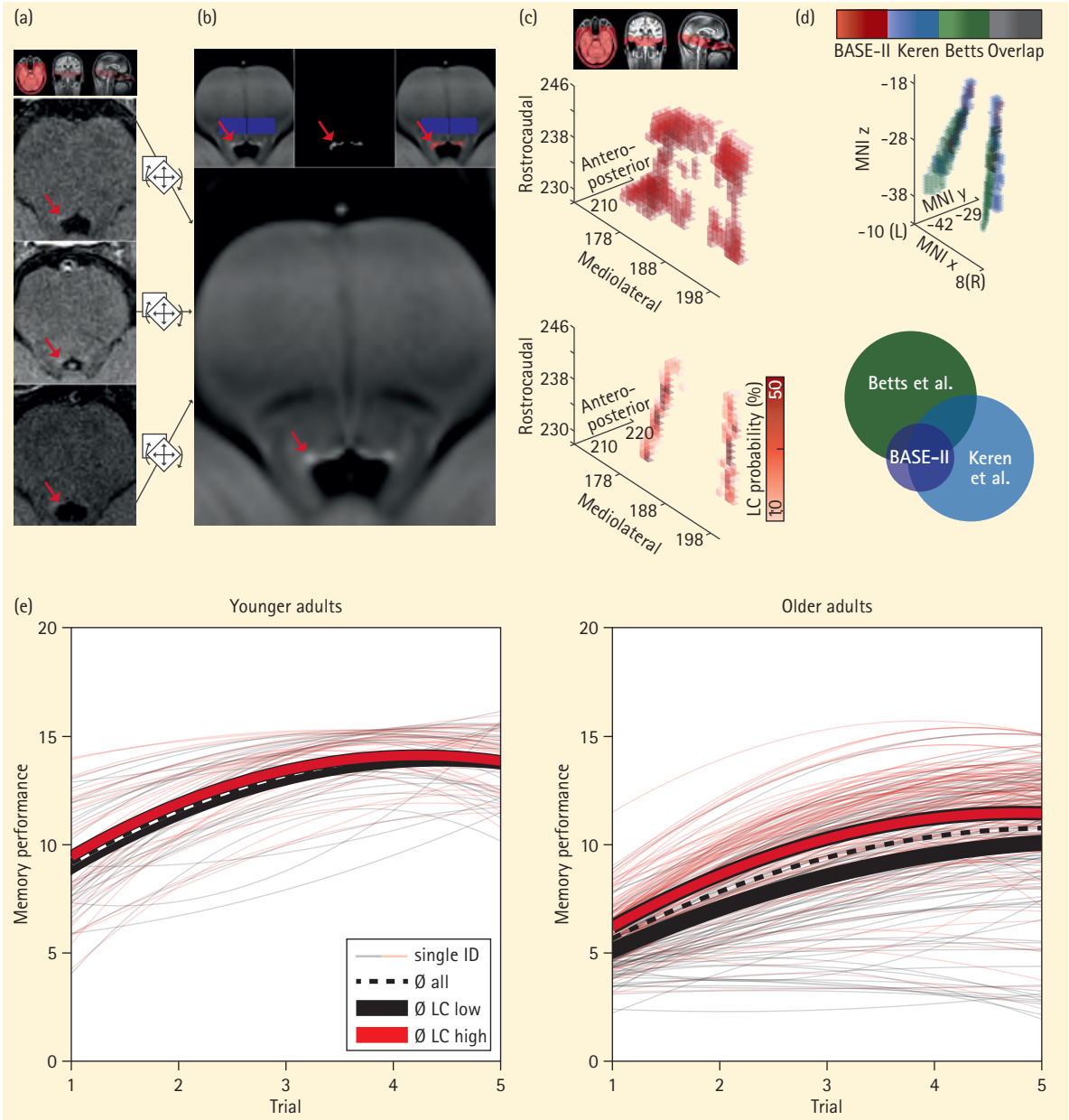

Figure 5. Schematic overview of the semiautomatic analysis procedure developed to extract individual locus coeruleus (LC) intensity values across the rostrocaudal extent. (a) Native-space neuromelanin-sensitive brainstem scans of three randomly selected participants (axial slices are shown). Hyperintensities corresponding to the LC are indicated by red arrows. (b) Neuromelanin-sensitive scans were aligned and pooled across participants to increase the signal-to-noise ratio and to facilitate LC delineation using a template-based approach. On a group level, LC location (red) was semiautomatically determined based on an intensity threshold relative to a pontine reference area (blue; see inlays). (c) Areas surviving the thresholding were grouped into a volume of interest (search space: upper plot; 3D representation) and used to restrict automatized extraction of individual peak intensities and their location. Observed peak LC locations were converted to a LC probability map (lower plot). (d) In standard space, the LC probability map was successfully validated using previously published maps. Circle radius indicates map size (i.e., number of voxels). (e) Estimated learning and memory performance trajectories for younger and older adults. To enable visualization of the association between LC integrity and memory performance, single participants (thin lines; ID) are color-coded based on LC integrity (median-split), and mean trajectories for subgroups are displayed (thick lines). Left: $n = 33$ younger adults in the low- and high-LC groups respectively; right: $n = 114$ older adults each in the low- and high-LC groups, respectively (adapted from Dahl, Mather et al., 2019).

Key Reference

Muehlroth, B. E., Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., Shing, Y. L., & **Werkle-Bergner, M.** (2020). Memory quality modulates the effect of aging on memory consolidation during sleep: Reduced maintenance but intact gain. *Neuroimage, 209*, Article 116490. https://doi.org/10.1016/j.neuroimage.2019.116490

attention task reinstated the acquired arousal response in the absence of reinforcements. When combining the behavioral and physiological data in a structural equation model, we found that a more responsive noradrenergic system was associated with more proficient attention performance and that older adults showed a reduced responsiveness of the NE system relative to young adults (Dahl et al., 2020).

Taken together, these findings indicate that reduced structural integrity and functional responsiveness of the central noradrenergic system is associated with age differences in attention and memory. Specifically, our multimodal data suggest that age-related changes in noradrenergic neuromodulation might affect attention and memory through alterations in low-frequency rhythmic neural activity.

The Co-Development of Brain, Sleep, and Cognition

Sleep, like breathing, arguably belongs to the most basic bodily needs. Healthy sleep supports learning and memory, whereas lack of sleep hinders knowledge acquisition. After a day full of learning, sleep supports the stabilization and integration of experiences into a framework of personal memories while setting the stage for continued learning during ensuing wakefulness.

Thus far, most research into the causes of memory decline during adulthood and old age has focused on the encoding of new and the retrieval of previously acquired experiences. However, the long-term maintenance of new experiences also requires consolidation, defined as the stabilization of memory representations beyond initial encoding. According to the Active System Consolidation framework introduced by Jan Born and colleagues, sleep plays a central role in consolidation by facilitating interactions between fast-learning HC and slow-learning cortical systems.

Normal human aging entails fundamental changes in sleep and brain structure, even in the absence of pathology. To date, only few studies have attempted to unravel age differences in sleep physiology, brain structure, and memory consolidation. In part, this lack of relevant research reflects methodological problems when attempting to compare this triad across age groups.

In collaboration with Björn Rasch (University of Fribourg, Switzerland), we conducted a large age-comparative study on the influence of memory quality on encoding, consolidation, and retrieval (Dissertation Beate E. Mühlroth). The study consisted of a multisession protocol including behavioral, EEG, and MRI assessments, as well as ambulatory polysomnographic sleep monitoring. Healthy younger and older adults worked on an age-adapted associative memory task for two consecutive days. The task was developed to assess memory strength at the single-item level within each study participant. We aimed at disentangling the effects of reduced overnight forgetting from active enhancement of initially labile memory traces.

A first set of analyses targeted two main questions: first, whether age differences in sleep-dependent consolidation depend on the quality of memory representations formed during learning; and second, whether individual differences in sleep physiology and brain structure predict differences in consolidation within and across age groups (see Muehlroth, Sander et al., 2020). As expected, age differences in sleep-dependent memory stabilization were most pronounced at medium levels of encoding quality. Partial least squares (PLS) analyses identified differences in sleep physiology and brain structure that were associated with older age. However, when selecting younger and older adults based on their similarity in sleep physiology and brain structure, as reflected in the PLS scores, neither of the two in isolation was sufficient to account for age differences in consolidation (see Figure 6).

We next sought to better understand what might drive the observed age differences in sleep-dependent consolidation. Active System Consolidation theory suggests that the transfer of labile HC-dependent representations into more stable cortical networks critically depends on the precise temporal coordination of cortical slow oscillations (SO) with fast-frequency thalamo-cortical spindles (Sp). Accordingly, animal research indicates that precise SO–Sp coupling is critical for consoli-

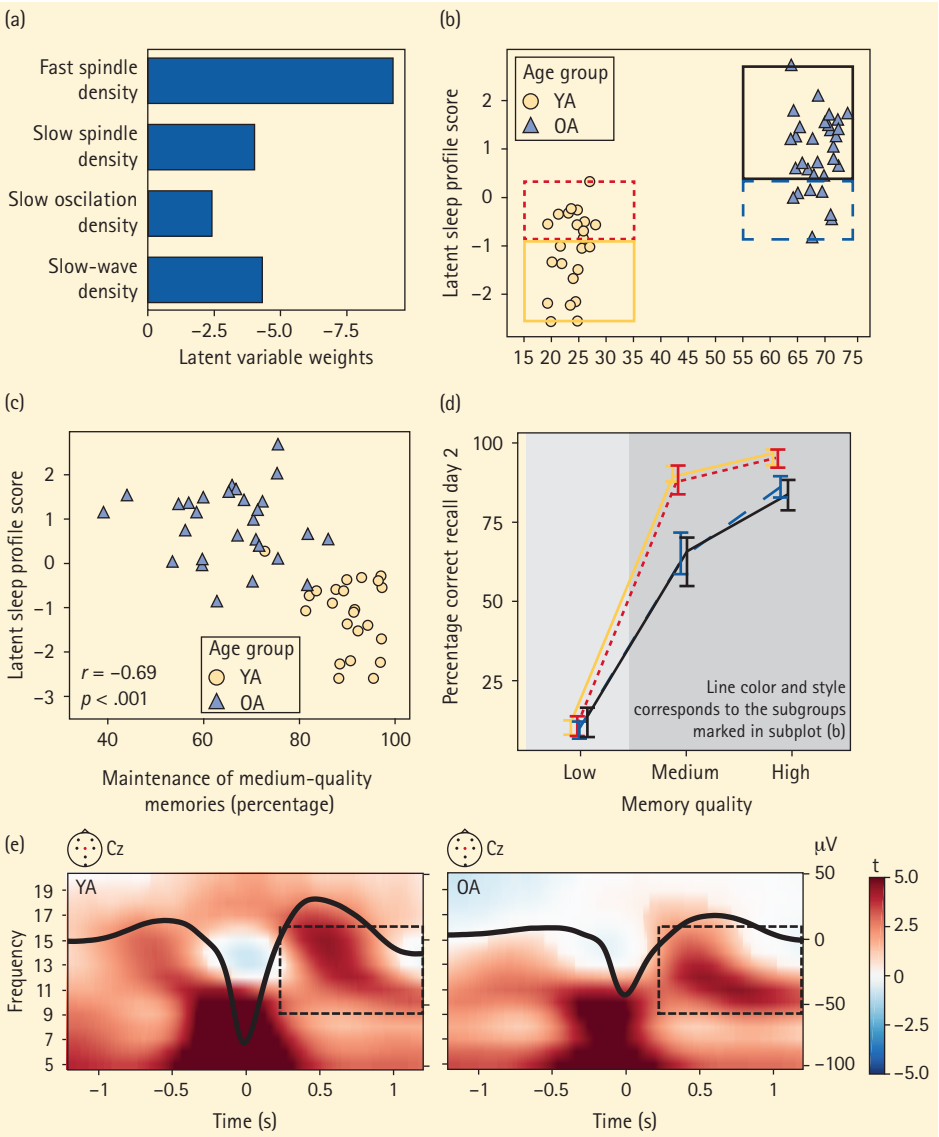

Figure 6. Sleep–memory associations in younger and older adults (adapted from Muehlroth et al., 2019, 2020). (a) Partial-least-squares solution relating physiological sleep indicators to age. The resulting latent variable captures the common variance between participants' age and sleep. Latent variable weights (in *Z*-scores) demonstrate that all physiological sleep indicators have a stable negative relation to age. (b) Each participant's expression of the latent variable is plotted against age. Overlap between the age groups is marked by dashed boxes. (c) Each participant's latent sleep-profile score is plotted as a function of memory performance. Spearman's rank-order correlation coefficients for the whole sample are displayed. Maintenance of medium-quality memories relates to the latent sleep-profile score across age groups. (d) Median behavioral performance for all subgroups is displayed, with grouping, line color, and style corresponding to (b). The first and third quartiles are depicted as error bars. Memory gain (shaded in light gray) is similar in all subgroups. Memory maintenance (shaded in darker gray) is modulated by sleep profile, but differs between younger and older adults even when they have the same sleep profile. (e) Age differences in slow-oscillation-spindle coupling (Muehlroth et al., 2019). Differences in wavelet power for slow-oscillations (SO) trials (respective down peak ± 1.2 s) compared to trials without SOs are depicted (in *t*-score units). The average frontal SO for each age group is inserted in black (the scale in μV is indicated on the right of each time–frequency graph). In both age groups, EEG power is modulated as a function of the SO phase. In younger adults (on the left), fast spindle activity (12–15 Hz) peaks during the up peak of the SO. Slow spindle power (9–12 Hz) is strongest at the up- to down-state transition. In older adults (on the right), power increases are delayed and shifted to lower frequencies as compared to younger adults.
YA: younger adults; OA: older adults.

Key Reference

Muehlroth, B. E., Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., **Shing, Y. L.,** & **Werkle-Bergner, M.** (2019). Precise slow oscillation-spindle coupling promotes memory consolidation in younger and older adults. *Scientific Reports, 9,* Article 1940. https://doi.org/10.1038/s41598-018-36557-z

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Muehlroth, B. E., & **Werkle-Bergner, M.** (2020). Understanding the interplay of sleep and aging: Methodological challenges. *Psychophysiology, 57* (3), Article e13523. https://doi.org/10.1111/psyp.13523

dation. Most studies in humans thus far have looked at the contributions of each of the two components, but not at the precision of their coupling.

We used individually adjustable detection algorithms to identify individual SO and Sp events (see Muehlroth et al., 2019). On that basis, we were able to show that less precise coupling between slow waves and spindles is indeed associated with lower overnight memory maintenance among older adults. In addition, older adults with greater structural integrity of brain regions relevant for sleep and memory were more likely to show precise coupling patterns resembling those of younger adults than older adults with lower brain integrity.

In sum, this line of research suggests that age differences in sleep-associated consolidation depend on the precise coupling among cardinal neural sleep rhythms supported by the integrity of relevant brain structures.

Research on sleep and aging has sought to develop new approaches to identify and possibly treat age-associated pathological conditions. In particular, attempts to establish sleep as a novel biomarker and treatment target for Alzheimer's disease have led to a growing interest in research on sleep and aging. This rise in interest has not been matched by a careful scrutiny of data-analytic procedures.

In a theoretical and empirical analysis (Muehlroth & Werkle-Bergner, 2020), we used electrophysiological sleep and structural brain data of healthy younger and older adults to identify, illustrate, and resolve methodological core challenges in the study of sleep and aging. We demonstrated potential biases in common analytic approaches when applied to heterogeneous populations, especially regarding markers of rhythmic neural activity during sleep. Using empirical demonstrations, we show that uncovering age-dependent alterations in the physiology of sleep requires the development and use of age-group adjusted and individualized data-analytic procedures. Ultimately, these innovations may yield valid and reliable biomarkers that discriminate between normal and pathological age-related changes in sleep physiology.

A key challenge for the age-adapted analysis of rhythmic neural activity—like sleep oscillations—is the identification of individual rhythmic events and their separation from arrhythmic background activity. In collaboration with the Lifespan Neural Dynamics Group (see also pp. 195 ff.), we extended and improved an existing rhythm detection method (Kosciessa et al., 2020; see also p. 199 for further details).

Development of Memory Specificity and Intra-Hippocampal Maturation

At the other end of the lifespan, the project has begun to link HC maturation to memory development. Just as any other adaptive learning system, children are confronted with two conflicting goals. They need to detect regularities in the world through generalization while remembering specific events through disambiguation. Core aspects of these functions are implemented in the internal 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 its contribution to generalization and specificity in cognitive development remains elusive. In a study using high-resolution in-vivo MRI data from children (6–14 years old) and younger adults (Keresztes et al., 2017), 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. 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 (for a theoretical overview, see Keresztes et al., 2018).