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Neuromodulation and rhythmic neural activity shape cognition across the adult lifespan

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt,

- dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,
- dass ich die Dissertation an keiner anderen Universität eingereicht habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze und,
- dass mir die Promotionsordnung zum Dr. rer. nat./Ph. D. des Fachbereichs Erziehungswissenschaft und Psychologie der Freien Universität Berlin vom 8. August 2016 (Amtsblatt der Freien Universität Berlin 35/2016) bekannt ist.

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List of publications

This doctoral dissertation is based on the following original publications:

Study I

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Study II

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Study III

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List of abbreviations

ACh	Acetylcholine
ARAS	Ascending reticular activating system
BOLD	Blood oxygen level-dependent
CSF	Cerebrospinal fluid
CS+	Conditional stimulus
CS–	Neutral control stimulus
DA	Dopamine
EEG	Electroencephalography
ERD	Event-related desynchronization
ERP	Event-related potential
ERS	Event-related synchronization
FLASH	Fast low angle shot
fMRI	Functional magnetic resonance imaging
LFP	Local field potential
GABA	gamma-Aminobutyric acid
Hz	Hertz
LC	Locus coeruleus
LTD	Long-term depression
LTP	Long-term potentiation
MRI	Magnetic resonance imaging
MT	Magnetization transfer
MEG	Magnetoencephalography
NET	Norepinephrine transporter
NE	Norepinephrine
PET	Positron emission tomography
qMRI	Quantitative anatomical magnetic resonance imaging
RAVLT	Rey auditory verbal learning test
rTMS	Rhythmic transcranial magnetic stimulation
5-HT	Serotonin
tACS	Transcranial alternating current stimulation
TSE	Turbo spin echo
US	Unconditional stimulus

Summary

With advancing age, humans' ability to filter out relevant pieces of information and maintain them over extended periods wanes. In the brain, the preferential processing of relevant information is supported by the transient synchronization of rhythmic neural activity within a distributed network including frontal and parietal cortical structures, orchestrated by the thalamus. To tune synchronization in thalamocortical networks according to current demands, neural communication is dynamically sculpted by the timed release of neuromodulators. However, while evidence about the roles of neuromodulation and neural synchronization in cognitive aging is accumulating, their interplay in the aging brain is much less understood.

This dissertation presents three empirical studies which bridge levels of analysis to highlight the role of noradrenergic neuromodulation in preserving late-life cognition, presumably mediated via modulations of low frequency synchronization (<30 Hz).

Specifically, in the first study, we assessed magnetic resonance imaging (MRI) indices for the structural integrity of the locus coeruleus (LC), the source of cortical norepinephrine, in large samples of younger and older adults. Individual differences in learning and memory were positively associated with LC integrity across a variety of memory tasks. Moreover, we discovered functionally relevant, spatially confined age differences in LC integrity in rostral parts of the nucleus that project to memory-relevant areas like the hippocampus.

In the second study, compromised selective attention in older adults was linked to a partial reorganization of rhythmic neural responses as assessed using electroencephalography (EEG). In particular, we found a behaviorally relevant, age-graded shift from a preparatory modulation of lateralized rhythmic activity roughly in the alpha band (~6–16 Hz) to an externally driven response in the alpha–beta range (9–30 Hz).

Finally, the third study established a link between low frequency EEG desynchronization and pupil dilation, a marker for noradrenergic activity, suggesting a common dependence on phasic norepinephrine release. In addition, noradrenergic responsiveness, as indexed by combined pupil and EEG measures, declined with advancing age and was strongly related to individual differences in selective attention.

The presented findings fill the gap between previous animal studies and human research on the neural underpinning of selective attention and memory. Taken together, this dissertation highlights the interplay of noradrenergic neuromodulation and neural synchronization in shaping aging cognition.

Zusammenfassung

Die Fähigkeit relevante Informationen aus der Umwelt herauszufiltern und sich über eine längere Zeit zu merken nimmt mit zunehmendem Alter ab. Im Gehirn wird die bevorzugte Verarbeitung relevanter Informationen durch eine vorübergehende Synchronisierung der neuronalen Aktivität in einem ausgedehnten Netzwerk ermöglicht. Zu diesem neuronalen Netzwerk gehören unter anderem frontale und parietale kortikale Strukturen, welche vom Thalamus koordiniert werden. Die zeitlich fein abgestimmte Ausschüttung von Neuromodulatoren erlaubt dabei, die Synchronisierung in thalamokortikalen Netzwerken dynamisch an die gegenwärtigen Anforderungen anzupassen.

Während unser Wissen über die jeweilige Rolle von Neuromodulatoren und neuronaler Synchronisierung in Bezug auf kognitives Altern wächst, ist ihr Zusammenspiel im alternden Gehirn weit weniger verstanden.

Diese Dissertation umfasst drei empirische Studien, welche unterschiedliche Analyseebenen verknüpfen, um die Bedeutung noradrenerger Neuromodulation für die Erhaltung kognitiver Fähigkeiten im Alter aufzuzeigen. Der Einfluss Noradrenalins auf Aufmerksamkeits- und Gedächtnisprozesse wird dabei vermutlich durch eine Modulation niederfrequenter neuronaler Synchronisierung (<30 Hz) vermittelt.

In der ersten Studie nutzten wir Magnetresonanztomografie, um Rückschlüsse auf die strukturelle Integrität des Locus Coeruleus (LC), der Quelle kortikalen Noradrenalins, zu ziehen. In großen Stichproben von jüngeren und älteren Erwachsenen beobachteten wir einen positiven Zusammenhang zwischen der Integrität des LC und interindividuellen Unterschieden in der Gedächtnisleistung, erfasst über eine Vielzahl von Gedächtnisaufgaben. Darüber hinaus deckte diese Studie verhaltensrelevante, räumlich begrenzte Altersunterschiede in gerade den Abschnitten des LC auf, welche zu gedächtnisrelevanten Gehirnregionen wie dem Hippokampus projizieren.

In der zweiten Studie beobachteten wir eine Assoziation zwischen altersbedingten Einbußen in selektiver Aufmerksamkeit und einer teilweisen Neuorganisation synchronisierter neuronaler Reaktionen, gemessen mittels Elektroenzephalographie (EEG). Im Speziellen deckten wir eine altersabhängige, verhaltensrelevante Verlagerung auf – von einer vorrausschauenden Modulation lateralisierter Aktivität annähernd im Alpha-Freuenzbereich (~6–16 Hz) hin zu einer extern gesteuerten Reaktion im Alpha–Beta-Frequenzband (9–30 Hz).

Die dritte Studie stellte schließlich eine Verbindung zwischen EEG-Desynchronisierung und Pupillenweitung, einem Marker noradrenerger Aktivität, her. Dieser Befund deutet darauf hin, dass sowohl neuronale Synchronisierung als auch Pupillenweitung durch die phasische

Aktivität des noradrenergen Systems beeinflusst werden. Wir beobachteten zudem, dass die Reaktionsfähigkeit des noradrenergen Systems, gemessen über Pupillenweite und EEG-Synchronisierung, mit zunehmendem Alter abnimmt und eng mit interindividuellen Unterschieden in selektiver Aufmerksamkeit im Zusammenhang steht.

Die präsentierten Ergebnisse schlagen eine Brücke zwischen vorherigen Tierstudien und Humanforschung zu den neuronalen Grundlagen von Aufmerksamkeits- und Gedächtnisprozessen. Zusammengenommen zeigt diese Dissertation auf, dass das Zusammenspiel noradrenerger Neuromodulation und neuronaler Synchronisierung die Entwicklung unsere Kognition im Alter prägt.

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Introduction

Daily situations confront us with a multitude of sensations that far exceed neural processing resources. They thus pose a complex computational problem: What aspects of the environment are crucial for current and future goal-directed actions and how can they be selected for further analysis (Buschman & Kastner, 2015; Desimone & Duncan, 1995; Foster & Awh, 2019; Thiele & Bellgrove, 2018)? Selective attention denotes a filter mechanism that allows for the preferential processing of relevant over irrelevant information (Buschman & Kastner, 2015; Halassa & Kastner, 2017; Thiele & Bellgrove, 2018; van Diepen, Foxe, & Mazaheri, 2019). On a conceptual and neural level, selective attention is tightly interwoven with the ability to encode, maintain, and consciously recollect experiences acquired in a certain time and place (i.e., episodic memory; Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Halassa & Kastner, 2017; Hanslmayr, Staresina, & Bowman, 2016; Hanslmayr, Staudigl, & Fellner, 2012; Sara, 2009, 2015; Tulving, 1983; van Ede, 2018): Both attention and memory allow goal-directed behavior by facilitating access to relevant over irrelevant information (Awh et al., 2006). In particular, attention has been conceptualized as a gatekeeper for memory that biases encoding and retrieval towards prioritized information (Awh et al., 2006; Gazzaley, Cooney, Rissman, & D'Esposito, 2005). Similarly, memory retrieval has been described as a form of selective attention towards internal mnemonic representations (Chun & Turk-Browne, 2007). In turn, previous experiences, as stored in episodic memory, determine which aspects of the environment are preferentially attended to and selected for further processing (Chun & Turk-Browne, 2007).

In later life, the ability to selectively process relevant aspects of the environment fades (Craik & Bialystok, 2006; Grady, 2012; Lindenberger & Mayr, 2014). Despite considerable interindividual differences in onset and rate of change (Lindenberger & von Oertzen, 2006), healthy aging is associated with progressive declines in attention (Erel & Levy, 2016; Kennedy & Mather, 2019; Plude, Enns, & Brodeur, 1994; Sander, Lindenberger, & Werkle-Bergner, 2012; Staub, Doignon-Camus, Després, & Bonnefond, 2013) and episodic memory (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012; Nyberg & Pudas, 2019; Shing et al., 2010; Tromp, Dufour, Lithfous, Pebayle, & Després, 2015; Werkle-Bergner, Müller, Li, & Lindenberger, 2006). At the same time, aging affects brain structure and function across multiple levels of analysis (e.g., the genetic, cellular, and systems level; Cabeza, Nyberg, & Park, 2004; Grady, 2012). Research in the cognitive neuroscience of aging attempts to elucidate the neural mechanisms of age-related cognitive decline (Cabeza et al., 2018, 2004), which is a prerequisite for the development of effective interventions (Quentin & Cohen, 2019). Progress in

this endeavor will not only be substantial for understanding late-life cognitive development, but also advance the general knowledge about brain–cognition interactions, since periods of change offer valuable insights into the dynamics of complex systems (Lindenberger, Li, & Bäckman, 2006). The work described in the following chapters integrates across both neural and behavioral levels of analysis (Li & Lindenberger, 1999; Li, Lindenberger, & Sikström, 2001; Lindenberger, Li, Lövdén, & Schmiedek, 2007) to investigate the mechanisms underlying age-related differences in selective information processing.

On a neural level, a highly overlapping network of frontoparietal cortical regions, interconnected via the thalamus, supports selective information processing and is implicated in attention (Buschman & Kastner, 2015; Corbetta & Shulman, 2002; Fiebelkorn, Pinsk, & Kastner, 2018, 2019; Halassa & Kastner, 2017) and episodic memory (Cabeza et al., 2008; Simons & Spiers, 2003). Neural information processing in this distributed network is orchestrated by means of temporally synchronized activation patterns which arise from the dynamic interplay of intrinsic cellular and circuit properties (also termed neural oscillations; Buschman & Kastner, 2015; Buzsáki & Draguhn, 2004; Fries, 2005, 2015; Ketz et al., 2015; Voytek & Knight, 2015). The state and functionality of processing in frontoparietal networks is moreover contingent on the precisely controlled release of neuromodulators from brainstem nuclei (Arnsten & Li, 2005; Robbins & Arnsten, 2009; Thiele & Bellgrove, 2018). Neuromodulators are a group of chemicals that upon release, alter the cellular properties of neurons in their brain-wide terminal fields as well as the efficacy of their synaptic transmission (Lőrincz & Adamantidis, 2017; Sara, 2009). Importantly, neuromodulatory and rhythmic neural activity are not independent but show mutual dependencies (Mather, Clewett, Sakaki, & Harley, 2016; McCormick, 1989; McCormick, Pape, & Williamson, 1991; Sara, 2009, 2015; Stitt, Zhou, Radtke-Schuller, & Fröhlich, 2018). Stimulation of neuromodulatory brainstem nuclei, for instance, is associated with profound changes in cortical synchronization (Carter et al., 2010; Moruzzi & Magoun, 1949; Neves, van Keulen, Yang, Logothetis, & Eschenko, 2018). On the other hand, state-dependent firing of neuromodulatory nuclei precisely linked in time to forebrain oscillations has been observed (i.e., phase-locked; Safaai et al., 2015; Sara, 2015; Sara & Bouret, 2012), underlining the interdependence of neuromodulation and rhythmic neural activity. Accordingly, recent investigations have demonstrated that neuromodulation plays a crucial role in dynamically sculpting the communication (i.e., synchronized firing patterns) in distributed cortical and corticothalamic networks that underlies cognition (Stitt et al., 2018).

Previous research in the cognitive neuroscience of aging separately linked altered neuromodulation (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Braver & Barch, 2002; Li

& Lindenberger, 1999; Li et al., 2001; Li & Sikström, 2002; Mather & Harley, 2016) and patterns of synchronized neural activity (Sander, Lindenberger, et al., 2012; Werkle-Bergner et al., 2006) to age-related differences in cognition. Although both neuromodulation and rhythmic neural activity interactively bias information processing in neural networks such that relevant information is prioritized (Jensen & Mazaheri, 2010; Stitt et al., 2018; Thiele & Bellgrove, 2018), their interplay in the aging brain is poorly understood. In this dissertation, these separate lines of research are first extended (Studies I and II) and then combined (Study III) to arrive at a more holistic, mechanistic explanation of late-life age differences in attention and memory (Li & Lindenberger, 1999; Li et al., 2001; Lindenberger et al., 2007).

Theoretical and empirical foundations

This chapter reviews relevant literature to provide the theoretical and empirical foundation for this dissertation. Here, I will place a special emphasis on (1) noradrenergic neuromodulation and (2) rhythmic neural activity in the alpha frequency range (i.e., ~8–12 Hz), as well as age-related changes in both. While undoubtedly several neuromodulatory systems (e.g., norepinephrine [NE], dopamine [DA], acetylcholine [ACh], serotonin [5-HT]) interactively shape cognition (Noudoost & Moore, 2011; Robbins & Arnsten, 2009; Sara, 2009; Thiele & Bellgrove, 2018), recent theories of both healthy (Mather & Harley, 2016) and pathological (Weinshenker, 2018) cognitive aging emphasize a prominent role of the noradrenergic system in shaping cognition in later life. In addition, methodological advances provide surrogate measures for noradrenergic activity (Breton-Provencher & Sur, 2019; Joshi, Li, Kalwani, & Gold, 2016; Reimer et al., 2016; Vazey, Moorman, & Aston-Jones, 2018) and structural integrity (Keren et al., 2015; Liu et al., 2017; Sasaki et al., 2006; Watanabe, Tan, Wang, Martinez-Hernandez, & Frahm, 2019), for the first time overcoming long-standing technical challenges in non-invasive assessments (Astafiev, Snyder, Shulman, & Corbetta, 2010; Keren, Lozar, Harris, Morgan, & Eckert, 2009; Nieuwenhuis & Jepma, 2011). However, clearly dopaminergic (Bäckman et al., 2006; Braver & Barch, 2002; Li et al., 2001; Li & Rieckmann, 2014) and cholinergic (Muir, 1997) neuromodulation, in particular, also determine cognitive changes in aging – a long-term goal in the cognitive neuroscience of aging is to delineate their interaction.

On a electrophysiological level, I focus on alpha-oscillatory activity in view of its distinct role in selective information processing (Foster & Awh, 2019; Hanslmayr et al., 2012; Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007; van Diepen et al., 2019), cognitive aging (Sander, Lindenberger, et al., 2012; Werkle-Bergner et al., 2006), and, importantly, the interaction of low frequency synchronization and noradrenergic neuromodulation (Buzsáki, Kennedy, Solt, & Ziegler, 1991; Carter et al., 2010; Marzo, Totah, Neves, Logothetis, & Eschenko, 2014; McCormick, 1989; McCormick et al., 1991; McGinley, David, & McCormick, 2015; Neves et al., 2018; Safaai et al., 2015; Stitt et al., 2018). Notably, however, similar computational roles in selective information processing have been postulated for other low frequencies (<30 Hz; e.g., theta [~3–8 Hz]: Fiebelkorn & Kastner, 2019; beta [~12–30 Hz]: Hanslmayr et al., 2012), which also demonstrate changes with age (Ishii et al., 2017; Klimesch, 1999; Voytek & Knight, 2015). To conclude, the selective focus on NE and alpha arises here (1) on a conceptual level from their shared selectivity-increasing effect and similar changes with age (Mather et al., 2016; Sander, Lindenberger, et al., 2012), (2) on a neural level

from evidence for their interaction (Buzsáki et al., 1991; McCormick et al., 1991; Rougeul-Buser & Buser, 1997; Stitt et al., 2018), and finally, (3) the underexplored role of this interplay in shaping late-life developments of cognition (cf. Kennedy and Mather, 2019).

Neural mechanisms of selective information processing

Selection among environmental inputs can be achieved by biasing their competition for neural processing resources in favor of goal-relevant stimuli (Buschman & Kastner, 2015; Desimone & Duncan, 1995). Goals, also called attentional templates or attentional sets, are represented in prefrontal and parietal areas and bias processing in posterior sensory cortices (Banich, 2009; Braver & Barch, 2002; Buschman & Kastner, 2015; Corbetta & Shulman, 2002; Fiebelkorn et al., 2018; Halassa & Kastner, 2017; Noudoost & Moore, 2011). On a neural level, an elevated baseline firing rate in sensory regions that process target attributes is considered a likely correlate of this top-down bias (Buschman & Kastner, 2015; Desimone & Duncan, 1995; Hillyard, Vogel, & Luck, 1998). In addition to this tonic or baseline effect, studies applying functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and positron emission tomography (PET) have also identified an attentional modulation of stimulus-evoked activity in sensory areas (Buschman & Kastner, 2015; Hillyard et al., 1998; Noudoost & Moore, 2011). This mechanism, termed attentional gain modulation, comprises the enhanced and attenuated processing of attended and unattended inputs, respectively (Buschman & Kastner, 2015; Hillyard et al., 1998). Gain modulation increases the signal-to-noise ratio of attended stimuli at early stages of sensory processing and thus influences the fidelity of their subsequent processing, including memory (Hillyard et al., 1998; Li & Lindenberger, 1999; Li et al., 2001; Thiele & Bellgrove, 2018). Note that the existence of tonic bias and gain modulation effects is not mutually exclusive but rather both mechanisms are thought to act in concert.

Importantly, noradrenergic neuromodulation and alpha-oscillatory activity have been implicated in changes in the excitability of cortical tissue, in line with a tonic bias effect (NE: Martins & Froemke, 2015; McGinley et al., 2015; alpha: Iemi, Chaumon, Crouzet, & Busch, 2017; Jensen & Mazaheri, 2010; Klimesch et al., 2007; Rihs, Michel, & Thut, 2009; Romei et al., 2008; Romei, Gross, & Thut, 2010; Thut, Nietzel, Brandt, & Pascual-Leone, 2006). Moreover, both have been linked to altered gain modulation, underlining their particular importance for the selective processing of goal-relevant information (NE: Aston-Jones & Cohen, 2005; Mather et al., 2016; Servan-Schreiber, Printz, & Cohen, 1990; Thiele & Bellgrove, 2018; alpha: Scheeringa, Mazaheri, Bojak, Norris, & Kleinschmidt, 2011; van Diepen et al., 2019; Womelsdorf, Valiante, Sahin, Miller, & Tiesinga, 2014). The next sections will thus introduce the noradrenergic and alpha-oscillatory systems in more detail, including a review of their age-related changes, followed by a sketch of their interaction.

Noradrenergic neuromodulation supports selective information processing

In humans, the bodies of noradrenergic cells cluster in distinct, pigmented nuclei in the brainstem. Although it has a length of only about 15 mm, the largest and most important of these is the cylindrical locus coeruleus (LC; Fernandes, Regala, Correia, & Gonçalves-Ferreira, 2012), located in the dorsorostral tegmentum, adjacent to the fourth ventricle (Szabadi, 2013). The LC receives afferent input from a variety of cortical and subcortical structures, including the spinal cord, different brainstem nuclei, hypothalamus, amygdala and, crucially, prefrontal cortex (Samuels & Szabadi, 2008a; Szabadi, 2013; Totah, Logothetis, & Eschenko, 2019). The LC-NE system thus integrates information from evolutionarily conserved regions controlling autonomic functions and arousal as well as phylogenetically younger forebrain areas implicated in higher-order cognition (Chandler, 2016; Totah et al., 2019). Via an ascending pathway, the LC in turn provides the primary noradrenergic innervation for structures in the midbrain, the thalamus, limbic system, and almost all areas of neocortex (with the notable exception of the basal ganglia; Berridge & Waterhouse, 2003; Szabadi, 2013). This connectivity pattern grants prefrontal regions a top-down regulatory influence on noradrenergic neuromodulation with its pronounced effect on prefrontal functioning (especially the anterior cingulate and orbitofrontal cortex; Arnsten, 2007; Aston-Jones & Cohen, 2005; Robbins & Arnsten, 2009).

Traditionally, the LC has been considered a homogenous structure that uniformly broadcasts its noradrenergic output throughout diverse neural networks via diffuse and highly arborized projections (for overviews of earlier studies, see Sara, 2009; Totah, Neves, Panzeri, Logothetis, & Eschenko, 2018). Importantly, such an arrangement would argue against a noradrenergic role in higher-order cognitive processing, such as selective attention and memory, which requires a spatially highly specific innervation of the cortex (Thiele & Bellgrove, 2018). However, recently, several groups have provided evidence for a more differentiated structural and functional organization of the LC (Breton-Provencher & Sur, 2019; Chandler, 2016; Mather et al., 2016; Schwarz & Luo, 2015; Totah et al., 2019; Uematsu et al., 2017). In particular, noradrenergic cells that innervate the forebrain are located more rostrally in the nucleus while those that project to the cerebellum and spinal cord are found in more caudal LC compartments (Schwarz & Luo, 2015). Further, discrete subpopulations of LC neurons with distinct molecular phenotypes and electrophysiological profiles terminate in prefrontal cortical and primary motor areas (Chandler, 2016). Importantly, frontally projecting LC neurons demonstrate a higher baseline firing rate and responsiveness to glutamate, thereby evincing increased NE release in prefrontal target regions (Aston-Jones & Waterhouse, 2016; Chandler, 2016; Sara, 2015).

Similarly, using optogenetic, viral tracing and electrophysiological approaches, Uematsu and colleagues (2017) have provided conclusive evidence that functionally distinct LC populations with connections to the amygdala and medial prefrontal cortex are involved in the acquisition and extinction of fear memories, respectively. Finally, contrary to earlier assumptions of a synchronized, electrotonically coupled activation of all LC cells, Totah and colleagues (2018) observed multiple distinct LC ensembles (i.e., subsets of synchronized LC neurons) with the potential for a more targeted noradrenergic forebrain modulation. Together, these findings suggest an anatomically and functionally more heterogeneous neuromodulatory system that is recruited in a demand-driven manner (e.g., during conditions of high cognitive load) to bias competition for neural processing resources towards currently relevant representations (cf. Seo & Bruchas, 2017).

In its terminal regions, NE binds to three major metabotropic receptor classes: α_2-, α_1- and β-adrenoceptors (listed in order of their affinity for NE). The pre- and postsynaptically located α_2-receptors mediate inhibition, whereas the postsynaptic α_1- and β-adrenoceptors typically have excitatory effects (Mather et al., 2016; Robbins & Arnsten, 2009; Samuels & Szabadi, 2008a; Thiele & Bellgrove, 2018). An additional degree of specialization is thus provided by NE's differential binding potential for its receptor subtypes (Arnsten, 2007; Mather et al., 2016). While modest NE levels primarily engage α_2-receptors and strengthen prefrontal operations, higher NE release engages α_1- and β-adrenoceptors and supports processing in more posterior regions (e.g., amygdala, hippocampus and sensory cortices; Arnsten, 2007).

In addition to release and binding sites, NE's impact depends on the temporal organization of LC firing: Noradrenergic neurons show two distinguishable but mutually dependent modes of activity (Aston-Jones & Cohen, 2005; Berridge & Waterhouse, 2003). First, LC cells fire in a state-dependent, slow (i.e., tonic; 0.5–5 Hz) rhythm with highest discharge during active wakefulness, followed by drowsy, inattentive states, slow-wave sleep and, finally, minimal release during rapid-eye movement sleep (Aston-Jones, Gonzalez, & Doran, 2007; Berridge, 2009; Neves et al., 2018). Crucially, an optogenetic study revealed that tonic LC activity is causally linked to the maintenance of a vigilant, wakeful behavioral state in mice (Carter et al., 2010; cf. Aston-Jones et al., 2007; Berridge & Waterhouse, 2003). Second, in the waking state, LC neurons respond with a brief, burst-like (i.e., phasic; 8–10 Hz) firing pattern to stimuli of all modalities, given that they are salient (e.g., aversive [noxious, fear-evoking etc.] or novel; Berridge & Waterhouse, 2003; Bouret & Sara, 2005). However, phasic LC activity may also be recruited internally via top-down mechanisms to support processing in the forebrain (Neves et

al., 2018; Robbins & Arnsten, 2009). Phasic LC activity is associated with rapid attention allocation (thus also conceptualized as a temporal attentional filter; Aston-Jones & Cohen, 2005; Berridge, 2009; Bouret & Sara, 2005; Corbetta, Patel, & Shulman, 2008; Sara & Bouret, 2012) and essential for feed forward signaling of salient sensory inputs (Neves et al., 2018; Safaai et al., 2015; Vazey et al., 2018). Reduced phasic LC activity is observed in low as well as high states of tonic discharge (e.g., during drowsiness and stress, respectively; Berridge, 2009). Accordingly, optimal task performance has been observed with moderate tonic NE levels (i.e., baseline LC activity) and selective bursts of phasic activity following task-relevant stimuli (i.e., an inverted U-shaped relationship; Aston-Jones & Cohen, 2005; McGinley et al., 2015).

Taken together, LC-NE activity profoundly influences selective information processing via several mechanisms (Berridge & Waterhouse, 2003): First, LC-NE activity is associated with the transition to, and the maintenance of a vigilant behavioral state (Berridge, 2009; Berridge & Waterhouse, 2003; Buzsáki et al., 1991; Carter et al., 2010; Harris & Thiele, 2011) that allows for the optimal processing of sensory information (McGinley et al., 2015). This effect is presumably mediated via intrathalamic NE release (Buzsáki et al., 1991; McCormick, 1989; McCormick et al., 1991; Stitt et al., 2018) and a noradrenergic activation of the cholinergic basal forebrain (Berridge & Waterhouse, 2003; Buzsáki et al., 1988). Second, in the dorsolateral prefrontal cortex, NE acts on α_{2A}-adrenoceptors to increase the signal in attention and working memory networks while leaving the noise unchanged (i.e., it increases persistent, spatially tuned network firing in the absence of external stimulation; Robbins & Arnsten, 2009; Thiele & Bellgrove, 2018). Third, in the sensory cortices, NE enhances the selective processing of currently relevant representations, probably mediated via α_{2A}-and β-adrenoceptors in interaction with local glutamate levels (Harris & Thiele, 2011; Mather et al., 2016). In particular, in monkeys local NE application to the sensory cortex preceding receptive field stimulation decreased the rate of spontaneous firing while sparing stimulus-evoked responses (i.e., increased signal-to-noise ratios; McCormick, 1989; Sara, 2009). Moreover, NE application revealed stimulus-evoked activity in previously unresponsive sensory neurons (i.e., sensory gating; Martins & Froemke, 2015). Recently, enhanced selective information processing in the thalamus was also associated with LC-NE's action on α-adrenoceptors (Rodenkirch, Liu, Schriver, & Wang, 2019). Fourth, mediated via β-adrenoceptors, NE facilitates long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus and thus synaptic plasticity (Hansen, 2017; O'Dell, Connor, Guglietta, & Nguyen, 2015; Sara, 2009, 2015), potentially supported by co-release of dopamine (McNamara & Dupret, 2017; Takeuchi et al., 2016; Wagatsuma et al., 2018). Similarly, NE release has been linked to synaptic plasticity in the sensory cortices

(Martins & Froemke, 2015), facilitating the selective routing of relevant information. Finally, phasic NE activity has been conceptualized as a circuit breaker that interrupts ongoing processing in the dorsal attention network and supports the reorienting of attention towards salient stimuli, mediated via activation of the ventral attention network (Bouret & Sara, 2005; Corbetta et al., 2008).

To conclude, noradrenergic activity biases neural information processing towards salient or prioritized representations at multiple brain sites in parallel (e.g., sensory cortices, thalamus, hippocampus, prefrontal, and parietal cortices). Although its effect varies across release and binding sites as well as LC firing modes, NE generally increases signal-to-noise ratios of salient or prioritized stimuli (Aston-Jones & Waterhouse, 2016; Sara, 2009; Thiele & Bellgrove, 2018) and thereby supports their preferential processing, strengthening attentional and mnemonic processes (Berridge & Waterhouse, 2003). However, most of the current knowledge about the mechanisms of noradrenergic neuromodulation is based on either animal or post-mortem human studies. The next section thus reviews recent methodological advancements that now offer non-invasive, in vivo indices of the LC-NE system and carry great potential for human aging research (e.g., Betts, Cardenas-Blanco, Kanowski, Jessen, & Düzel, 2017; Betts, Kirilina, et al., 2019; Hämmerer et al., 2018; Lee et al., 2018; Liu et al., 2019).

Non-invasive surrogate measures of noradrenergic neuromodulation

Research in the cognitive neuroscience of aging has long acknowledged the relationship between age-related changes in neuromodulation and age-related cognitive deficits. Already in the 1980s and 1990s, post-mortem and in vivo molecular imaging analyses revealed an age-related loss of dopaminergic receptor and transporter densities of ~10% per decade, which gave rise to influential dopaminergic theories of cognitive aging (Bäckman et al., 2006; Braver & Barch, 2002; Li & Lindenberger, 1999; Li et al., 2001; Li & Sikström, 2002). DA and NE share a broadly similar biosynthesis and degradation (from tyrosine; via monoamine oxidase and catchechol-O-methyl transferase, respectively; Eisenhofer, 2004). Further, both neuromodulatory systems are similarly targeted by psychiatric medication (e.g., atomoxetine, methylphenidate) and drugs of abuse (e.g., amphetamine-like stimulants, including cocaine), indicating a shared receptor affinity (Berridge & Waterhouse, 2003). In addition, both DA and NE show similar release conditions (Sara, 2009), have gain-modulatory effects in their target regions (Servan-Schreiber et al., 1990), and are thought to interactively shape prefrontal

operations (Robbins & Arnsten, 2009). These wide-ranging similarities between the dopaminergic and noradrenergic neuromodulatory systems have not been reflected to a similar extent in the cognitive neuroscience of aging, however (for notable exceptions, see Arnsten & Contant, 1992; Arnsten & Goldman-Rakic, 1985; Leslie et al., 1985, for early studies in aged animals; and Manaye, McIntire, Mann, & German, 1995, for an overview of early post-mortem human studies). This imbalance may have resulted from technical challenges in reliably targeting the tiny noradrenergic brainstem nucleus in vivo, for example due to a lack of suitable radioligands (Ding et al., 2006) or insufficient resolution and contrast of standard MRI sequences (Astafiev et al., 2010; Keren et al., 2009; Nieuwenhuis & Jepma, 2011).

Recent developments in MRI techniques, however, now allow the non-invasive assessment of LC structure (Betts, Kirilina, et al., 2019; Keren et al., 2015; Liu et al., 2017; Sasaki et al., 2006; Watanabe et al., 2019). In particular, when using T_1-weighted Turbo Spin Echo and Fast Low Angle Shot sequences (TSE; FLASH; Betts et al., 2017; Clewett et al., 2016; Keren et al., 2009; Shibata et al., 2006) or T_1-weighted MRI with Magnetization Transfer (MT) preparation (Chen et al., 2014; Liu et al., 2019; Priovoulos et al., 2017; Watanabe et al., 2019), an elevated signal or hyperintensity is observed in the dorsal pons, adjacent to the fourth ventricle. Applying a combination of ultra-high field MRI and histology of human post-mortem samples, Keren and colleagues (2015) investigated whether this MRI signal elevation originates from the LC and may serve as surrogate measure for LC integrity (i.e., a proxy for cell density). The hyperintensities detected in brainstem areas on T_1-weighted LC-MRI scans indeed closely corresponded to the location of noradrenergic cells that contained neuromelanin, as confirmed by subsequent histological analyses (Keren et al., 2015). The dark, insoluble pigment neuromelanin is a by-product of catecholamine synthesis and thus accumulates in the LC across the lifespan (Mann & Yates, 1974; Zecca et al., 2004). Within LC cells, neuromelanin scavenges metals such as iron and copper and, as a compound, produces paramagnetic, T_1-shortening effects (i.e., chelation; Sasaki et al., 2008; Trujillo et al., 2017). Therefore, neuromelanin-metal compounds may serve as endogenous contrast agent that allows the non-invasive, in vivo assessment of LC integrity using MRI (Trujillo et al., 2017) – at least in aging, when cells in the LC are saturated with neuromelanin (Hämmerer et al., 2018; Liu et al., 2019; Mann & Yates, 1974). Watanabe and colleagues (2019) further demonstrated that, in contrast to wild-type mice, transgenic mice with a ~70% reduction of noradrenergic neurons do not show an elevated MRI signal from the LC, again suggesting noradrenergic cells as being the source of the hyperintensity. However, to date, a complete understanding of the contrast mechanisms producing signal differences in TSE, FLASH, and MT sequences is still lacking (Liu et al., 2017). In particular,

recent findings of elevated MRI contrast in rodents naturally lacking neuromelanin rather point to LC's high water content (i.e., proton density) and T_1-shortening effects of metal ions, which are abundant in the LC, as sources of the contrast differences (Watanabe et al., 2019). Irrespective of the precise contrast mechanism within the LC, recent clinical MRI studies have consistently observed reduced LC-MRI contrast in patients suffering from conditions associated with noradrenergic neurodegeneration (e.g., Parkinson's disease; Liu et al., 2017; Marien, Colpaert, & Rosenquist, 2004). Further, repeated assessments of LC-MRI contrast yielded a moderate to high reproducibility (Betts et al., 2017; Langley, Huddleston, Liu, & Hu, 2017; Tona et al., 2017). Together this indicates the validity and reliability of LC-MRI and thus its utility as a research tool.

In addition to structural LC measures, studies in rats and monkeys using a combination of electrophysiological, fluorescence imaging, and optogenetic approaches established pupil dilation, in the absence of interfering visual inputs, as a valid surrogate measure of noradrenergic activity (optogenetics: Breton-Provencher & Sur, 2019; electrophysiology: Joshi et al., 2016; fluorescence imaging: Reimer et al., 2016). Pupil dilation reflects the outcome of an interaction of two opposing muscles: The dilator pupillae (innervated by the sympathetic nervous system) and the sphincter pupillae (innervated by the parasympathetic nervous system; Andreassi, 2007). Critically, the LC functions as a premotor nucleus for both, by stimulating/inhibiting sympathetic and parasympathetic preganglionic neurons, respectively (Samuels & Szabadi, 2008b; Szabadi, 2012). Accordingly, an optogenetic activation of the LC was causally related to pupil dilation, whereas an optogenetic inhibition reliably produced pupil constriction (via light-induced activation/silencing of channelrhodopsin-/archaerhodopsin-expressing LC cells, respectively; Breton-Provencher & Sur, 2019). Together with electrophysiological and fluorescence imaging studies that demonstrate LC spiking and noradrenergic axon activity before spontaneous and stimulus-evoked pupil dilations (Joshi et al., 2016; Reimer et al., 2016), this suggests that pupil dilation may serve as a moment-to-moment index of noradrenergic neural activity (Costa & Rudebeck, 2016).

In later life, cognitive abilities decline while neuromodulatory systems undergo changes (Liu et al., 2019; Shibata et al., 2006). The next section reviews associations between age-related changes in the LC-NE system and selective information processing, incorporating evidence based on the recent methodological advancements.

Senescent changes in noradrenergic neuromodulation

Early investigations of age-related differences in LC cell count in human post-mortem samples suggested a substantial neuronal decline with advancing age, especially in rostral, forebrain-projecting LC compartments (for a review, see Manaye et al., 1995). However, more recent post-mortem research using unbiased stereological estimation procedures did not confirm this trajectory (Fernandes et al., 2012; Mouton, Pakkenberg, Gundersen, & Price, 1994; Ohm, Busch, & Bohl, 1997; Theofilas et al., 2017). These conflicting findings resulted probably partly due to different exclusion criteria for cases with markers of age-related neurodegeneration (for discussions, see Mather & Harley, 2016; Satoh & Iijima, 2019, and below). Spatially confined age differences across the rostrocaudal LC axis (Betts et al., 2017; Keren et al., 2009; Liu et al., 2019; Manaye et al., 1995) as well as high interindividual variability in LC cell population estimates (Theofilas et al., 2017) may have moreover contributed to the discrepant findings in later life. Notably, in vivo studies investigating large lifespan samples observed a rise in LC-MRI contrast (i.e., a proxy for noradrenergic cells in aging; Keren et al., 2015; Watanabe et al., 2019) until around 60 years of age with a subsequent decline (Liu et al., 2019; Shibata et al., 2006). For instance, in over 600 participants of the Cambridge Centre for Ageing and Neuroscience study (Cam-CAN; ages 18–88 years), Liu and colleagues (2019) detected a negative quadratic relation between age and MRI contrast in the rostral LC, compatible with a loss of noradrenergic cells in later life (cf. Manaye et al., 1995).

In addition to hints for LC cell loss, a decline in the density of the NE transporter (NET) has been observed in healthy aging, which may occur due to diminished LC–forebrain projections in old age (Apparsundaram, 2007; Ding et al., 2006, 2010; Samuels & Szabadi, 2008b). Afferent connections to the LC also demonstrate age-related changes, with a pronounced loss of excitatory inputs from the hypothalamus (Arnsten, 2007). Moreover, infusions of noradrenergic drugs into the LC produced less behavioral changes in aged compared to young rodents, suggesting a lower adrenoceptor responsiveness with increasing age (Samuels & Szabadi, 2008b). Finally, analyses of pupil dilation (i.e., a proxy of noradrenergic activity; Breton-Provencher & Sur, 2019) revealed a decreased overall dilation and a larger variability in pupil estimates with age (Andreassi, 2007; Samuels & Szabadi, 2008b). Taken together, aging affects the noradrenergic system at multiple points (e.g., LC cell bodies, afferent and efferent projections; NE receptors and transporters) suggesting a less reliable noradrenergic neuromodulation in later life (Apparsundaram, 2007; Arnsten, 2007; Liu et al., 2019; Mather & Harley, 2016; Samuels & Szabadi, 2008b).

What causes these senescent changes in the LC-NE system? Recent theories of cognitive aging posit a high susceptibility of LC neurons to neurodegeneration, presumably resulting from their exposure to natural stressors (Mather & Harley, 2016; Weinshenker, 2018). For instance, LC's anatomical location adjacent to the ventricular system and its widespread, unmyelinated axons expose it to toxins from cerebrospinal fluid (CSF) and blood circulation (Chalermpalanupap, Weinshenker, & Rorabaugh, 2017; Mather, in press; Mather & Harley, 2016; Satoh & Iijima, 2019; Weinshenker, 2018). Neuromelanin accumulating in the LC may pose another source of toxins. While neuromelanin initially chelates free metals and thus reduces their toxicity, upon cell death it eventually releases them and may thus accelerate neuronal decline (Zecca et al., 2004, 2001). Further, LC's constant, tonic firing rhythm produces a high bioenergetic demand associated with an increased risk of oxidative stress and subsequent cell damage (Chalermpalanupap, Weinshenker, & Rorabaugh, 2017; Mather, in press; Mather & Harley, 2016; Satoh & Iijima, 2019; Weinshenker, 2018). Analyses of post-mortem samples moreover identified the LC as one of the first brain sites in which aberrant tau proteins accumulate (i.e., neurofibrillary changes; Braak, Thal, Ghebremedhin, & Del Tredici, 2011; Ehrenberg et al., 2017; Theofilas et al., 2017). In particular, in a large post-mortem investigation, aggregated tau, a hallmark of age-related neurodegenerative diseases like Alzheimer's, has been observed in the LC of the majority of participants who deceased in young adulthood (Braak et al., 2011). Tau aggregates are thought to spread from the brainstem with increasing age in a stereotypical topographical pattern to noradrenergic projection targets like the medial-temporal lobe (denoted as Braak stages, a classification system of the progression of tau spread; Braak et al., 2011; Chalermpalanupap et al., 2017). Tau burden in the LC linearly increases with the progression of Braak stages and, crucially, is associated with the shrinkage and subsequent decline of LC neurons, already at presymptomatic stages of Alzheimer's disease (i.e., before the onset of disease-defining memory loss; Ehrenberg et al., 2017; Theofilas et al., 2017). These findings highlight that the threshold between healthy brain aging and early manifestations of neurodegenerative disease is not yet delineated (Grinberg & Heinsen, 2017) and the transition between both likely occurs along a continuum (Clewett et al., 2016; Mather & Harley, 2016). Note that the differential sensitivity of in vivo and post-mortem methods to detect underlying, presymptomatic tau accumulation may have contributed to the discrepant LC integrity findings in later life discussed above. Besides its influence on cognitive processing (Berridge & Waterhouse, 2003; Sara, 2009), noradrenergic neuromodulation subserves critical neuroprotective functions (e.g., anti-inflammatory effects mediated via action on β-

adrenoceptors on microglia; Chalermpalanupap et al., 2017; Mather & Harley, 2016) and thus a loss of LC cells may exacerbate the progression of age-related neurodegenerative diseases (Betts et al., 2018; Mather, in press).

In sum, due to its exposure to various stressors (e.g., toxins, oxidative stress and aberrant tau) the LC shows a high vulnerability for age-related neurodegeneration with probably deleterious consequences for late-life cognitive abilities. In accordance with this notion, Wilson and colleagues (2013) demonstrated the importance of LC integrity, here operationalized as cell density, for the maintenance of cognitive performance in aging. Older adults annually completed a battery of cognitive tests, including assessments of memory, for about six years before their death. Crucially, higher post-mortem LC integrity was observed in those individuals with higher baseline cognitive abilities and attenuated rates of senescent cognitive decline, even after accounting for other neuromodulatory systems and signs of neuropathology (Wilson et al., 2013). Similarly, in older adults LC integrity, this time assessed in vivo via MRI, was positively associated with memory performance for stimuli linked to aversive events (i.e., situations that elicit phasic LC activity; Hämmerer et al., 2018). Supporting these observations, impaired working memory performance in aged monkeys can be temporarily reinstated by administering of noradrenergic agonists (Arnsten, 2007; Arnsten & Contant, 1992; Arnsten & Goldman-Rakic, 1985; Wang et al., 2011), suggesting a causal role of noradrenergic neuromodulation in senescent cognitive decline. In particular, NE agonists restore the persistent firing of prefrontal networks that code task-relevant information in the absence of external stimulation via α_{2A}-adrenoceptor mediated mechanisms (Robbins & Arnsten, 2009; Wang et al., 2011).

Taken together, noradrenergic neuromodulation is critically implicated in the selective processing of salient or prioritized information. Moreover, initial evidence suggests that senescent cognitive decline is associated with age-related changes in the LC-NE system. On a more macroscopic, neural ensemble level, variations in noradrenergic neuromodulation are closely linked to changes in rhythmic neural activity (Buzsáki et al., 1991; Marzo et al., 2014; Neves et al., 2018; Stitt et al., 2018) that again play a prominent role in selective information processing (e.g., Jensen & Mazaheri, 2010).

Modulations of alpha-oscillatory activity support selective information processing

Low frequency rhythmic neural activity, as recorded via EEG (Biasiucci et al., 2019), reflects the spatial summation (i.e., ensemble activity) of rhythmic postsynaptic potentials originating from apical dendrites (Birbaumer & Schmidt, 2010; Lopes da Silva, 1991; Lopes da Silva & Storm van Leeuwen, 1977; Nunez & Srinivasan, 2006; van Diepen et al., 2019). The precise physiological origin of the most prominent low frequency oscillation in the waking state, the cortical alpha rhythm, is not fully elucidated (Crunelli et al., 2018; Klimesch et al., 2007; Lozano-Soldevilla, 2018; van Diepen et al., 2019). Most likely, several distinct generators contribute to its existence (Clayton, Yeung, & Cohen Kadosh, 2018; Crunelli et al., 2018; Fiebelkorn et al., 2019; Lopes da Silva, van Lierop, Schrijer, & Storm van Leeuwen, 1973; Sokoliuk et al., 2019). One probable candidate is the thalamus, given that (1) thalamic lesions are associated with diminished posterior alpha activity, (2) intrathalamic injections of neuromodulators alter cortical alpha activity, (3) blood oxygen level-dependent (BOLD) responses in the thalamus covary with posterior alpha power, and (4) spiking in thalamocortical neurons shows a temporal association with ongoing posterior alpha activity (i.e., phase coherence; Buzsáki et al., 1991; Clayton et al., 2018; Crunelli et al., 2018; Ketz et al., 2015; Lopes da Silva, 1991; Lopes da Silva et al., 1973; Lozano-Soldevilla, 2018; Moosmann et al., 2003; Womelsdorf et al., 2014). However, several lines of evidence also indicate a cortical role in the generation of the alpha rhythm. For instance, in-vitro preparations of cortical pyramidal cells demonstrate rhythmic activity in the alpha range, even when isolated from thalamic influences. Further, posterior cortical regions typically show stronger phase coherence in the alpha band with one another than with the thalamus (Clayton et al., 2018; Lopes da Silva, 1991; Lopes da Silva & Storm van Leeuwen, 1977; Lopes da Silva et al., 1973; Lozano-Soldevilla, 2018; Womelsdorf et al., 2014). Accordingly, the alpha rhythm is considered a complex product of thalamocortical as well as corticocortical influences (Crunelli et al., 2018; Fiebelkorn et al., 2019).

Besides its role in the generation of low frequency rhythmic neural activity, the thalamus constitutes a critical node which allows for low frequency synchronization and thus dynamic communication between frontal and posterior brain structures (Buschman & Kastner, 2015; Buzsáki & Draguhn, 2004; Fiebelkorn et al., 2018, 2019; Fries, 2005, 2015; Saalmann, Pinsk, Wang, Li, & Kastner, 2012; Voytek & Knight, 2015; Zhou, Schafer, & Desimone, 2016).

Specifically, a corticothalamocortical circuit has been postulated, which synchronizes medial, orbital, and lateral prefrontal areas with posterior, parietal, and sensory areas via the pulvinar (Fiebelkorn et al., 2019; Halassa & Kastner, 2017; Ketz et al., 2015; Stitt et al., 2018). This circuit offers a mechanism for frontally mediated top-down control over sensory processing through long-range synchronization in the alpha frequency band (Clayton et al., 2018; Fiebelkorn et al., 2019; Ketz et al., 2015; Lakatos, O'Connell, & Barczak, 2016; Saalmann et al., 2012; Schmid, Singer, & Fries, 2012; Stitt et al., 2018; Zhou et al., 2016).

Concerning their functional role, current conceptualizations regard posterior alpha oscillations as phasic pulses of inhibition that temporarily disengage parts of the brain and thus serve the parcellation of information processing and the (re)distribution of processing resources (Clayton et al., 2018; van Diepen et al., 2019; but see Foster & Awh, 2019, for a facilatory account). In particular, top-down mediated alpha-oscillatory bouts of inhibition regulate the windows for feed forward processing (e.g., indicated by spiking, high frequency [~30–80 Hz; gamma] or BOLD activity; Clayton et al., 2018; Jensen & Mazaheri, 2010; Voytek & Knight, 2015) and thus allow the timed expression of a neural code necessary for the representation of information (Hanslmayr et al., 2016, 2012).

More specifically, within an alpha-oscillatory cycle, inhibitory and excitatory phases alternate in a cyclic succession indicated by the peaks and troughs of the oscillation (Jensen & Mazaheri, 2010; Klimesch et al., 2007). Local increases in alpha amplitude during the inhibitory up-phases lead to elevated neural response thresholds, resulting in a reduced likelihood of action potential initiation (cf. Nandy, Nassi, Jadi, & Reynolds, 2019). Massed neural firing is therefore more likely during release from inhibition during the down-phases of the corresponding alpha cycle (also called the oscillatory microstate of cortical excitability; Mathewson et al., 2009). Accordingly, visual stimuli presented during inhibitory relative to excitatory alpha phases are associated with reduced BOLD responses in occipital cortex (Qian & Di, 2011; Scheeringa et al., 2011) and a lower likelihood to elicit a behavioral response (i.e., detection; Busch, Dubois, & VanRullen, 2009; Mathewson et al., 2009; but see Ruzzoli, Torralba, Morís Fernández, & Soto-Faraco, 2019). However, to date, it still remains an open question whether top-down influences can reliably modulate the phase of alpha oscillations to aid selectivity (for a discussion, see van Diepen et al., 2019).

With increasing alpha amplitude, the time windows for neuronal processing, as reflected in spiking or high frequency activity, become shorter (sometimes called duty cycle; Jensen & Mazaheri, 2010), whereas decreases in alpha activity allow for longer processing windows (i.e., wider troughs). In contrast to alpha phase, attentional modulations of alpha amplitude have

consistently emerged as a mechanism via which relevant information can be selected for processing (Clayton et al., 2018; Foster & Awh, 2019; Jensen & Mazaheri, 2010; Klimesch et al., 2007; Strauß, Wöstmann, & Obleser, 2014; van Diepen et al., 2019; Weisz, Hartmann, Müller, Lorenz, & Obleser, 2011). In particular, covert spatial shifts of attention (e.g., to one side of a visual display in a spatial orienting task; Buschman & Kastner, 2015) reliably produce decreases in posterior alpha power in the hemisphere processing the attended space (i.e., contralateral to the focused hemifield), whereas increases are observed in the opposite hemisphere (i.e., ipsilateral). More recent research further indicates that the topography of attentional alpha modulations varies not only with the attended hemifield but rather tracks the precise spatial location of relevant information (Bahramisharif, van Gerven, Heskes, & Jensen, 2010; Foster & Awh, 2019; Kelly, Lalor, Reilly, & Foxe, 2006, 2005; Popov, Gips, Kastner, & Jensen, 2019). Lateralized patterns of alpha-oscillatory activity after spatial attentional cues have most commonly been investigated in the visual domain but are also reliably observed in somatosensory or auditory tasks and associated brain areas (Clayton et al., 2018; Jensen & Mazaheri, 2010; Strauß et al., 2014; van Diepen et al., 2019; Weisz et al., 2011), pointing to a domain-general selection mechanism (Frey et al., 2014; Spitzer & Blankenburg, 2012). In particular, event-related ipsilateral alpha synchronization (ERS; Jensen & Mazaheri, 2010; Pfurtscheller & Aranibar, 1977; Pfurtscheller & Lopes da Silva, 1999) and event-related contralateral alpha desynchronizations (ERD; Foster & Awh, 2019; Pfurtscheller & Aranibar, 1977; Pfurtscheller & Lopes da Silva, 1999) relative to the side of target presentation in spatial attention tasks are thought to reflect the cortical dis/engagement of currently ir/relevant areas, respectively. Accordingly, higher ERS and ERD have both been associated with improved performance in attention paradigms (Foster & Awh, 2019; Jensen & Mazaheri, 2010). While spontaneous (i.e., not event-related) fluctuations of alpha amplitude are also associated with cortical excitability and behavioral performance (i.e., stimulus detection; Busch et al., 2009; Iemi et al., 2017; Mathewson et al., 2009), they are less closely related to top-down mediated changes in selectivity (Foster & Awh, 2019).

Several studies suggest that top-down modulations of alpha amplitude may provide a causal mechanism for the flexible selection of relevant information (Nandy et al., 2019; Romei et al., 2010; Wöstmann, Vosskuhl, Obleser, & Herrmann, 2018). First, in line with its inhibitory function, an increase in posterior alpha synchronization, elicited using rhythmic transcranial magnetic stimulation (rTMS), was associated with a retinotopically-organized suppression of visual target detection (Romei et al., 2010). In particular, Romei and colleagues (2010) reported

a frequency- and spatially specific modulation of visual perception via rTMS. Stimulation within the alpha (10 Hz), but not theta (5 Hz) or beta (20 Hz) control frequencies impaired performance contralateral to the stimulated hemisphere, while increased ipsilateral target detection was observed (cf. Buschman & Kastner, 2015; Desimone & Duncan, 1995). In other words, artificially increasing alpha synchronization biased attention away from the visual space processed by the stimulated brain site (Romei et al., 2010). Similarly, directly inducing low frequency neural synchronization via rhythmic optogenetic activation of occipital regions (V4) reduced visual attention performance in monkeys (Nandy et al., 2019). Stimulation in low but not high frequencies impaired attention for the area of visual space coded by the optically activated brain region, whereas no change was observed at the contralateral location. Together these findings support the hypothesis that attention-related decreases in alpha activity provide a mechanism for improved performance at attended locations.

Notably, modulations of alpha activity are not only observed in attentional paradigms but also subserve mnemonic functions (van Ede, 2018). Typically, during the encoding of items that are later remembered relative to those that are forgotten, brain areas processing stimulus attributes demonstrate alpha desynchronization (Griffiths et al., 2019; Hanslmayr et al., 2016, 2012; Sander, Fandakova, Grandy, Shing, & Werkle-Bergner, 2019; Werkle-Bergner et al., 2006). Again, external modulations of low frequency synchronization during stimulus encoding using rTMS suggest that this desynchronization is causally implicated in mnemonic processing (Hanslmayr, Matuschek, & Fellner, 2014). During the later retrieval from long-term memory, alpha desynchronization is also reported for brain areas processing the reactivated target material, whereas regions storing competing distractors show alpha synchronization (Griffiths et al., 2019; Hanslmayr et al., 2016; Waldhauser, Johansson, & Hanslmayr, 2012). Taken together, these observations suggest that alpha desynchronization across mnemonic processes reflects active information processing in currently relevant cortical regions. In working memory paradigms, in contrast, increased alpha synchronization during the retention interval between encoding and responding is usually reported (Bonnefond & Jensen, 2012; Spitzer & Blankenburg, 2012; van Ede, 2018; Wöstmann, Herrmann, Wilsch, & Obleser, 2015). Functionally, this alpha synchronization over posterior areas may shield the encoded information by suppressing potentially interfering sensory inputs (Clayton et al., 2018; van Ede, 2018). In sum, these findings underline the more generalized role of alpha-oscillatory activity in selectively facilitating access to relevant internal representations and sensory inputs (Jensen & Mazaheri, 2010; van Diepen et al., 2019; van Ede, 2018).

How do decreases in alpha amplitude (i.e., alpha desynchronization) mechanistically relate to improved selective attention and episodic memory? First, low frequency desynchronization may constitute a release from (physiological) inhibition, mediated by local inhibitory neurons (Clayton et al., 2018), and thus increase the firing of neuronal ensembles coding selected stimuli (Jensen & Mazaheri, 2010). Second, synchronization in low frequencies increases the trial-by-trial variability of neural firing (i.e., noise correlation) and thereby reduces the reliability of the transmitted neural code (Hanslmayr et al., 2016; Nandy et al., 2019). Desynchronization of low frequency activity, in turn, enhances the information-coding capacity of neural ensembles representing prioritized stimuli (Griffiths et al., 2019; Hanslmayr et al., 2012).

Given that modulations of alpha activity play a key role in healthy cognition across attentional and mnemonic domains as well as across sensory modalities, its dysfunction likely constitutes a crucial component in senescent cognitive decline (Grandy et al., 2013; Mazaheri, Slagter, Thut, & Foxe, 2018; Voytek & Knight, 2015).

Senescent changes in alpha-oscillatory activity

The aging human brain demonstrates overall spectral changes. In particular, older adults show a general slowing (Grandy et al., 2013) and amplitude decrease in the alpha band when compared to younger adults (Ishii et al., 2017; Kennedy & Mather, 2019; Klimesch, 1999). Notably, overall changes in the spectral characteristics of alpha activity have moreover been linked to age-related neurodegenerative diseases like Alzheimer's (Ishii et al., 2017; Klimesch, 1999). However, in contrast to event-related alpha modulations that are under volitional control, overall spectral changes are less closely related to top-down processing (Klimesch, 1999). Importantly, evidence has accumulated over the last years that points to age differences in the dynamic modulation of alpha de/synchronization during attention and memory as well (Deiber, Ibañez, Missonnier, Rodriguez, & Giannakopoulos, 2013; Deiber et al., 2010; Henry, Herrmann, Kunke, & Obleser, 2017; Hong, Sun, Bengson, Mangun, & Tong, 2015; Leenders, Lozano-Soldevilla, Roberts, Jensen, & De Weerd, 2018; Mok, Myers, Wallis, & Nobre, 2016; Rogers, Payne, Maharjan, Wingfield, & Sekuler, 2018; Sander, Werkle-Bergner, & Lindenberger, 2012; Vaden, Hutcheson, McCollum, Kentros, & Visscher, 2012; van der Waal, Farquhar, Fasotti, & Desain, 2017; Wöstmann et al., 2015; Zanto et al., 2011). For instance, a delayed and diminished alpha synchronization for task-irrelevant visual stimuli has been

observed in older adults, which suggests a less reliable attentional filter mechanism in aging (Deiber et al., 2010; cf. Gazzaley et al., 2005). Similarly, while younger adults maintained elevated posterior alpha levels during prolonged challenging listening conditions, alpha synchronization was shortened in older adults (Wöstmann et al., 2015; cf. Henry et al., 2017). Wöstmann and colleagues interpreted enhanced posterior alpha levels as indicative of the active inhibition of the task-irrelevant visual modality during demanding acoustic stimulation. Hence, age differences in alpha synchronization again indicate an impaired maintenance of selective attention in aging (Wöstmann et al., 2015). In line with this, Leenders and colleagues (2018) reported an initially intact lateralization of posterior alpha activity during the attentional cue period of a visual working memory task which broke down, however, during the subsequent retention phase in older adults (Leenders et al., 2018; but see Mok et al., 2016). To further isolate the temporal dynamics of age differences in selective attention, Deibner and colleagues (2013) compared younger and older adults' alpha modulation during anticipatory (i.e., attention cue-related) and target stimulus-driven attentional processes. Age differences were most pronounced in the anticipatory interval (i.e., before target onset; cf. Hong et al., 2015), especially when no cue predicted the time of stimulus occurrence (Deiber et al., 2013). Following target presentation, both age groups demonstrated a reliable modulation of rhythmic neural activity, but it extended to more central electrodes and the beta frequency band in older adults (Deiber et al., 2013; cf. Mok et al., 2016). Taken together, these findings suggest age-related changes in the temporal characteristics of top-down mediated posterior alpha modulations during attentional and mnemonic processes, as evident in a delayed or shortened de/synchronization.

However, age differences in alpha dynamics appear to be contingent on the specific task demands. Using a visuospatial selective attention task, Sander and colleagues (2012) observed a breakdown of alpha modulation with excessive cognitive load in older adults. In particular, they showed a load-dependent increase in lateralized alpha activity (i.e., the alpha power difference between target- and distractor-processing hemispheres). However, in marked contrast to younger adults, hemispheric differences in alpha power were no longer present in older adults under conditions of high load (i.e., no reliable alpha lateralization; Sander, Werkle-Bergner, et al., 2012). In line with the dependence of age differences in alpha modulation on task demands (Sander, Werkle-Bergner, et al., 2012), intact alpha lateralization was observed in middle-aged to older adults in the absence of behavioral impairments in an auditory attention task (Tune, Wöstmann, & Obleser, 2018; cf. Wöstmann, Herrmann, Maess, & Obleser, 2016).

Notably, initial studies suggest a causal link between altered dynamics of low frequency rhythmic neural activity in aging and impaired cognition (Borghini et al., 2018; Reinhart &

Nguyen, 2019). In particular, an experimental manipulation of posterior alpha activity using transcranial alternating current stimulation (tACS) selectively restored older adults' performance in a working memory paradigm that required the inhibition of distracting information (Borghini et al., 2018; but see Asamoah, Khatoun, & Mc Laughlin, 2019, for a recent discussion of potential mechanisms underlying tACS effects).

To conclude, the top-down modulation of posterior alpha activity is critically implicated in the selective processing of prioritized information. In addition, accumulating evidence links senescent cognitive decline to age-related changes in low frequency rhythmic neural dynamics. In particular, the reviewed findings indicate that inhibitory processes, as expressed in posterior alpha modulations, operate less reliably in older adults, chiefly at high levels of task difficulty. In addition, observations of a functionally relevant, task-related lateralization of beta-band activity point to a partial reorganization of rhythmic neural responses in later life.

While the previous sections separately outlined how noradrenergic and alpha-oscillatory mechanisms support selectivity (in aging), there are indications for their interplay, both on a conceptual and neural level (Buzsáki et al., 1991; McCormick, 1989; McCormick et al., 1991; Rougeul-Buser & Buser, 1997; Sara & Bouret, 2012; Stitt et al., 2018).

Interactions of noradrenergic neuromodulation and alpha-oscillatory activity

Although on different levels of analysis, noradrenergic and alpha-oscillatory activity share many commonalities. For instance, both are related to the global level of behavioral and cortical activation. In particular, the degree of low frequency cortical synchronization varies across behavioral states with the cortex operating in a more synchronized mode during (slow-wave) sleep and inattentive states, whereas alert wakefulness is linked to a highly desynchronized state (Buzsáki et al., 1991; Crunelli et al., 2018; Harris & Thiele, 2011). Accordingly, the LC shows an inverse, state-dependent firing pattern with the rate of tonic discharge increasing from sleep to active wakefulness (Berridge, 2009; Berridge & Waterhouse, 2003; Carter et al., 2010). However, is there a functional link between NE and alpha activity beyond their mere temporal coincidence? Indeed, an activation of the noradrenergic and related ascending subcortical neuromodulatory systems (grouped together as the ascending reticular activating system, ARAS) changes the firing pattern within the thalamus and thereby modulates the level of cortical low frequency synchronization (Berridge, 2009; Buzsáki et al., 1988, 1991; Eschenko, 2019; McCormick, 1989; McCormick et al., 1991; Stitt et al., 2018). This effect is mediated via

excitatory α_1-adrenoceptors abundant in the thalamus, as well as β- and a smaller population of α_2-adrenoceptors (Buzsáki et al., 1991; McCormick et al., 1991; Samuels & Szabadi, 2008a; Szabadi, 2013).

Delagrange and colleagues (1993, 1989), for instance, investigated the effect of pharmacological NE blockade as well as selective lesions in the dorsal noradrenergic bundle on alpha activity in sensory cortices in awake cats. They observed an increase in alpha activity after NE suppression, leading them to the conclusion that the LC-NE system exerts an inhibitory effect on thalamocortical alpha generators (Delagrange, Canu, Rougeul, Buser, & Bouyer, 1993; Delagrange, Tdjer, Bouyer, Rougeul, & Conrath, 1989). In phases of elevated alpha activity, induced by NE blockade, the animals would stand motionless, as if they were waiting for nothing – their behavior had become detached from the environment (see Rougeul-Buser & Buser, 1997, for a review). Buzsáki and colleagues (1991) moreover demonstrated a dual effect of direct intrathalamic injections of noradrenergic drugs on cortical synchronization in awake, immobile rats. While α_1-antagonists and α_2-agonists (i.e., prazosin and clonidine, respectively) promoted cortical synchronization at around 8 Hz in a dose-dependent manner, α_2-antagonists reduced synchronization and were associated with increased behavioral activation (e.g., locomotion). Buzsáki and colleagues thus suggested that the release of large amounts of NE produces cortical desynchronization, mediated via thalamic α_1-adrenoceptors, and allows for reliable thalamocortical information transfer (cf. McCormick, 1989; McCormick et al., 1991). Low NE levels during states of inattentiveness in turn are presumed to promote cortical synchronization via action on postsynaptic α_2-adrenoceptors (cf. differential α_2/α_1-adrenoceptor affinity above; Buzsáki et al., 1991). Mechanistically, via depolarization of the membrane potential, NE suppresses rhythmic burst activity in thalamic neurons and promotes a mode of neural activity that allows for faithful information transfer (i.e., single-spike mode; McCormick, 1989; McCormick et al., 1991). As explained above, rhythmic firing within the thalamus is crucially implicated in the generation of the cortical alpha rhythm (Crunelli et al., 2018).

In line with these earlier studies, a more recent investigation observed a reduction in low frequency EEG synchronization (<10 Hz) and a transition towards more activated behavioral states (e.g., sleep-to-wake transitions, locomotion) after optogenetic LC activation in mice (Carter et al., 2010). McGinley and colleagues (2015) moreover established a link between spontaneous fluctuations in pupil-indexed noradrenergic tone and variations in cortical membrane potentials in awake mice. Constricted pupils, as observed during periods of drowsiness or inattentiveness, were associated with increased relative levels of low frequency (<10 Hz) fluctuations in membrane potentials. In contrast, with greater pupil diameters there was a shift

towards increased power at higher frequencies (50–100 Hz; McGinley et al., 2015; cf. Reimer et al., 2014; Safaai et al., 2015; Vinck et al., 2015). The mice in this study were additionally trained to complete a challenging auditory detection task. Optimal performance occurred at intermediate pupil dilation, in line with an inverted U-shaped relationship between tonic NE levels and performance (cf. Aston-Jones & Cohen, 2005). McGinley and colleagues thus concluded that NE allows for a more reliable processing of sensory inputs in thalamocortical circuits via low frequency desynchronization (McGinley et al., 2015; cf. Nandy et al., 2019).

Taken together, across species and measures, these studies consistently demonstrate a link between the level of tonic LC-NE activity and the levels of cortical synchronization as well as behavioral activation, presumably mediated via a thalamocortical mechanism. A recent animal study set out to explicitly test this thalamocortical circuit and its modulation via pupil-indexed neuromodulatory inputs (Stitt et al., 2018). In states of low noradrenergic tone, indicated by constricted pupils, communication between the thalamus and parietal cortex was synchronized in the alpha frequency range, as measured by intracranially recorded neural ensemble activity (i.e., local field potentials, LFP). In contrast, greater pupil dilation was associated with alpha desynchronization, increased high frequency LFP oscillations (>30 Hz) and a transition towards the theta carrier frequency in thalamocortical interactions (Stitt et al., 2018; cf. Fiebelkorn et al., 2019). On a behavioral level, in periods of thalamocortical alpha synchronization, animals engaged less with the environment, indicating that neuromodulatory inputs allow dynamic switching between behavioral states (Stitt et al., 2018; cf. Fiebelkorn et al., 2019; McCormick et al., 1991).

Crucially, the neural processes that mediate selective information processing are thought to be similar to those underpinning global changes in cortical synchronization (i.e., cortical state), but acting on a more circumscribed spatial and temporal scale (Harris & Thiele, 2011; cf. Stitt et al., 2018). In particular, local cortical desynchronization, as observed during selective attention and memory (van Diepen et al., 2019; van Ede, 2018), has been suggested to arise as a result of phasic neuromodulatory action that gains spatial specificity by focused glutamatergic inputs (Harris & Thiele, 2011; cf. Mather et al., 2016). The tight interplay of neuromodulation and cortical synchronization in mediating selectivity is readily illustrated by the fact that the orienting of attention to salient, novel environmental stimuli (i.e., the orienting response) always entails a transient desynchronization of the cortical EEG and a dilation of the pupils (i.e., a marker of LC-NE activity; Breton-Provencher & Sur, 2019; Sara & Bouret, 2012). In fact, the

behavioral manifestation of attention (e.g., indicated by a saccade to the novel object) is highly predictable by the level of EEG desynchronization and pupil dilation (Sara & Bouret, 2012; Sokolov, 1963).

A few animal studies, have investigated the association between phasic LC-NE activation and circumscribed changes in cortical oscillatory dynamics more systematically. First, Bouret and Sara (2002) demonstrated enhanced sensory responses, both in terms of spike count and, more importantly, temporal organization (i.e., synchronicity) in urethane-anesthetized rats after priming phasic LC stimulation (see Sara, 2009, for a review). Note that synchronous firing patterns underlie neural oscillations and are closely linked to more efficient information transmission and attention (Buschman & Kastner, 2015; Fries, 2005, 2015).

Further, naturally occurring (Neves et al., 2018) and artificially induced (Marzo et al., 2014) phasic LC activity have been related to modulations of excitability in the medial prefrontal cortex (mPFC), a prominent LC projection target that is implicated in a variety of cognitive functions (cf. Chandler, 2016). After pulse trains of LC stimulation that mimicked naturalistic LC bursts in response to salient stimuli, a transient decrease in low frequency LFP power (<11 Hz) and a concomitant increase in high frequency (>45 Hz) power in the mPFC were observed (Marzo et al., 2014; cf. Eschenko, 2018, for similar findings in the thalamus). A pharmacological reduction of central NE transmission (via pretreatment with the α_2-agonist clonidine) abolished these LFP effects, suggesting an underlying noradrenergic mechanism of action (Marzo et al., 2014). A follow-up study that investigated naturally occurring, as well as sensory evoked phasic LC activity in response to salient, noxious stimuli (foot shock) replicated and extended these findings (Neves et al., 2018). Sensory stimulation produced robust phasic activity within the LC that preceded prefrontal low frequency desynchronization (<15 Hz) as well as high frequency synchronization (>30 Hz) by about 150–200 ms (Neves et al., 2018; cf. Headley & Weinberger, 2013, for similar findings). Importantly, these mPFC LFP power changes linearly correlated with the amplitude of LC responses and were eliminated after complete disruption of LC discharge via infusion of the α_2-agonist clonidine (Neves et al., 2018). Taken together, these studies suggest that phasic LC activation rapidly promotes a transition towards a more excitable cortical state, including a transient alpha desynchronization and gamma synchronization, which is essential for the selective processing of salient information (Eschenko, 2019; Marzo et al., 2014; Neves et al., 2018). These NE-induced changes in forebrain synchronization are thought to arise via a thalamic mechanism and a noradrenergic activation of cholinergic and GABAergic nuclei in the basal forebrain (Buzsáki et al., 1988, 1991; Marzo et al., 2014; McCormick, 1989; McCormick et al., 1991; Neves et al., 2018).

To summarize, early investigations linked tonic changes in NE levels, produced via selective lesions, pharmacological interventions, or direct application, to the level of cortical alpha synchronization (Buzsáki et al., 1991; McCormick, 1989; McCormick et al., 1991; Rougeul-Buser & Buser, 1997). Specifically, they demonstrated that NE modulates cortical synchronization by shifting thalamic neurons from a rhythmic firing pattern (i.e., burst mode) to a mode of neural activity that allows for faithful information transfer (i.e., single-spike mode; McCormick, 1989; McCormick et al., 1991). Note that the rhythmic firing of thalamic nuclei is directly implicated in the generation of the cortical alpha rhythm (Crunelli et al., 2018; Lopes da Silva, 1991). Beyond that, more recent investigations have established an association between ongoing, pupil-inferred NE activity and low frequency synchronization in thalamocortical circuits (McGinley et al., 2015; Reimer et al., 2014; Stitt et al., 2018; Vinck et al., 2015). Similar to the modulation of global cortical state by tonic noradrenergic activity, phasic LC activation induces a transient cortical desynchronization, presumably via a thalamic mechanism (Eschenko, 2019; Marzo et al., 2014; Neves et al., 2018). As introduced above, top-down modulations of low frequency synchronization in thalamocortical networks represent a prominent mechanism involved in selective attention and memory (Fiebelkorn et al., 2019; Halassa & Kastner, 2017; Hanslmayr et al., 2016, 2012; Jensen & Mazaheri, 2010; Saalmann et al., 2012; Zhou et al., 2016). This is in line with the notion that the neural mechanisms that mediate selectivity are similar to those that produce global cortical state changes (Harris & Thiele, 2011). To conclude, phasic LC activation may facilitate selective responses to relevant over irrelevant stimuli by flexibly adjusting local cortical excitability via transient modulations of low frequency synchronization (Safaai et al., 2015; Stitt et al., 2018). However, how this interplay shapes selective information processing in aging is currently unknown.

Summary and research objectives

As reviewed in the preceding sections, the selective processing of prioritized information as implicated in attention and memory (Awh et al., 2006; Chun & Turk-Browne, 2007) relies on activity within an extended cortical network. This network incorporates among others frontal, parietal, and sensory brain areas (Buschman & Kastner, 2015; Cabeza et al., 2008; Corbetta & Shulman, 2002; Simons & Spiers, 2003). Frontoparietal structures represent the source of top-down control that biases processing in posterior sensory cortices, which maintain currently active representations, in favor of prioritized information (Banich, 2009; Braver & Barch, 2002; Buschman & Kastner, 2015; Corbetta & Shulman, 2002; Halassa & Kastner, 2017; Noudoost & Moore, 2011). Specifically, this bias can be exerted via a change in the excitability and gain of target regions (e.g., indicated by a change in baseline firing rate and a modulation of sensory evoked responses, respectively; Buschman & Kastner, 2015; Hillyard et al., 1998; Noudoost & Moore, 2011; Thiele & Bellgrove, 2018).

Parallel processing in this distributed frontoparietal network is orchestrated by means of rhythmic neural activity (Buzsáki & Draguhn, 2004; Voytek & Knight, 2015). In particular, top-down modulations of posterior alpha activity, mediated via a thalamic pathway (Fiebelkorn et al., 2019; Halassa & Kastner, 2017; Ketz et al., 2015; Saalmann et al., 2012; Stitt et al., 2018; Zhou et al., 2016), temporarily disengage task-irrelevant parts of the brain and thus serve the flexible gating of information (Jensen & Mazaheri, 2010; Klimesch et al., 2007; van Diepen et al., 2019). Mechanistically, alpha desynchronization during attention deployment and mnemonic processing is thought to facilitate information processing via a reduction of noise correlations, which increases the reliability of the transmitted neural code (Griffiths et al., 2019; Hanslmayr et al., 2016, 2012; cf. Nandy et al., 2019).

The state and functionality of selective information processing in frontoparietal networks is moreover critically dependent on the release of neuromodulators from subcortical structures (Noudoost & Moore, 2011; Robbins & Arnsten, 2009; Thiele & Bellgrove, 2018). In particular, phasic activation of the LC-NE system in response to salient stimuli (or recruited via top-down mechanisms) increases the signal-to-noise ratio of currently relevant representations and thus biases the competition for processing resources in their favor across multiple levels of the cortical hierarchy (Berridge & Waterhouse, 2003; Mather et al., 2016).

Importantly, animal studies have demonstrated that activation within the LC-NE system translates into dynamic changes in low frequency synchronization on a more macroscopic level, presumably mediated via a thalamic mechanism (Buzsáki et al., 1991; Eschenko, 2019; Marzo

et al., 2014; McCormick, 1989; McCormick et al., 1991; Neves et al., 2018; Stitt et al., 2018). Thus, phasic LC activity is thought to subserve the selective processing of prioritized information by dynamically regulating the balance of cortical excitation and inhibition via low frequency de/synchronization in task-ir/relevant brain regions (Safaai et al., 2015; Stitt et al., 2018).

Despite considerable interindividual differences in onset and rate of decline (Lindenberger & von Oertzen, 2006), the ability to selectively process relevant information wanes with increasing age (Craik & Bialystok, 2006; Grady, 2012; Lindenberger, 2014). Age differences in noradrenergic neuromodulation as well as the modulation of posterior alpha activity have each been associated with senescent declines in selectivity (Mather & Harley, 2016; Sander, Lindenberger, et al., 2012). However, it is currently unknown how their interaction shapes selectivity in the aging brain (cf. Kennedy & Mather, 2019).

Previous theories within the cognitive neuroscience of aging emphasized the importance of considering the dynamic interplay of frontoparietal brain networks and the differential age-related changes of its constituents to promote a better understanding of declines in selectivity (Sander, Lindenberger, et al., 2012; Shing et al., 2010; Werkle-Bergner et al., 2006). Adopting this notion, I hypothesize that age differences in the coordinated communication in frontoparietal networks, as assessed by rhythmic neural activity in the alpha band (Fiebelkorn et al., 2019; Ketz et al., 2015; Saalmann et al., 2012; Stitt et al., 2018; Zhou et al., 2016), are related to age differences in the release of noradrenergic neuromodulation (Mather & Harley, 2016; Robbins and Arnsten, 2009; Thiele and Bellgrove, 2018; cf. Braver & Barch, 2002; Li et al., 2001). This position explicitly acknowledges the interplay between different levels of analysis (i.e., the cellular and neural ensemble level) and incorporates both to advance a more mechanistic understanding of age-related cognitive decline (Li & Lindenberger, 1999; Li et al., 2001; Lindenberger et al., 2007).

The following section highlights three empirical studies that employed a combination of neuroimaging techniques and behavioral assessments to target age-related differences in selective information processing. The first two studies separately explored the roles of noradrenergic neuromodulation and rhythmic neural activity in memory and attention while the third investigated their interplay.

Specifically, I hypothesized that MRI-indexed LC integrity (Betts, Kirilina, et al., 2019; Liu et al., 2017) is linked to episodic memory performance – in particular in older adults (Study I; cf. Mather & Harley, 2016; Nyberg et al., 2012; Wilson et al., 2013).

Further, I expected that the dynamic modulation of alpha–beta synchronization in posterior brain regions, as assessed using EEG, is associated with selective attention performance and explains age-related differences therein (Study II; Sander, Lindenberger, et al., 2012; Tune et al., 2018).

Finally, I postulated that increases in noradrenergic neuromodulation, assessed via pupil dilation, translate to changes in low frequency EEG synchronization and both jointly relate to age differences in selective attention (Study III; Neves et al., 2018; Safaai et al., 2015; Stitt et al., 2018).

Taken together, the goal of this work was to link age-related differences in attention and memory to differences in noradrenergic neuromodulation, rhythmic neural activity and their interaction.

Overview of publications

Study I

Dahl, M. J., Mather, M., Düzel, S., Bodammer, N. C., Lindenberger, U., Kühn, S., & Werkle-Bergner, M. (2019). Rostral locus coeruleus integrity is associated with better memory performance in older adults. *Nature Human Behaviour*, 3(11):1203–1214. https://doi.org/10.1038/s41562-019-0715-2

Objective. The aim of this study was to establish non-invasive, in vivo MRI markers of structural LC integrity as a proxy of interindividual and age differences in episodic memory performance.

Theoretical background. Previous animal and post-mortem human research revealed an association between declining memory performance in aging and the integrity of the central noradrenergic system (Arnsten & Goldman-Rakic, 1985; Leslie et al., 1985; Wilson et al., 2013). Mechanistically, neurons within the rostral LC project to the hippocampus (Schwarz & Luo, 2015), where NE acts on β-adrenoceptors to promote synaptic plasticity and thus memory (Hansen, 2017; O'Dell et al., 2015; Sara, 2009, 2015). Accordingly, recent investigations employing optogenetic stimulation demonstrated LC's causal role in hippocampal long-term potentiation and memory formation, presumably supported via co-release of DA (Hansen, 2017; McNamara & Dupret, 2017; Takeuchi et al., 2016; Wagatsuma et al., 2018).

With increasing age, the LC becomes a likely target for neurodegeneration due to the accumulation of aberrant tau, the exposure to blood and CSF-bound toxins, as well as oxidative stress (Braak et al., 2011; Chalermpalanupap et al., 2017; Mather & Harley, 2016; Satoh & Iijima, 2019; Weinshenker, 2018). Consistent with this vulnerability, early post-mortem (Manaye et al., 1995; but see Mather & Harley, 2016, for a discussion) and recent in vivo investigations (Liu et al., 2019) suggested a rostrally accentuated decline of LC integrity in healthy aging.

In line with LC-NE's role in memory formation and its age-related decline, Wilson and colleagues (2013) reported initial evidence indicating the importance of LC integrity, here assessed post-mortem via cell count, for the maintenance of cognitive abilities in old age. Direct in vivo investigations of this link in humans, however, are scarce due to methodological

difficulties in assessing LC integrity reliably (Astafiev et al., 2010; Keren et al., 2009; Nieuwenhuis & Jepma, 2011; but see Hämmerer et al., 2018, for data on emotional memory).

Methods. Here, we took advantage of recent developments in MRI techniques to image the LC using high-resolution T_1-weighted MRI (Betts, Kirilina, et al., 2019; Keren et al., 2015; Liu et al., 2017; Sasaki et al., 2006; Watanabe et al., 2019). In addition, we assessed younger (n = 66; aged 32.5 ± 3.5 years) and older adults' (n = 228; aged 72.3 ± 4.1 years) learning and memory performance using a validated neuropsychological measure of memory functioning (Rey Auditory Verbal Learning Test, RAVLT; Schmidt, 2004) along with a variety of alternative memory tasks (Bertram et al., 2014; Delius, Düzel, Gerstorf, & Lindenberger, 2015; Düzel et al., 2016; Gerstorf et al., 2016). Memory performance was assessed at two time points that were, on average, 2.21 years apart (± 0.52 years). We hypothesized that MRI-indexed LC integrity, that is, a ratio score of peak LC MRI intensity relative to peak intensity in a dorsal pontine reference region (Liu et al., 2017), would be closely associated with individual differences in memory performance and learning rates.

First, we developed a semi-automatic procedure that allowed us to extract individual LC intensity ratios across the rostrocaudal extent from brainstem MRI. Specifically, we pooled across subjects over aligned brainstem scans to facilitate automatized LC localization at a group level (Avants et al., 2011; Avants, Tustison, & Song, 2009; cf. Betts et al., 2017). This group information was then used to restrict automatized extraction of individual peak LC intensities (cf. Chen et al., 2014; Langley et al., 2017). The LC topography generated at the group level matched recent histological analyses that described a densely packed, thin central LC compartment and a dispersion towards rostral and caudal extremities (Fernandes et al., 2012). To further establish the validity of the semi-automatic LC extraction, we demonstrated high accordance with (1) previously published LC maps (Betts et al., 2017; Keren et al., 2009) and (2) manually assessed LC ratings. In addition, repeated measurements of an independent younger adult sample confirmed high reproducibility of the procedure.

Main results. Using a structural equation modeling approach (Kievit et al., 2018; McArdle, 1988; von Oertzen, Brandmaier, & Tsang, 2015; Zimprich, Rast, & Martin, 2008), we demonstrated reduced learning and memory performance in older relative to younger adults (cf. Poreh, 2005). Critically, individual differences in learning and memory in the RAVLT, a widely used neuropsychological test of memory functioning, and, moreover, a range of alternative memory tasks (cf. Düzel et al., 2016), were positively associated with LC integrity across age groups as

well as in the subgroup of older adults. We replicated this finding making use of the longitudinal nature of this data set (Bertram et al., 2014; Delius et al., 2015; Gerstorf et al., 2016), pointing to stable and lasting rather than short-lived LC–memory dependencies.

Finally, analyses across the rostrocaudal LC extent revealed spatially confined and functionally relevant age differences in LC intensity ratios (cf. Betts et al., 2017; Keren et al., 2009; Liu et al., 2019; Manaye et al., 1995), potentially indicating noradrenergic neurodegeneration (Braak et al., 2011; Chalermpalanupap et al., 2017; Ehrenberg et al., 2017; Mather & Harley, 2016; Satoh & Iijima, 2019; Theofilas et al., 2017; Zecca et al., 2004, 2001). In particular, those older adults who showed more youth-like intensity ratios in rostral, hippocampus-projecting LC segments also demonstrated preserved memory performance (cf. Schwarz & Luo, 2015; Wilson et al., 2013).

Taken together, our findings highlight the utility of non-invasive, in vivo markers of LC integrity and support current theories about the role of the LC-NE system in senescent decline (Mather & Harley, 2016; Weinshenker, 2018). Consistent with previous animal research (Leslie et al., 1985; Luo et al., 2015; Wang et al., 2011) as well as post-mortem human work (Wilson et al., 2013), our observations suggest that older adults with more preserved LC integrity, as indexed via MRI, are equipped with more proficient episodic memory (Cabeza et al., 2018; Nyberg et al., 2012; Nyberg & Lindenberger, in press).

Study II

Dahl, M. J., Ilg, L., Li, S.-C., Passow, S., & Werkle-Bergner, M. (2019). Diminished pre-stimulus alpha-lateralization suggests compromised self-initiated attentional control of auditory processing in old age. *NeuroImage, 197*, 414–424. https://doi.org/10.1016/j.neuroimage.2019.04.080

Objective. The aim of this study was to demonstrate that modulations of rhythmic EEG activity in the alpha–beta range (8–30 Hz) in posterior brain areas reflect age differences in auditory spatial attention.

Theoretical background. Older adults experience difficulties in situations in which a multitude of simultaneous signals compete for limited processing resources and selective attention is needed to preferentially process relevant inputs (Erel & Levy, 2016; Kennedy & Mather, 2019; Plude et al., 1994; Sander, Lindenberger, et al., 2012; Staub et al., 2013). In particular, cognitive aging is associated with a shift from internally driven towards externally driven attentional control (Craik & Bialystok, 2006; Grady, 2012; Lindenberger & Mayr, 2014). An increased reliance on external control, also called environmental support, may reflect an adaption to declining attentional resources with advancing age, considering that self-initiated control is more arduous (Craik, 1983; Craik & Bialystok, 2006; Lindenberger & Mayr, 2014). This shift, however, results in impaired performance in situations that require a flexible adaption to changing demands, for instance, multi-talker situations (Passow et al., 2014, 2012).

Across modalities, attention deployment has been linked to modulations of rhythmic neural activity in the alpha and beta frequency range in sensory and higher order brain areas (e.g., Frey et al., 2014; Spitzer & Blankenburg, 2012). In particular, rhythmic alpha activity is thought to reflect the temporary inhibition of task-irrelevant brain regions, which allows the routing of relevant information (Jensen & Mazaheri, 2010; Klimesch et al., 2007; van Diepen et al., 2019; see Hanslmayr et al., 2012, for a similar role of beta activity). Typically, in spatial attention tasks (Buschman & Kastner, 2015), lateralized alpha activity is observed in parietooccipital brain areas. This consists of alpha synchronization in the (ipsilateral) hemisphere processing distracting information and desynchronization in the (contralateral) hemisphere processing the target (van Diepen et al., 2019). Importantly, posterior alpha lateralization has already been observed during target anticipation (i.e., after the presentation of spatial attention

cues), indicating preparatory attention deployment – a largely internally driven process (e.g., Bauer, Stenner, Friston, & Dolan, 2014).

In older adults, a delayed and diminished modulation of posterior alpha–beta activity during visual attention and working memory has been reported, especially at high task difficulty (e.g., Deiber et al., 2013, 2010; Hong et al., 2015; Leenders et al., 2018; Mok et al., 2016; Sander, Werkle-Bergner, et al., 2012). However, studies investigating age-related changes in alpha lateralization in the auditory domain are scarce, and the only study showed preserved alpha lateralization and youth-like attentional performance in middle-aged to older adults (Tune et al., 2018).

Methods. Here, we re-analyzed EEG data of a previously published event-related potential (ERP) study (Passow et al., 2014) in which younger (n = 25; aged 25.8 ± 2.7 years) and older adults (n = 26; aged 70.0 ± 4.1 years) completed an attention-modulated dichotic listening task (cf. Westerhausen et al., 2009). In this task, participants were cued to focus their attention on the information presented to one ear and to block out interfering input from the other, while two streams of highly similar input were presented simultaneously to both ears (i.e. dichotically). In line with previous research in the visual domain, we hypothesized that older adults would demonstrate compromised auditory selective attention along with a reduced or absent alpha lateralization as compared to younger adults.

Main results. On a behavioral level, older adults showed impaired task performance when compared to younger adults, indicating a reduced ability to adjust their attentional focus according to cue condition (cf. Passow et al., 2014; Westerhausen, Bless, Passow, Kompus, & Hugdahl, 2015).

On an electrophysiological level, younger adults demonstrated a sustained period of lateralized activity roughly in the alpha band (6–16 Hz) that was significantly more pronounced in correct than in incorrect trials, indicating its behavioral relevance (Jensen & Mazaheri, 2010; Klimesch et al., 2007). Specifically, in younger adults, lateralized rhythmic activity in parietooccipital brain areas emerged during the anticipatory, pre-stimulus phase and was sustained until well after stimulus presentation (cf. Clayton et al., 2018; van Diepen et al., 2019; Weisz et al., 2011). In contrast, no reliable lateralization was detected before stimulus onset in older adults, whereas a topographically distinct, lateralized response in the alpha–beta frequency (9–30 Hz) range was observed after a stimulus presentation (cf. Deiber et al., 2013; Gola, Kamiński, Brzezicka, & Wróbel, 2012; Gola, Magnuski, Szumska, & Wróbel, 2013).

When comparing the lateralized rhythmic neural activity patterns that were associated with successful (relative to unsuccessful) selective attention performance in each age group, we observed a stronger modulation of pre- and post-stimulus activity in younger and older adults, respectively (Craik & Bialystok, 2006; Grady, 2012; Lindenberger & Mayr, 2014).

Finally, to demonstrate their functional significance, the identified age-specific patterns of lateralized rhythmic neural activity were used to predict attentional performance on a single-trial level (cf. Sander et al., 2019; Wöstmann, Alavash, & Obleser, 2019). While stronger preparatory, pre-stimulus alpha lateralization was linked to better performance in younger adults, it was associated with lower accuracy in older adults. In contrast, lateralization of alpha–beta activity after stimulus presentation predicted more accurate performance in older adults, whereas it was not reliably related to younger adults' performance.

Taken together, our findings relate compromised selective attention in later life to a partial reorganization of attention-related rhythmic neural responses (cf. Deiber et al., 2013). Specifically, we found an age-graded shift from a preparatory modulation of lateralized alpha activity to an externally driven response in the alpha–beta range (Craik & Bialystok, 2006; Lindenberger & Mayr, 2014), whose behavioral relevance was supported by single-trial predictions (cf. Sander et al., 2019; Wöstmann et al., 2019).

Study III

Dahl, M. J., Mather, M. M., Sander, M. C., & Werkle-Bergner, M. (2019). Noradrenergic responsiveness supports selective attention across the adult lifespan. *The Journal of Neuroscience, 40*(22), 4372–4390. https://doi.org/10.1523/jneurosci.0398-19.2020

Objective. The aim of this study was to explore the effect of noradrenergic responsiveness, as assessed by the interplay of arousal-induced pupil dilation and low frequency EEG desynchronization, on age differences in selective attention.

Theoretical background. The ability to dynamically select and prioritize relevant information from the plethora of competing sensory inputs is crucial for adaptive behavior (Desimone & Duncan, 1995; Thiele & Bellgrove, 2018), yet with advancing age, deficits emerge in attentional selectivity (Erel & Levy, 2016; Kennedy & Mather, 2019; Plude et al., 1994; Sander, Lindenberger, et al., 2012; Staub et al., 2013).

Studies with aged rats and monkeys point to altered noradrenergic neuromodulation as one potential reason for age-related decrements in attention (Arnsten & Goldman-Rakic, 1985; Ramos, Stark, Verduzco, van Dyck, & Arnsten, 2006; Wang et al., 2011). In particular, a phasic activation of the noradrenergic system is thought to support selective attention by dynamically adjusting local cortical excitability via modulations of low frequency EEG synchronization (Buzsáki et al., 1991; Eschenko, 2019; Harris & Thiele, 2011; Marzo et al., 2014; McCormick, 1989; McCormick et al., 1991; Neves et al., 2018; Safaai et al., 2015; Stitt et al., 2018).

Recent theories of both healthy (Mather & Harley, 2016) and pathological aging (Weinshenker, 2018) assume a critical role of the LC-NE system in shaping late-life cognition. However, research explicitly establishing this link in aging humans is rare, presumably owing to methodological challenges in non-invasive LC-NE assessments (Astafiev et al., 2010; Nieuwenhuis & Jepma, 2011).

Methods. Here, we investigated in younger (n = 39; aged 25.2 ± 3.2 years) and older adults (n = 38; aged 70.6 ± 2.7 years) whether individual differences in selective attention are related to the noradrenergic system. To this end, we used fear conditioning, an experimental manipulation that reliably drives LC-NE activity, as indicated by markers of neuronal activity in animals (e.g., LC spiking activity: Rasmussen & Jacobs, 1986, and c-Fos: Uematsu et al., 2017; cf. Szabadi, 2012). Concurrently, we assessed pupil dilation, a non-invasive proxy for

noradrenergic activity (Breton-Provencher & Sur, 2019; Joshi et al., 2016; Reimer et al., 2016), and the EEG to establish successful NE manipulation (Biasiucci et al., 2019; Buzsáki et al., 1991; Harris & Thiele, 2011; McCormick et al., 1991; Vazey et al., 2018). Reliable pupil and EEG signatures associated with elevated LC-NE activity were identified in repeated daily conditioning sessions.

In addition, we evaluated participants' general selective attention ability using a multimodal cognitive assessment (cf. Brickenkamp & Zillmer, 1998; Kray & Lindenberger, 2000; Passow et al., 2014; Wechsler, 1981). Specifically, participants completed an arousal-manipulated auditory spatial attention task (i.e., dichotic listening), in which they were cued to attend selectively to either the left or right ear while highly similar syllable pairs were presented simultaneously to both ears (cf. Passow et al., 2014). During this attention task, fear-conditioned (CS+) or perceptually matched control stimuli (CS–) were presented on a trial-by-trial basis to dynamically modulate arousal-related noradrenergic drive (cf. Lee et al., 2018).

Main results. Replicating previous findings, older adults demonstrated compromised selective attention performance in the dichotic listening paradigm (cf. Study II; Passow et al., 2014, 2012), and also across a variety of further attention tasks (cf. Kennedy & Mather, 2019).

On a physiological level, presentation of fear-conditioned stimuli during the dichotic listening task reinstated the acquired arousal response in the absence of reinforcements (i.e., unconditioned stimuli, US). That is, relative to perceptually matched control stimuli (CS–), conditioned stimuli (CS+) induced a multimodal arousal response, consisting of pupil dilation and EEG desynchronization (Breton-Provencher & Sur, 2019; Lee et al., 2018; Stitt et al., 2018). Crucially, greater pupil dilation in response to the CS+ was associated with a stronger transient alpha–beta desynchronization (9–30 Hz) at parietooccipital electrodes, indicating a common underlying dependence on phasic NE release (Buzsáki et al., 1991; Marzo et al., 2014; McCormick, 1989; McCormick et al., 1991; Neves et al., 2018; Sara & Bouret, 2012; Stitt et al., 2018). Using a structural equation modeling approach (Kievit et al., 2018; von Oertzen et al., 2015), we therefore integrated over (pupil-related) EEG desynchronization and pupil dilation markers to derive a single, multimodal index reflecting the responsiveness of the noradrenergic system to arousing stimuli.

Combining behavioral and physiological data, we observed that a more responsive noradrenergic system was associated with more proficient attention performance (Neves et al., 2018; Robbins & Arnsten, 2009; Safaai et al., 2015; Thiele & Bellgrove, 2018). In particular, we found that noradrenergic responsiveness was associated with interindividual differences in

attention on a latent construct level, measured by several indicator tasks. Finally, we were able to show that older age is associated with lower pupil- and EEG-indexed noradrenergic responsiveness (Liu et al., 2019; Mather & Harley, 2016).

Taken together, our findings indicate that (1) noradrenergic neuromodulation dynamically sculpts low frequency oscillatory dynamics in posterior brain areas (Neves et al., 2018; Safaai et al., 2015; Stitt et al., 2018) and (2) this interaction supports selective attention across the lifespan (Arnsten & Goldman-Rakic, 1985; Wang et al., 2011).

Discussion

Building on previous research in the cognitive neuroscience of aging that separately highlighted the prominent roles of neuromodulation and neural oscillations in shaping aging cognition (Li et al., 2001; Mather & Harley, 2016; Sander, Lindenberger, et al., 2012; Werkle-Bergner et al., 2006), the studies outlined in the preceding section tested the following hypotheses:

On a neural level, age-related decrements in selective attention and episodic memory are related to differences in:

1. noradrenergic neuromodulation, as assessed using LC-MRI (Study I),
2. the modulation of alpha–beta rhythmic activity, as assessed using EEG (Study II) and
3. the interplay of noradrenergic neuromodulation and rhythmic neural activity, as assessed using concurrent pupil dilation and EEG (Study III).

In the following, I will summarize my key findings and relate them to the current state of research. In particular, I will first discuss the obtained results with respect to the neural underpinnings of selective information processing in general (i.e., independent of age effects, focusing largely on younger adults). Second, I will discuss what these findings add to our understanding of age-graded differences in selective attention and memory (i.e., now focusing on older adults). Third, the challenges and limitations of age-comparative neuroscientific studies in general, and the presented work in particular, will be acknowledged. Finally, I will end by pointing out directions for future research and providing general conclusions.

Noradrenergic neuromodulation and modulations of alpha-oscillatory activity jointly support selective information processing

Based on previous research, mainly relying on animal studies, the present work was guided by the theoretical rationale that the interplay between noradrenergic neuromodulation and low frequency rhythmic activity underpins selective neural processing. In short, according to this view, selective attention and memory are mediated by the dynamic interplay of a spatially distributed frontoparietal network (Buschman & Kastner, 2015; Cabeza et al., 2008; Corbetta & Shulman, 2002; Simons & Spiers, 2003), whose processing is coordinated via reciprocal connections with the thalamus (Buschman & Kastner, 2015; Fiebelkorn et al., 2019; Halassa & Kastner, 2017;

Ketz et al., 2015; Saalmann et al., 2012; Stitt et al., 2018; Zhou et al., 2016). Communication within this interconnected thalamocortical network arises from the transient synchronization of its rhythmic neural activity (Buzsáki & Draguhn, 2004; Fries, 2015; Voytek & Knight, 2015). Crucially, recent animal research suggests that noradrenergic neuromodulation dynamically sculpts the patterns of thalamocortical synchronization and thus facilitates the preferential processing of relevant information (Eschenko, 2019; Marzo et al., 2014; Neves et al., 2018; Safaai et al., 2015; Stitt et al., 2018).

The presented in vivo human findings comply with and extend several aspects of this theoretical framework. First, across a variety of attention paradigms, the modulation of posterior low frequency rhythmic activity was associated with better performance (Studies II and III), in line with its role in selectively routing relevant information through thalamocortical networks (Fiebelkorn et al., 2019; Jensen & Mazaheri, 2010; Klimesch et al., 2007; Saalmann et al., 2012; Zhou et al., 2016). Crucially, the behavioral relevance of low frequency modulations was evident even on a single trial level (Study II; cf. Wöstmann et al., 2019), complementing earlier research in the perceptual and mnemonic domains (e.g., Benwell et al., 2017; Sander et al., 2019). While modulations of posterior alpha oscillations are widely embraced as a neural correlate of both the locus and timing of selective attention (Clayton et al., 2018; Jensen & Mazaheri, 2010; Klimesch et al., 2007; Strauß et al., 2014; van Diepen et al., 2019; Weisz et al., 2011), some discussion persists about whether this effect is mediated via a suppression or enhancement of ir/relevant information, respectively (i.e., inhibition or facilitation; e.g., Foster & Awh, 2019; Wöstmann et al., 2019). Our analyses (Study II) add to this question by demonstrating that successful attention performance was accompanied by signatures of both inhibition and facilitation: We observed alpha synchronization in distractor-processing brain regions while target-processing areas showed alpha desynchronization (i.e., a reliable hemisphere by performance interaction; Foster & Awh, 2019; Jensen & Mazaheri, 2010; Klimesch et al., 2007).

Second, our findings also support the notion of a role of noradrenergic neuromodulation in facilitating access to relevant information (Studies I and III). In particular, across age groups, interindividual differences in memory performance were positively related to MRI-indexed LC integrity, even when statistically controlling for participants' age (Study I). Mechanistically, the observed LC–memory association may reflect LC-NE's gain-modulating function (Robbins & Arnsten, 2009; Thiele & Bellgrove, 2018; cf. Li et al., 2001) as well as its modulation of synaptic plasticity (Hansen, 2017; O'Dell et al., 2015; Sara, 2009, 2015; Takeuchi et al., 2016;

Wagatsuma et al., 2018). However, while our analyses across age groups indicate an association between LC integrity and memory performance irrespective of age, several aspects may have limited the effectiveness of our neural and cognitive measures to reliably detect this link in younger adults alone: That is, the lower sensitivity of LC-MRI as an integrity proxy in younger adults (cf. Clewett et al., 2016; Hämmerer et al., 2018), the ceiling effect younger adults showed in the memory assessment, and the lower sample size for younger adults. Our observations (Study III) further suggest an association between markers of noradrenergic activation (i.e., arousal-induced pupil dilation; Breton-Provencher & Sur, 2019; Joshi et al., 2016; Lee et al., 2018; Rasmussen & Jacobs, 1986; Reimer et al., 2016; Szabadi, 2012; Uematsu et al., 2017) and the ability to separate and filter relevant from irrelevant information. Participants who demonstrated higher pupil-indexed noradrenergic activity performed better in a multimodal attention assessment, consistent with NE's role in the preferential processing of salient information (Aston-Jones & Cohen, 2005; Berridge & Waterhouse, 2003; Mather et al., 2016; Robbins & Arnsten, 2009; Sara, 2009; Sara & Bouret, 2012; Thiele & Bellgrove, 2018).

Importantly, third, we obtained evidence for an association between noradrenergic neuromodulation and low frequency desynchronization (Study III). Specifically, we observed stronger EEG desynchronization in individuals with greater pupil dilation, which we take as indication of a common underlying noradrenergic factor (Buzsáki et al., 1991; McCormick, 1989; McCormick et al., 1991; Sara & Bouret, 2012; Stitt et al., 2018). In agreement, previous animal research demonstrated that an activation of ascending neuromodulatory systems like the noradrenergic LC induces changes in cortical synchronization (i.e., cortical state changes; Carter et al., 2010; Marzo et al., 2014; Moruzzi & Magoun, 1949; Neves et al., 2018), presumably mediated via a thalamic pathway (Buzsáki et al., 1991; McCormick, 1989; McCormick et al., 1991; Stitt et al., 2018). Integrating performance over tasks, we found that greater pupil- and EEG-indexed noradrenergic responsiveness was linked to better attention performance on a latent construct level (Study III; cf. Robbins & Arnsten, 2009; Sara & Bouret, 2012; Thiele & Bellgrove, 2018). Our observations are thus in accordance with the notion that phasic LC activation facilitates selective responses to relevant stimuli by flexibly adjusting local cortical excitability via a transient modulation of low frequency synchronization (McCormick et al., 1991; Safaai et al., 2015; Stitt et al., 2018).

Taken together, across studies and measures, our findings indicate similar, partly intertwined actions of LC-NE- and alpha-oscillatory systems in promoting selectivity on different levels of analysis. Our results bridge animal and human studies on the neural underpinning of

selective information processing and highlight the dynamic interplay of noradrenergic neuromodulation and neural synchronization in shaping cognition (cf. Stitt et al., 2018).

Age differences in noradrenergic neuromodulation and the modulation of alpha-oscillatory activity relate to age differences in selective information processing

Across levels of analysis, aging is associated with manifold, often nonlinear changes in brain structure and function that are thought to result in cognitive decline (e.g., Cabeza et al., 2004; Grady, 2012; Raz et al., 2005). In particular, deficits in effectively exerting cognitive control emerge (Craik & Bialystok, 2006; Grady, 2012; Lindenberger & Mayr, 2014) that are closely linked to the ability to selectively process goal-relevant information (Buschman & Kastner, 2015; Desimone & Duncan, 1995; Halassa & Kastner, 2017; Thiele & Bellgrove, 2018). Age-related changes in selectivity become evident as progressive declines in attention (Studies II and III; Erel & Levy, 2016; Kennedy & Mather, 2019; Plude et al., 1994; Sander, Lindenberger, et al., 2012; Staub et al., 2013) and episodic memory (Study I; Nyberg et al., 2012; Nyberg & Pudas, 2019; Shing et al., 2010; Tromp et al., 2015; Werkle-Bergner et al., 2006).

As highlighted above, neuromodulation may shape selective information processing in distributed cortical networks via dynamic changes in rhythmic neural activity (Buzsáki et al., 1991; McCormick, 1989; McCormick et al., 1991; Safaai et al., 2015; Stitt et al., 2018). Accordingly, age-related changes in neuromodulation are considered crucial determinants of aging cognition (Studies I and III; Bäckman et al., 2006; Braver & Barch, 2002; Li et al., 2001; Li & Rieckmann, 2014; Mather, in press; Mather & Harley, 2016). Moreover, age differences in the modulation of rhythmic neural activity have been tied to differences in attention and memory (Studies II and III; Sander, Lindenberger, et al., 2012; Werkle-Bergner et al., 2006). However, the cognitive neuroscience of aging (Cabeza et al., 2004; Grady, 2012) currently lacks studies linking these fields of research. Integrating neuromodulatory and oscillatory changes in aging, below I propose a theoretical framework that unifies these levels of analysis (see Figure 1; Li & Lindenberger, 1999; Li et al., 2001; Lindenberger et al., 2007):

Noradrenergic neurodegeneration, for instance, resulting from the accumulation of toxins and aberrant tau (Braak et al., 2011; Chalermpalanupap et al., 2017; Ehrenberg et al., 2017; Mather & Harley, 2016; Satoh & Iijima, 2019; Theofilas et al., 2017; Weinshenker, 2018; Zecca et al., 2004, 2001), may lead to age-related neuronal loss in the LC (Liu et al., 2019; Manaye et al., 1995; Shibata et al., 2006). As a consequence of structural decline, older adults may

demonstrate a limited effectiveness in phasically recruiting noradrenergic neuromodulation to bias information processing according to current goals (Robbins & Arnsten, 2009; Thiele & Bellgrove, 2018; Wang et al., 2011). As detailed above, neural synchronization in thalamocortical networks is dynamically modulated via phasic noradrenergic inputs (Eschenko, 2019; Marzo et al., 2014; Neves et al., 2018). Hence, age-related impairments in modulating alpha synchronization to selectively route relevant information through thalamocortical networks (Deiber et al., 2013; Henry et al., 2017; Sander, Werkle-Bergner, et al., 2012; Wöstmann et al., 2015) may partly reflect diminishing noradrenergic drive (Stitt et al., 2018).

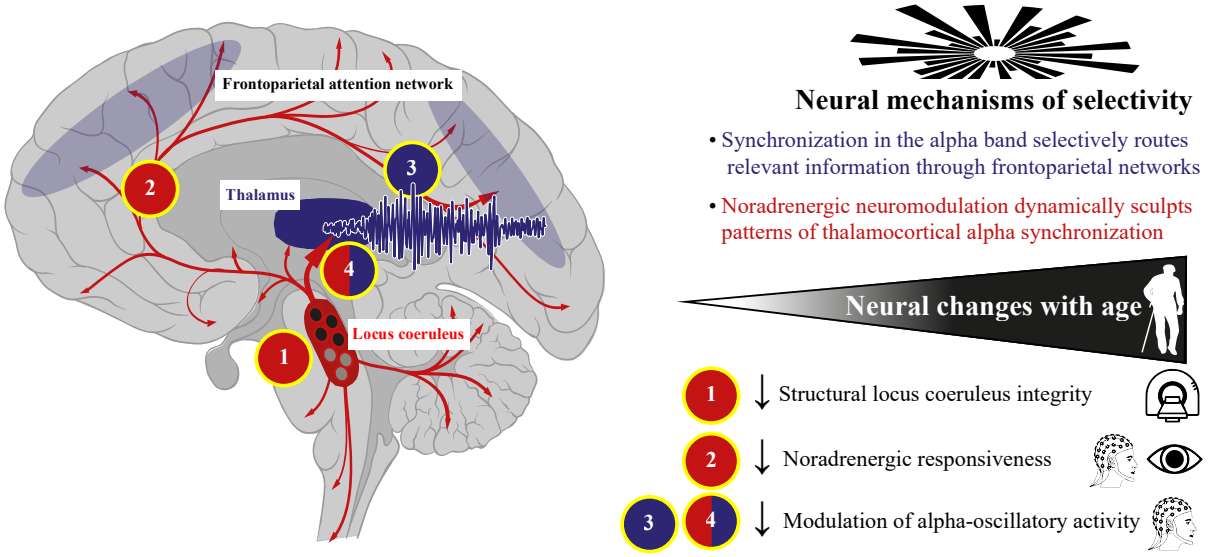

Figure 1 | Schematic overview of neural mechanisms of selectivity and their changes with advancing age. On a neural level, selective processing is mediated by the dynamic interplay of a spatially distributed frontoparietal network (blue semitransparent areas), whose processing is coordinated via reciprocal connections with the thalamus (blue opaque area). Communication within this interconnected thalamocortical network arises from the transient synchronization of its rhythmic neural activity (blue oscillation). Crucially, recent animal research suggests that noradrenergic neuromodulation, originating from the locus coeruleus (red opaque area), dynamically sculpts the patterns of thalamocortical synchronization and thus facilitates the preferential processing of relevant information. **1,** In later life, noradrenergic neurons decline, in particular in rostral segments of the locus coeruleus (black circles; see Study I). **2,** In consequence, older adults cannot recruit noradrenergic neuromodulation to bias processing in frontoparietal networks according to current demands to a similar extent as younger adults (see Study III). **3/4,** As phasic noradrenergic inputs modulate thalamocortical synchronization (Study III), diminishing noradrenergic drive in aging may contribute to an impaired modulation of alpha-oscillatory activity (Study II). For references, see main text. Locus coeruleus, thalamus and frontoparietal attention network are not drawn to scale. Credits: Sagittal brain section, adapted from Patrick J. Lynch under a Creative Commons Attribution 2.5 License 2006.

How may the presented in vivo human findings fit in this theoretical framework? First, in line with early post-mortem assessments (Manaye et al., 1995) and a recent large-scale in vivo investigation (Liu et al., 2019), we observed rostrally-accentuated age differences in MRI-indexed LC integrity (Study I), which may indicate LC neuronal death. Further, probing the responsiveness of older adults' LC-NE system (Study III), we observed that age differences in arousal-related pupil responses emerged when older adults were no longer supported by external reminders (i.e., reinforcements; US; cf. Craik & Bialystok, 2006; Lindenberger & Mayr, 2014; van Gerven et al., 2004). Lower pupil responses in aging presumably reveal underlying age differences in the phasic recruitment of the central noradrenergic system (Arnsten, 2007; Breton-Provencher & Sur, 2019; Samuels & Szabadi, 2008b). Taken together, our observations (Studies I and III) provide novel evidence for age differences in both structural and functional markers of noradrenergic neuromodulation that are closely related to attentional and mnemonic performance.

Second, adding to previous research in the visual domain that observed a reduced modulation of alpha rhythmic activity in later life (Hong et al., 2015; Leenders et al., 2018; Mok et al., 2016; Sander, Werkle-Bergner, et al., 2012), we found an age-related impairment in the proactive recruitment of alpha lateralization (Study II). As earlier investigations demonstrated that older adults fail to uphold heightened levels of attention-related alpha activity over sustained periods of time (Henry et al., 2017; Wöstmann et al., 2015), our observation (Study II) may indicate a mismatch between neural resources and task demands (i.e., a supply-demand gap; Cabeza et al., 2018). Accordingly, we detected a behaviorally relevant shift to a, presumably less demanding, reactive spectral response in older adults that was expressed in higher frequencies and at more central electrodes relative to younger adults (Study II). This observation is consistent with the previously reported recruitment of alternative, centroparietal circuits operating in the lower beta frequency in later life (Deiber et al., 2013; Gola et al., 2012, 2013). Moreover, it suggests age-related difficulties in internally triggering proactive attentional processes and thus a shift towards less demanding external control (Craik & Bialystok, 2006; Lindenberger & Mayr, 2014). As our observations (Study III) indicate an association between noradrenergic neuromodulation and the modulation of low frequency rhythmic activity, this age-graded shift may reflect an adaption to decreasing neuromodulatory drive in aging (Studies II and III; Li et al., 2001; Mather & Harley, 2016). That is, declining neuromodulation in later life may contribute to older adults' shift from a metabolically costly internally driven control

of attentional and mnemonic processing towards a less demanding external control mode (Lindenberger & Mayr, 2014).

In sum, using a multimodal assessment (i.e., MRI, EEG, and pupil dilation) across studies, we revealed age differences in noradrenergic neuromodulation and low frequency rhythmic neural activity that explain differences in selective information processing. In line with its role in regulating younger adults' cognition, the presented results underscore the role of maintained noradrenergic neuromodulation in preserving late-life cognition (Cabeza et al., 2018; Nyberg et al., 2012), presumably via a dynamic modulation of synchronization in thalamocortical networks (Stitt et al., 2018). In short, our findings can be summarized in the proposition that age-related decline in lower-level neuromodulatory systems impinges on higher levels of neural processing where it disrupts effective communication in distributed brain networks necessary for cognition.

Challenges of age-comparative neuroscientific studies on selective information processing and proposed solutions

As summarized in the preceding sections, this dissertation provides novel evidence regarding the neural underpinning of age differences in selectivity. However, research targeting the neural correlates of age-related cognitive decline using non-invasive and indirect measures like pupil dilation, EEG, and (f)MRI faces serious methodological challenges (Muehlroth & Werkle-Bergner, 2019; Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Rugg & Morcom, 2004; Samanez-Larkin & D'Esposito, 2008; van Gerven et al., 2004). Below, core challenges faced in the presented studies will be discussed along with the efforts that we made to overcome them in order to guarantee age-fair group comparisons. In particular, a first challenge concerns unspecific confounding factors associated with the aging process. In the presented studies, for instance, age-related changes of the eyes (e.g., blink characteristics; van der Werf & Smit, 2008), increases in head motion (Madan, 2018), as well as differences in the level of neuromelanin accumulation (Mann & Yates, 1974; Zecca et al., 2004) may differentially affect the signal-to-noise ratio in pupil, EEG, and MRI measures (Park et al., 2001; Samanez-Larkin & D'Esposito, 2008). Importantly, group differences in signal-to-noise ratios lead to a differential reliability of the obtained indices and thus differences in statistical power to detect effects within age groups (Rugg & Morcom, 2004; Samanez-Larkin & D'Esposito, 2008). As a consequence, caution is warranted in the interpretation of attenuated (e.g., in amplitude/cluster extent)

or non-significant effects between age groups. Depending on the measure, age differences in reliability may not only disadvantage older adults but also adversely affect younger adults' data – as, for instance, due to the lower sensitivity of LC-MRI as a LC integrity proxy in earlier life (see above and Clewett et al., 2016; Hämmerer et al., 2018; Mann & Yates, 1974). Of note, however, in most of the presented analyses (Studies II and III), we detected reliable associations between neural and cognitive factors that were of comparable magnitude in both age groups (for a sketch of the analysis procedure, see below).

Age-related changes in brain morphology constitute another potentially confounding factor that may cause differences in the scalp distribution of EEG responses (Müller, Brehmer, von Oertzen, Li, & Lindenberger, 2008; Rugg & Morcom, 2004; Sander, Werkle-Bergner, & Lindenberger, 2011) and spatial location of small brain structures like the LC (e.g., due to ventricle enlargement; Keren et al., 2009; Samanez-Larkin & D'Esposito, 2008). In the presented work (Studies I–III), several efforts were made to counteract the confounding influence of age-related changes in brain morphology and thus increase the validity of age comparisons. In particular, to isolate pupil and EEG correlates of attention in an age-fair manner (Studies II and III), analyses were first conducted within subjects (i.e., across trials; first level), followed by within age group statistics (i.e., second level). First-level analyses included a bootstrapping procedure to counteract potentially unequal distributions of trials per condition across age groups that could otherwise lead to age differences in variances (cf. Samanez-Larkin & D'Esposito, 2008). Further, a data-driven approach was implemented that allowed for idiosyncrasy concerning the temporal, spatial, and spectral characteristics of the physiological responses (Karch, Sander, von Oertzen, Brandmaier, & Werkle-Bergner, 2015; Müller et al., 2008; Nesselroade, Gerstorf, Hardy, & Ram, 2007; Sander et al., 2011). Finally, after identifying age-specific pupil and EEG responses, these were evaluated for age differences on a third level (Study II). In other words, we first evaluated effects within the groups of younger and older adults (second level), followed by the analysis of group differences in within-group effects (third level). This procedure is in compliance with recommendations for the analysis of age-comparative neuroimaging studies (Samanez-Larkin & D'Esposito, 2008) and reduces the influence of age-related confounding factors, such as changes in brain morphology.

In a similar way, analyses of MRI-indexed LC integrity (Study I) allowed for interindividual variability in the precise spatial location of peak intensity voxels which was constrained to anatomically plausible regions using a sample-specific volume of interest (search space). Moreover, MRI analyses were conducted using advanced normalization tools (ANTS; Avants et al., 2011, 2009) to guarantee an age-fair spatial normalization of brainstem MRI (Klein et

al., 2009; Park et al., 2001; Samanez-Larkin & D'Esposito, 2008). Neural and cognitive measures were then analyzed in a common, multiple-group structural equation model (von Oertzen et al., 2015), after explicitly testing for factorial invariance across groups (Studies I and III; Meredith & Teresi, 2006). Hence, in the present analyses (Studies I–III) major efforts were made to minimize potential influences of age-related cofounding factors, such as brain morphology, by using age-fair analysis methods (Karch et al., 2015; Muehlroth & Werkle-Bergner, 2019; Park et al., 2001; Samanez-Larkin & D'Esposito, 2008).

Besides potential age-related confounding factors, a second challenge concerns the interpretability of the employed non-invasive neural and cognitive measures. For instance, a major shortcoming of conventional MRI sequences, like the applied TSE sequence (Study I), is that they produce grayscale images lacking a meaningful scale. Thus, to derive MRI-based estimates for LC integrity that allow comparisons between subjects and across groups, normalization to a reference region becomes necessary (most commonly in the dorsal pons; Liu et al., 2017). In line with substantial changes of brain structure with age (Raz et al., 2005), age-related signal decline in the pontine reference region has been demonstrated (Clewett et al., 2016; Keren et al., 2009). Hence, analyses of age differences in the LC that are based on a ratio score of LC and pons MRI intensity may be confounded (Keren et al., 2009). The development of quantitative anatomical MRI (qMRI) that provides absolute measures (Weiskopf et al., 2013) promises to overcome this interpretational problem by deriving reference-free LC integrity proxies (Betts, Kirilina, et al., 2019; Liu et al., 2017). Of note, however, in the presented work (Study I) we did not detect a reliable correlation between age and the signal in the pontine reference region in older adults who showed the LC–cognition association. Moreover, in our analyses (Study I), LC–memory associations were detected selectively for the rostral LC, in line with its connectivity to memory-relevant areas (Schwarz & Luo, 2015). In contrast, more caudal aspects that project to the cerebellum and spinal cord did not reliably relate to behavior, arguing against unspecific reference-driven effects. Thus, while interpretational problems are inherent in the analysis of conventional MRI sequences, our findings (Study I) suggest that interindividual differences in LC but not reference integrity are associated with memory in aging.

Two additional aspects may further complicate the interpretation of LC-MRI findings (Study I): First, while several studies indicated that paramagnetic compounds in noradrenergic neurons form the basis of contrast variations in LC-MRI (Keren et al., 2015; Trujillo et al., 2017), the precise physical mechanisms are still debated (see above; Watanabe et al., 2019).

Second, several recent investigations revealed (co-)release of dopamine and GABA from the LC (Breton-Provencher & Sur, 2019; McNamara & Dupret, 2017; Takeuchi et al., 2016; Wagatsuma et al., 2018), questioning a selective attribution of MRI-indexed LC–memory effects to NE. Hence, as described below in more detail, future research is needed to resolve these interpretational difficulties in LC-MRI. Notably, however, our attribution of LC-MRI effects to NE constitutes a parsimonious explanation that is in accordance with animal studies demonstrating noradrenergic influences on synaptic plasticity and memory (Brzosko, Mierau, & Paulsen, 2019; O'Dell et al., 2015; Sara, 2009).

Similar caution is warranted in the interpretation of pupil dilation as a pure index of noradrenergic activity, as a recent study demonstrated that, in addition to NE, cholinergic activation produces sustained pupil dilation (Reimer et al., 2016). Thus, as detailed below, future research that simultaneously manipulates different neuromodulatory systems while assessing pupil dilation is required to further uncover the neural underpinning of this measure. In the presented work (Study III), we applied an experimental manipulation that is known to elicit LC activity (e.g., indicated by LC spiking activity: Rasmussen & Jacobs, 1986, and c-Fos: Uematsu et al., 2017; cf. Szabadi, 2012) and assessed its effectiveness combining multiple measures sensitive to LC activity (pupil dilation: Breton-Provencher & Sur, 2019; Joshi et al., 2016; Reimer et al., 2016; ERPs [P 300]: Vazey et al., 2018; and low frequency EEG desynchronization: Marzo et al., 2014; Neves et al., 2018). Importantly, we observed converging evidence across the employed pupil and electrophysiological measures suggesting a successful assessment of the LC-NE system (Study III).

Interpretational difficulties, however, do not only apply to surrogate measures for noradrenergic neuromodulation but also pertain to the cognitive level. In Studies I and III, cognitive measures were analyzed employing multivariate approaches in which the observed task performance across various attention and memory paradigms (i.e., manifest variables) was used to estimate cognitive performance on a latent construct level (using SEM; von Oertzen et al., 2015). By accounting for measurement error in observed scores, latent variables have the benefit of increasing statistical power (Curran, Obeidat, & Losardo, 2010; Kievit et al., 2018). Further, by integrating performance over multiple cognitive paradigms and thus demonstrating task-overarching brain–cognition associations, the presented results yield a higher validity. However, while increasing generalizability, the adopted multivariate approach reduces the specificity of conclusions regarding the separate cognitive processes entailed. That is, it becomes more difficult to relate neural measures to specific cognitive operations, such as memory encoding, consolidation or retrieval. Future age-comparative research that experimentally

manipulates putatively implicated cognitive processes (see Fandakova, Werkle-Bergner, & Sander, 2019; Muehlroth et al., 2019a; Sander et al., 2019; Sommer et al., 2019, for examples) while recording noradrenergic neuromodulation and rhythmic neural activity is needed to shed light on this question.

A third limitation concerns the inferences that can be drawn from cross-sectional research. In particular, the presented work (Studies I–III) mostly relied on age-comparative designs to infer potential interrelations of neural and cognitive changes (i.e., intraindividual variations) in later life. However, to allow such inference from cross-sectional data, the assumptions of sample homogeneity and ergodicity have to be met (Lindenberger, von Oertzen, Ghisletta, & Hertzog, 2011; Molenaar, 2004; Raz & Lindenberger, 2011). While parts of the presented work (Study I) targeted intraindividual change in memory performance over a ~2-year interval and its relation to noradrenergic neuromodulation, the observed cognitive changes appeared negligible (cf. Zimprich & Rast, 2009, for similar observations). Thus, future research that concurrently tracks changes in neural and cognitive parameters over extended time scales is needed to overcome the ambiguity of cross-sectional findings (for first ongoing longitudinal studies that monitor changes of MRI-indexed LC activity, markers of neurodegeneration, and cognition in aging, see Betts, Cardenas-Blanco, et al., 2019; Jessen et al., 2018). Intriguingly, follow-up cognitive assessments with the same participants as tested in Study I are underway which hold promise address this challenge in forthcoming analyses.

To conclude, age-comparative research employing indirect neural and cognitive measures as well as cross-sectional designs warrants some caution regarding specific conclusions about the neural underpinning of senescent cognitive changes. Thus, in the presented work (Studies I–III) major efforts were made to limit the influence of age-related confounding factors and guarantee age-fair group comparisons. Future longitudinal and experimental studies incorporating refined non-invasive measures of neuromodulation and rhythmic activity are required to overcome the remaining identified limitations.

Future research directions

Extending the here presented work, future investigations should further address how precisely the interaction of noradrenergic neuromodulation and rhythmic neural activity sculpts selective information processing in the aging brain. The majority of imperatives for future research thereby derives directly from the limitations of current methods and designs, as identified in the

preceding section. While some aspects may be addressed using in vivo age-comparative studies in humans, some foundational methodological work likely requires invasive research (cf. Keren et al., 2015).

Specifically, a better understanding is needed whether metal ions (e.g., iron, copper; Zecca et al., 2004) in combination with neuromelanin (Trujillo et al., 2017) or LC's water content (i.e., proton density; Watanabe et al., 2019) drive contrast variations in LC-MRI, since the different constituents presumably show differential age trajectories (Mann & Yates, 1974; Zecca et al., 2004). In addition, to delineate how MR-indexed structural LC integrity translate into noradrenergic dynamics, quantitative LC-MRI measures should be linked to newly established in vivo markers of NE transmission (in animal research; Feng et al., 2019) and pupil dilation (in human research; cf. Hämmerer et al., 2018). Moreover, the relative contributions of cholinergic and noradrenergic activation to the pupil signal should be uncovered (Reimer et al., 2016), for instance, by using pharmacological interventions (i.e., selective antagonists).

An avenue for future research could then be to link quantitative assessments of MR-indexed LC integrity (Betts, Kirilina, et al., 2019; Liu et al., 2017) and potential changes therein to long-term changes in mnemonic abilities in aging (see Betts et al., 2019; Jessen et al., 2018, for ongoing longitudinal studies). Recent reports indicated the LC as the earliest target of neurofibrillary changes that may lead to the development of Alzheimer's disease (Braak et al., 2011; Ehrenberg et al., 2017; Jagust, 2018; Theofilas et al., 2018). Accordingly, incorporating markers sensitive to early signs of neuropathology in longitudinal LC-MRI assessments (e.g., in vivo visualization of amyloid-β plaques and tau neurofibrillary tangles using repetitive PET; cf. Hanseeuw et al., 2019; Maass et al., 2019) may inform about the transitions between healthy and pathological cognitive aging (Grinberg & Heinsen, 2017; Jacobs, Riphagen, Ramakers, & Verhey, 2019; Jagust, 2018). The accumulation of aberrant tau in the LC has also been linked to neuropsychiatric symptoms such as agitation and sleep disturbances (Ehrenberg et al., 2018), in line with LC's role in the regulation of behavioral arousal (Carter et al., 2010). Crucially, oscillatory dynamics during sleep play an important role in the consolidation of newly encoded information (Diekelmann & Born, 2010; Klinzing, Niethard, & Born, 2019). As such, it would be intriguing to expand the focus of current LC–cognition analyses to additionally link LC-NE and memory to altered sleep dynamics in aging (Helfrich, Mander, Jagust, Knight, & Walker, 2018; Muehlroth et al., 2019b) to more clearly disentangle mechanisms of senescent memory decline (cf. Sara, 2015; Swift et al., 2018; Zhu et al., 2018).

Further, extending recent animal work to humans (Stitt et al., 2018), the influence of noradrenergic neuromodulation on the dynamic communication in thalamocortical circuits

(Buzsáki & Draguhn, 2004; Fries, 2015; McCormick et al., 1991; Stitt et al., 2018; Voytek & Knight, 2015) should be addressed in within-subject designs (Molenaar, 2004; Molenaar & Campbell, 2009; Nesselroade et al., 2007). Specifically, trial-by-trial modulations of alpha synchronization between posterior cortex and thalamus (Buschman & Kastner, 2015; Fiebelkorn et al., 2019; Ketz et al., 2015; Saalmann et al., 2012; Zhou et al., 2016) during selective attention and memory (Hanslmayr et al., 2016; Jensen & Mazaheri, 2010) could be monitored and source-localized using magnetoencephalography (MEG; e.g., Waldhauser et al., 2018). MEG would also allow reliable estimation of high frequency (gamma) activity (Hipp & Siegel, 2013; Waldhauser et al., 2018; Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008) and thus a simultaneous assessment of NE's role in the release from alpha-mediated inhibition and the shift to gamma-related feed forward processing (Marzo et al., 2014; Neves et al., 2018). Phasic and tonic NE levels could concurrently be modulated using pharmacological (Gelbard-Sagiv, Magidov, Sharon, Hendler, & Nir, 2018) and experimental (Lee et al., 2018) manipulations while recording pupil dilation (Breton-Provencher & Sur, 2019). Specifically, a second avenue for research could concern how the structural and functional integrity of the LC-NE system in aging influences rhythmic neural dynamics (Marzo et al., 2014; Neves et al., 2018; Safaai et al., 2015) based on a multimodal assessment including pupil dilation, MEG, and MRI. Combining the relative strengths of multiple neuroscientific methods in a multivariate framework (Kievit et al., 2018) would allow simultaneously investigating temporal, spatial, and spectral characteristics of age-related decline in noradrenergic neuromodulation. Taken together, the outlined approaches hold promise to advance a more holistic understanding of the neural underpinnings of age-related changes in selectivity across levels of neural processing.

Conclusions

Notwithstanding sizeable interindividual differences in onset and rate of change, later life is linked to progressive declines in selective attention and memory (Kennedy & Mather, 2019; Nyberg et al., 2012; Shing et al., 2010). On a neural level, noradrenergic neuromodulation (Mather & Harley, 2016) and rhythmic neural activity (Sander, Lindenberger, et al., 2012) have each been linked to declining cognition in aging, but their interplay in the aging brain is poorly understood.

In three empirical studies, this dissertation bridged levels of analysis (Li & Lindenberger, 1999; Li et al., 2001; Lindenberger et al., 2007) to highlight the role of maintained noradrenergic neuromodulation in preserving late-life cognition (see Figure 1; Cabeza et al., 2018; Nyberg et al., 2012). This function is presumably mediated via NE's dynamic modulation of low frequency synchronization in thalamocortical networks (Fiebelkorn et al., 2019; Stitt et al., 2018).

First, across multiple cognitive paradigms, MRI-indexed LC integrity was associated with individual differences in memory performance in older adults (Study I; cf. Hämmerer et al., 2018). Moreover, our analyses revealed spatially confined and functionally relevant age differences in forebrain-projecting LC compartments (cf. Liu et al., 2019; Schwarz & Luo, 2015).

Second, this work established a link between compromised selective attention in aging and a partial reorganization of attention-related rhythmic EEG responses (Study II; cf. Deiber et al., 2013). In particular, aging was associated with a behaviorally relevant shift from a preparatory top-down modulation of lateralized alpha activity to an externally driven response in the alpha–beta range (Craik & Bialystok, 2006; Grady, 2012; Lindenberger & Mayr, 2014).

Third, arousal-induced pupil dilation interacted with low frequency EEG desynchronization, suggesting a common underlying dependence on phasic NE release (Study III; cf. Breton-Provencher & Sur, 2019; Neves et al., 2018; Sara & Bouret, 2012; Stitt et al., 2018). Moreover, pupil- and EEG-indexed noradrenergic responsiveness declined with age and was strongly associated with individual differences in selective attention.

This dissertation provides linkages between previous animal research and human studies on the neural underpinning of selective attention and memory. Taken together, the presented findings highlight the interplay of noradrenergic neuromodulation and neural synchronization in shaping aging cognition.

References

Andreassi, J. L. (2007). *Psychophysiology: Human behavior and physiological response*. New York: Psychology Press.

Apparsundaram, S. P. D. (2007). The norepinephrine transporter and regulation of synaptic transmission. In G. A. Ordway, M. A. Schwartz, & A. Frazer (Eds.), *Brain norepinephrine: Neurobiology and therapeutics* (pp. 119–154). Cambridge: Cambridge University Press. https://doi.org/10.1017/cbo9780511544156.006

Arnsten, A. F. T. (2007). Norepinephrine and cognitive disorders. In G. A. Ordway, M. A. Schwartz, & A. Frazer (Eds.), *Brain norepinephrine: Neurobiology and therapeutics* (pp. 408–435). Cambridge: Cambridge University Press. https://doi.org/10.1017/cbo9780511544156.015

Arnsten, A. F. T., & Contant, T. A. (1992). Alpha-2 adrenergic agonists decrease distractibility in aged monkeys performing the delayed response task. *Psychopharmacology*, *108*(1–2), 159–169. https://doi.org/10.1007/bf02245302

Arnsten, A. F. T., & Goldman-Rakic, P. S. (1985). Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. *Science*, *230*(4731), 1273–1276. https://doi.org/10.1126/science.2999977

Arnsten, A. F. T., & Li, B. M. (2005). Neurobiology of executive functions: Catecholamine influences on prefrontal cortical functions. *Biological Psychiatry*, *57*(11), 1377–1384. https://doi.org/10.1016/j.biopsych.2004.08.019

Asamoah, B., Khatoun, A., & Mc Laughlin, M. (2019). tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nature Communications*, *10*: 266. https://doi.org/10.1038/s41467-018-08183-w

Astafiev, S. V., Snyder, A. Z., Shulman, G. L., & Corbetta, M. (2010). Comment on "Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI" and "Homeostatic sleep pressure and responses to sustained attention in the suprachiasmatic area." *Science*, *328*(5976): 309. https://doi.org/10.1126/science.1177200

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience*, *28*(1), 403–450. https://doi.org/10.1146/annurev.neuro.28.061604.135709

Aston-Jones, G., Gonzalez, M., & Doran, S. (2007). Role of the locus coeruleus-norepinephrine system in arousal and circadian regulation of the sleep–wake cycle. *Brain Norepinephrine: Neurobiology and Therapeutics*, 157–195. https://doi.org/10.1017/cbo9780511544156.007

Aston-Jones, G., & Waterhouse, B. (2016). Locus coeruleus: From global projection system to adaptive regulation of behavior. *Brain Research*, *1645*, 75–78. https://doi.org/10.1016/j.brainres.2016.03.001

Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, J. C. (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage*, *54*(3), 2033–2044. https://doi.org/10.1016/j.neuroimage.2010.09.025

Avants, B. B., Tustison, N., & Song, G. (2009). Advanced Normalization Tools: V1.0. *Insight Journal*, *2*. http://hdl.handle.net/10380/3113

Awh, E., Vogel, E. K., & Oh, S.-H. (2006). Interactions between attention and working memory. *Neuroscience*, *139*(1), 201–208. https://doi.org/10.1016/j.neuroscience.2005.08.023

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Neuroscience and Biobehavioral Reviews*, *30*(6), 791–807. https://doi.org/10.1016/j.neubiorev.2006.06.005

Bahramisharif, A., van Gerven, M., Heskes, T., & Jensen, O. (2010). Covert attention allows for continuous control of brain-computer interfaces. *European Journal of Neuroscience*, *31*(8), 1501–1508. https://doi.org/10.1111/j.1460-9568.2010.07174.x

Banich, M. T. (2009). Executive function: The search for an integrated account. *Current Directions in Psychological Science*, *18*(2), 89–94. https://doi.org/10.1111/j.1467-8721.2009.01615.x

Bauer, M., Stenner, M.-P., Friston, K. J., & Dolan, R. J. (2014). Attentional modulation of alpha/beta and gamma oscillations reflect functionally distinct processes. *Journal of Neuroscience*, *34*(48), 16117–16125. https://doi.org/10.1523/jneurosci.3474-13.2014

Benwell, C. S. Y., Tagliabue, C. F., Veniero, D., Cecere, R., Savazzi, S., & Thut, G. (2017). Prestimulus EEG power predicts conscious awareness but not objective visual performance. *eNeuro*, *4*(6): eNeuro.0182-17.2017. https://doi.org/10.1523/eneuro.0182-17.2017

Berridge, C. W. (2009). The locus coeruleus-noradrenergic system and stress: Implications for post-traumatic stress disorder. In P. J. Shiromani, T. M. Keane, & J. E. LeDoux (Eds.), *Post-traumatic stress disorder: Basic science and clinical practice* (pp. 213–230). Totowa, NJ: Humana Press. https://doi.org/10.1007/978-1-60327-329-9_10

Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, *42*(1), 33–84. https://doi.org/10.1016/S0165-0173(03)00143-7

Bertram, L., Böckenhoff, A., Demuth, I., Düzel, S., Eckardt, R., Li, S.-C., … Steinhagen-Thiessen, E. (2014). Cohort profile: The Berlin Aging Study II (BASE-II). *International Journal of Epidemiology*, *43*(3), 703–712. https://doi.org/10.1093/ije/dyt018

Betts, M. J., Cardenas-Blanco, A., Kanowski, M., Jessen, F., & Düzel, E. (2017). *In vivo* MRI assessment of the human locus coeruleus along its rostrocaudal extent in young and older adults. *NeuroImage*, *163*, 150–159. https://doi.org/10.1016/j.neuroimage.2017.09.042

Betts, M. J., Cardenas-Blanco, A., Kanowski, M., Spottke, A., Teipel, S. J., Kilimann, I., … Düzel, E. (2019). Locus coeruleus MRI contrast is reduced in Alzheimer's disease dementia and correlates with CSF Aβ levels. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *11*, 281–285. https://doi.org/10.1016/j.dadm.2019.02.001

Betts, M. J., Ehrenberg, A. J., Hämmerer, D., & Düzel, E. (2018). Commentary: Locus coeruleus ablation exacerbates cognitive deficits, neuropathology, and lethality in P301S tau transgenic mice. *Frontiers in Neuroscience*, *12*: 401. https://doi.org/10.3389/fnins.2018.00401

Betts, M. J., Kirilina, E., Otaduy, M. C. G., Ivanov, D., Acosta-Cabronero, J., Callaghan, M. F., … Hämmerer, D. (2019). Locus coeruleus imaging as a biomarker for noradrenergic dysfunction in neurodegenerative diseases. *Brain, 142*(9), 2558–2571. https://doi.org/10.1093/brain/awz193

Biasiucci, A., Franceschiello, B., & Murray, M. M. (2019). Electroencephalography. *Current Biology*, *29*(3), R80–R85. https://doi.org/10.1016/j.cub.2018.11.052

Birbaumer, N., & Schmidt, R. F. (2010). Methoden der Biologischen Psychologie. In N. Birbaumer & Schmidt Robert F. (Eds.), *Biologische Psychologie* (pp. 483–511). Berlin: Springer. https://doi.org/10.1007/978-3-662-06097-1_21

Bonnefond, M., & Jensen, O. (2012). Alpha oscillations serve to protect working memory maintenance against anticipated distracters. *Current Biology*, *22*(20), 1969–1974. https://doi.org/10.1016/j.cub.2012.08.029

Borghini, G., Candini, M., Filannino, C., Hussain, M., Walsh, V., Romei, V., … Cappelletti, M. (2018). Alpha oscillations are causally linked to inhibitory abilities in ageing. *Journal of Neuroscience*, *38*(18), 4418–4429. https://doi.org/10.1523/jneurosci.1285-17.2018

Bouret, S., & Sara, S. J. (2002). Locus coeruleus activation modulates firing rate and temporal organization of odour-induced single-cell responses in rat piriform cortex. *European Journal of Neuroscience*, *16*(12), 2371–2382. https://doi.org/10.1046/j.1460-9568.2002.02413.x

Bouret, S., & Sara, S. J. (2005). Network reset: A simplified overarching theory of locus coeruleus noradrenaline function. *Trends in Neurosciences*, *28*(11), 574–582. https://doi.org/10.1016/j.tins.2005.09.002

Braak, H., Thal, D. R., Ghebremedhin, E., & Del Tredici, K. (2011). Stages of the pathologic process in Alzheimer disease: Age categories from 1 to 100 years. *Journal of Neuropathology and Experimental Neurology*, *70*(11), 960–969. https://doi.org/10.1097/nen.0b013e318232a379

Braver, T. S., & Barch, D. M. (2002). A theory of cognitive control, aging cognition, and neuromodulation. *Neuroscience & Biobehavioral Reviews*, *26*(7), 809–817. https://doi.org/10.1016/S0149-7634(02)00067-2

Breton-Provencher, V., & Sur, M. (2019). Active control of arousal by a locus coeruleus GABAergic circuit. *Nature Neuroscience*, *22*(2), 218–228. https://doi.org/10.1038/s41593-018-0305-z

Brickenkamp, R., & Zillmer, E. (1998). *The d2 Test of Attention*. Seattle, WA: Hogrefe & Huber.

Brzosko, Z., Mierau, S. B., & Paulsen, O. (2019). Neuromodulation of spike-timing-dependent plasticity: Past, present, and future. *Neuron*, *103*(4), 563–581. https://doi.org/10.1016/j.neuron.2019.05.041

Busch, N. A., Dubois, J., & VanRullen, R. (2009). The phase of ongoing EEG oscillations predicts visual perception. *Journal of Neuroscience*, *29*(24), 7869–7876. https://doi.org/10.1523/jneurosci.0113-09.2009

Buschman, T. J., & Kastner, S. (2015). From behavior to neural dynamics: An integrated theory of attention. *Neuron*, *88*(1), 127–144. https://doi.org/10.1016/j.neuron.2015.09.017

Buzsáki, G., Bickford, R. G., Ponomareff, G., Thal, L. J., Mandel, R., & Gage, F. H. (1988). Nucleus basalis and thalamic control of neocortical activity in the freely moving rat. *Journal of Neuroscience*, *8*(11), 4007–4026. https://doi.org/10.1523/jneurosci.08-11-04007.1988

Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science*, *304*(5679), 1926–1929. https://doi.org/10.1126/science.1099745

Buzsáki, G., Kennedy, B., Solt, V. B., & Ziegler, M. (1991). Noradrenergic control of thalamic oscillation: The role of α-2 receptors. *European Journal of Neuroscience*, *3*(3), 222–229. https://doi.org/10.1111/j.1460-9568.1991.tb00083.x

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., … Rajah, M. N. (2018). Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nature Reviews Neuroscience*, *19*, 701–710. https://doi.org/10.1038/s41583-018-0068-2

Cabeza, R., Ciaramelli, E., Olson, I. R., & Moscovitch, M. (2008). The parietal cortex and episodic memory: An attentional account. *Nature Reviews. Neuroscience*, *9*(8), 613–625. https://doi.org/10.1038/nrn2459

Cabeza, R., Nyberg, L., & Park, D. C. (2004). Cognitive neuroscience of aging: Emergence of a new discipline. In R. Cabeza, L. Nyberg, & D. C. Park (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging*. New York: Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195156744.001.0001

Carter, M. E., Yizhar, O., Chikahisa, S., Nguyen, H., Adamantidis, A., Nishino, S., … De Lecea, L. (2010). Tuning arousal with optogenetic modulation of locus coeruleus neurons. *Nature Neuroscience*, *13*(12), 1526–1535. https://doi.org/10.1038/nn.2682

Chalermpalanupap, T., Weinshenker, D., & Rorabaugh, J. M. (2017). Down but not out: The consequences of pretangle tau in the locus coeruleus. *Neural Plasticity*, *2017*: 7829507. https://doi.org/10.1155/2017/7829507

Chandler, D. J. (2016). Evidence for a specialized role of the locus coeruleus noradrenergic system in cortical circuitries and behavioral operations. *Brain Research*, *1641*, 197–206. https://doi.org/10.1016/j.brainres.2015.11.022

Chen, X., Huddleston, D. E., Langley, J., Ahn, S., Barnum, C. J., Factor, S. A., … Hu, X. (2014). Simultaneous imaging of locus coeruleus and substantia nigra with a quantitative neuromelanin MRI approach. *Magnetic Resonance Imaging*, *32*(10), 1301–1306. https://doi.org/10.1016/j.mri.2014.07.003

Chun, M. M., & Turk-Browne, N. B. (2007). Interactions between attention and memory. *Current Opinion in Neurobiology*, *17*(2), 177–184. https://doi.org/10.1016/j.conb.2007.03.005

Clayton, M. S., Yeung, N., & Cohen Kadosh, R. (2018). The many characters of visual alpha oscillations. *European Journal of Neuroscience*, *48*(7), 2498–2508. https://doi.org/10.1111/ejn.13747

Clewett, D. V., Lee, T. H., Greening, S., Ponzio, A., Margalit, E., & Mather, M. (2016). Neuromelanin marks the spot: Identifying a locus coeruleus biomarker of cognitive reserve in healthy aging. *Neurobiology of Aging*, *37*, 117–126. https://doi.org/10.1016/j.neurobiolaging.2015.09.019

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: From environment to theory of mind. *Neuron*, *58*(3), 306–324. https://doi.org/10.1016/j.neuron.2008.04.017

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201–215. https://doi.org/10.1038/nrn755

Costa, V. D., & Rudebeck, P. H. (2016). More than meets the eye: The relationship between pupil size and locus coeruleus activity. *Neuron*, *89*(1), 8–10. https://doi.org/10.1016/j.neuron.2015.12.031

Craik, F. I. M. (1983). On the transfer of information from temporary to permanent memory. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *302*(1110), 341–359. https://doi.org/10.1098/rstb.1983.0059

Craik, F. I. M., & Bialystok, E. (2006). Cognition through the lifespan: Mechanisms of change. *Trends in Cognitive Sciences*, *10*(3), 131–138. https://doi.org/10.1016/j.tics.2006.01.007

Crunelli, V., Lőrincz, M. L., Connelly, W. M., David, F., Hughes, S. W., Lambert, R. C., … Errington, A. C. (2018). Dual function of thalamic low-vigilance state oscillations: Rhythm-regulation and plasticity. *Nature Reviews Neuroscience*, *19*(2), 107–118. https://doi.org/10.1038/nrn.2017.151

Curran, P. J., Obeidat, K., & Losardo, D. (2010). Twelve frequently asked questions about growth curve modeling. *Journal of Cognitive Development*, *11*(2), 121–136. https://doi.org/10.1080/15248371003699969

Deiber, M.-P., Ibañez, V., Missonnier, P., Rodriguez, C., & Giannakopoulos, P. (2013). Age-associated modulations of cerebral oscillatory patterns related to attention control. *NeuroImage*, *82*. https://doi.org/10.1016/j.neuroimage.2013.06.037

Deiber, M.-P., Rodriguez, C., Jaques, D., Missonnier, P., Emch, J., Millet, P., … Ibañez, V. (2010). Aging effects on selective attention-related electroencephalographic patterns during face

encoding. *Neuroscience*, *171*(1), 173–186. https://doi.org/10.1016/j.neuroscience.2010.08.051

Delagrange, P., Canu, M. H., Rougeul, A., Buser, P., & Bouyer, J. J. (1993). Effects of locus coeruleus lesions on vigilance and attentive behaviour in cat. *Behavioural Brain Research*, *53*(1–2), 155–165. https://doi.org/10.1016/S0166-4328(05)80275-X

Delagrange, P., Tdjer, D., Bouyer, J. J., Rougeul, A., & Conrath, M. (1989). Effect of DSP4, a neurotoxic agent, on attentive behaviour and related electrocortical activity in cat. *Behavioural Brain Research*, *33*(1), 33–43. https://doi.org/10.1016/S0166-4328(89)80016-6

Delius, J. A. M., Düzel, S., Gerstorf, D., & Lindenberger, U. (2015). Berlin Aging Studies (BASE and BASE-II). In N. A. Pachana (Ed.), *Encyclopedia of geropsychology* (pp. 386–395). New York: Springer. https://doi.org/10.1007/978-981-287-080-3_44-1

Desimone, R., & Duncan, J. S. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience*, *18*(1), 193–222. https://doi.org/10.1146/annurev.ne.18.030195.001205

Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nature Reviews Neuroscience*, *11*(2), 114–126. https://doi.org/10.1038/nrn2762

Ding, Y.-S., Lin, K.-S., & Logan, J. (2006). PET imaging of norepinephrine transporters. *Current Pharmaceutical Design*, *12*(30). https://doi.org/10.2174/138161206778559687

Ding, Y.-S., Singhal, T., Planeta-Wilson, B., Gallezot, J.-D., Nabulsi, N., Labaree, D., … Malison, R. T. (2010). PET imaging of the effects of age and cocaine on the norepinephrine transporter in the human brain using (S,S)-[^{11} C]O-methylreboxetine and HRRT. *Synapse*, *64*(1), 30–38. https://doi.org/10.1002/syn.20696

Düzel, S., Voelkle, M. C., Düzel, E., Gerstorf, D., Drewelies, J., Steinhagen-Thiessen, E., … Lindenberger, U. (2016). Supplementary material for: The Subjective Health Horizon Questionnaire (SHH-Q): Assessing future time perspectives for facets of an active lifestyle. *Gerontology*, *62*(3), 345–353. https://doi.org/10.6084/m9.figshare.5128939.v1

Ehrenberg, A. J., Nguy, A. K., Theofilas, P., Dunlop, S., Suemoto, C. K., Di Lorenzo Alho, A. T., … Grinberg, L. T. (2017). Quantifying the accretion of hyperphosphorylated tau in the locus coeruleus and dorsal raphe nucleus: The pathological building blocks of early Alzheimer's disease. *Neuropathology and Applied Neurobiology*, *43*(5), 393–408. https://doi.org/10.1111/nan.12387

Ehrenberg, A. J., Suemoto, C. K., de Paula França Resende, E., Petersen, C., Leite, R. E. P., Rodriguez, R. D., … Grinberg, L. T. (2018). Neuropathologic correlates of psychiatric symptoms in Alzheimer's disease. *Journal of Alzheimer's Disease*, *66*(1), 115–126. https://doi.org/10.3233/jad-180688

Eisenhofer, G. (2004). Catecholamine metabolism: A contemporary view with implications for physiology and medicine. *Pharmacological Reviews*, *56*(3), 331–349. https://doi.org/10.1124/pr.56.3.1

Erel, H., & Levy, D. A. (2016). Orienting of visual attention in aging. *Neuroscience & Biobehavioral Reviews*, *69*, 357–380. https://doi.org/10.1016/j.neubiorev.2016.08.010

Eschenko, O. (2019). The role of the locus coeruleus in cellular and systems memory consolidation. In D. Manahan-Vaughan (Ed.), *Handbook of behavioral neuroscience: Handbook of in vivo neural plasticity techniques* (Vol. 28, pp. 327–347). London: Elsevier. https://doi.org/10.1016/B978-0-12-812028-6.00018-5

Fandakova, Y., Werkle-Bergner, M., & Sander, M. C. (2019). (Only) time can tell: Age differences in false memory are magnified at longer delays. *PsyArXiv*. https://doi.org/10.31234/osf.io/eh5x7

Feng, J., Zhang, C., Lischinsky, J. E., Jing, M., Zhou, J., Wang, H., … Li, Y. (2019). A genetically encoded fluorescent sensor for rapid and specific in vivo detection of norepinephrine. *Neuron*, *102*(4), 745–761.e8. https://doi.org/10.1016/j.neuron.2019.02.037

Fernandes, P., Regala, J., Correia, F., & Gonçalves-Ferreira, A. J. (2012). The human locus coeruleus 3-D stereotactic anatomy. *Surgical and Radiologic Anatomy*, *34*(10), 879–885. https://doi.org/10.1007/s00276-012-0979-y

Fiebelkorn, I. C., & Kastner, S. (2019). A rhythmic theory of attention. *Trends in Cognitive Sciences*, *23*(2), 87–101. https://doi.org/10.1016/j.tics.2018.11.009

Fiebelkorn, I. C., Pinsk, M. A., & Kastner, S. (2018). A dynamic interplay within the frontoparietal network underlies rhythmic spatial attention. *Neuron*, *99*(4), 842–853.e8. https://doi.org/10.1016/j.neuron.2018.07.038

Fiebelkorn, I. C., Pinsk, M. A., & Kastner, S. (2019). The mediodorsal pulvinar coordinates the macaque fronto-parietal network during rhythmic spatial attention. *Nature Communications*, *10*(1): 215. https://doi.org/10.1038/s41467-018-08151-4

Foster, J. J., & Awh, E. (2019). The role of alpha oscillations in spatial attention: Limited evidence for a suppression account. *Current Opinion in Psychology*, *29*, 34–40. https://doi.org/10.1016/j.copsyc.2018.11.001

Frey, J. N., Mainy, N., Lachaux, J.-P., Muller, N., Bertrand, O., & Weisz, N. (2014). Selective modulation of auditory cortical alpha activity in an audiovisual spatial attention task. *Journal of Neuroscience*, *34*(19), 6634–6639. https://doi.org/10.1523/jneurosci.4813-13.2014

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*, *9*(10), 474–480. https://doi.org/10.1016/j.tics.2005.08.011

Fries, P. (2015). Rhythms for cognition: Communication through coherence. *Neuron*, *88*(1), 220–235. https://doi.org/10.1016/j.neuron.2015.09.034

Gazzaley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience*, *8*(10), 1298–1300. https://doi.org/10.1038/nn1543

Gelbard-Sagiv, H., Magidov, E., Sharon, H., Hendler, T., & Nir, Y. (2018). Noradrenaline modulates visual perception and late visually evoked activity. *Current Biology*, *28*(14), 2239–2249.e6. https://doi.org/10.1016/j.cub.2018.05.051

Gerstorf, D., Bertram, L., Lindenberger, U., Pawelec, G., Demuth, I., Steinhagen-Thiessen, E., & Wagner, G. G. (2016). The Berlin Aging Study II: An overview [Editorial]. *Gerontology*, *62*, 311–315. https://doi.org/10.1159/000441495

Gola, M., Kamiński, J., Brzezicka, A., & Wróbel, A. (2012). Beta band oscillations as a correlate of alertness — Changes in aging. *International Journal of Psychophysiology*, *85*(1), 62–67. https://doi.org/10.1016/j.ijpsycho.2011.09.001

Gola, M., Magnuski, M., Szumska, I., & Wróbel, A. (2013). EEG beta band activity is related to attention and attentional deficits in the visual performance of elderly subjects. *International Journal of Psychophysiology*, *89*(3), 334–341. https://doi.org/10.1016/j.ijpsycho.2013.05.007

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews Neuroscience*, *13*(7), 491–505. https://doi.org/10.1038/nrn3256

Grandy, T. H., Werkle-Bergner, M., Chicherio, C., Schmiedek, F., Lövdén, M., & Lindenberger, U. (2013). Peak individual alpha frequency qualifies as a stable neurophysiological trait marker in

healthy younger and older adults. *Psychophysiology*, *50*(6), 570–582. https://doi.org/10.1111/psyp.12043

Griffiths, B. J., Mayhew, S. D., Mullinger, K. J., Jorge, J., Charest, I., Wimber, M., & Hanslmayr, S. (2019). Alpha/beta power decreases track the fidelity of stimulus-specific information. *bioRxiv*: 633107. https://doi.org/10.1101/633107

Grinberg, L. T., & Heinsen, H. (2017). Light at the beginning of the tunnel? Investigating early mechanistic changes in Alzheimer's disease. *Brain*, *140*(11), 2770–2773. https://doi.org/10.1093/brain/awx261

Halassa, M. M., & Kastner, S. (2017). Thalamic functions in distributed cognitive control. *Nature Neuroscience*, *20*(12), 1669–1679. https://doi.org/10.1038/s41593-017-0020-1

Hämmerer, D., Callaghan, M. F., Hopkins, A., Kosciessa, J., Betts, M., Cardenas-Blanco, A., … Düzel, E. (2018). Locus coeruleus integrity in old age is selectively related to memories linked with salient negative events. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, 2228–2233. https://doi.org/10.1073/pnas.1712268115

Hanseeuw, B. J., Betensky, R. A., Jacobs, H. I. L., Schultz, A. P., Sepulcre, J., Becker, J. A., … Johnson, K. (2019). Association of amyloid and tau with cognition in preclinical Alzheimer disease. *JAMA Neurology*. Advance online publication. https://doi.org/10.1001/jamaneurol.2019.1424

Hansen, N. (2017). The longevity of hippocampus-dependent memory is orchestrated by the locus coeruleus-noradrenergic system. *Neural Plasticity*, *2017*: 2727602. https://doi.org/10.1155/2017/2727602

Hanslmayr, S., Matuschek, J., & Fellner, M. C. (2014). Entrainment of prefrontal beta oscillations induces an endogenous echo and impairs memory formation. *Current Biology*, *24*(8), 904–909. https://doi.org/10.1016/j.cub.2014.03.007

Hanslmayr, S., Staresina, B. P., & Bowman, H. (2016). Oscillations and episodic memory: Addressing the synchronization/desynchronization conundrum. *Trends in Neurosciences*, *39*(1), 16–25. https://doi.org/10.1016/j.tins.2015.11.004

Hanslmayr, S., Staudigl, T., & Fellner, M.-C. (2012). Oscillatory power decreases and long-term memory: The information via desynchronization hypothesis. *Frontiers in Human Neuroscience*, *6*: 74. https://doi.org/10.3389/fnhum.2012.00074

Harris, K. D., & Thiele, A. (2011). Cortical state and attention. *Nature Reviews Neuroscience*, *12*(9), 509–523. https://doi.org/10.1038/nrn3084

Headley, D. B., & Weinberger, N. M. (2013). Fear conditioning enhances gamma oscillations and their entrainment of neurons representing the conditioned stimulus. *Journal of Neuroscience*, *33*(13), 5705–5717. https://doi.org/10.1523/jneurosci.4915-12.2013

Helfrich, R. F., Mander, B. A., Jagust, W. J., Knight, R. T., & Walker, M. P. (2018). Old brains come uncoupled in sleep: Slow wave-spindle synchrony, brain atrophy, and forgetting. *Neuron*, *97*(1), 221-230.e4. https://doi.org/10.1016/j.neuron.2017.11.020

Henry, M. J., Herrmann, B., Kunke, D., & Obleser, J. (2017). Aging affects the balance of neural entrainment and top-down neural modulation in the listening brain. *Nature Communications*, *8*: 15801. https://doi.org/10.1038/ncomms15801

Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: Electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *353*(1373), 1257–1270.

https://doi.org/10.1098/rstb.1998.0281

Hipp, J. F., & Siegel, M. (2013). Dissociating neuronal gamma-band activity from cranial and ocular muscle activity in EEG. *Frontiers in Human Neuroscience*, *7*: 338. https://doi.org/10.3389/fnhum.2013.00338

Hong, X., Sun, J., Bengson, J. J., Mangun, G. R., & Tong, S. (2015). Normal aging selectively diminishes alpha lateralization in visual spatial attention. *NeuroImage*, *106*, 353–363. https://doi.org/10.1016/j.neuroimage.2014.11.019

Iemi, L., Chaumon, M., Crouzet, S. M., & Busch, N. A. (2017). Spontaneous neural oscillations bias perception by modulating baseline excitability. *Journal of Neuroscience*, *37*(4), 807–819. https://doi.org/10.1523/jneurosci.1432-16.2016

Ishii, R., Canuet, L., Aoki, Y., Hata, M., Iwase, M., Ikeda, S., … Ikeda, M. (2017). Healthy and pathological brain aging: From the perspective of oscillations, functional connectivity, and signal complexity. *Neuropsychobiology*, *75*(4), 151–161. https://doi.org/10.1159/000486870

Jacobs, H. I. L., Riphagen, J. M., Ramakers, I. H. G. B., & Verhey, F. R. J. (2019). Alzheimer's disease pathology: Pathways between central norepinephrine activity, memory, and neuropsychiatric symptoms. *Molecular Psychiatry*. Advance online publication. https://doi.org/10.1038/s41380-019-0437-x

Jagust, W. (2018). Imaging the evolution and pathophysiology of Alzheimer disease. *Nature Reviews Neuroscience*, *19*, 687–700. https://doi.org/10.1038/s41583-018-0067-3

Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: Gating by inhibition. *Frontiers in Human Neuroscience*, *4*: 186. https://doi.org/10.3389/fnhum.2010.00186

Jessen, F., Spottke, A., Boecker, H., Brosseron, F., Buerger, K., Catak, C., … Düzel, E. (2018). Design and first baseline data of the DZNE multicenter observational study on predementia Alzheimer's disease (DELCODE). *Alzheimer's Research & Therapy*, *10*: 15. https://doi.org/10.1186/s13195-017-0314-2

Joshi, S., Li, Y., Kalwani, R. M., & Gold, J. I. (2016). Relationships between pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. *Neuron*, *89*(1), 221–234. https://doi.org/10.1016/j.neuron.2015.11.028

Karch, J. D., Sander, M. C., von Oertzen, T., Brandmaier, A. M., & Werkle-Bergner, M. (2015). Using within-subject pattern classification to understand lifespan age differences in oscillatory mechanisms of working memory selection and maintenance. *NeuroImage*, *118*, 538–552. https://doi.org/10.1016/j.neuroimage.2015.04.038

Kelly, S. P., Lalor, E. C., Reilly, R. B., & Foxe, J. J. (2006). Increases in alpha oscillatory power reflect an active retinotopic mechanism for distracter suppression during sustained visuospatial attention. *Journal of Neurophysiology*, *95*(6), 3844–3851. https://doi.org/10.1152/jn.01234.2005

Kelly, S. P., Lalor, E., Reilly, R. B., & Foxe, J. J. (2005). Independent brain computer interface control using visual spatial attention-dependent modulations of parieto-occipital alpha. In *2nd International IEEE EMBS Conference on Neural Engineering* (Vol. 2005, pp. 667–670). IEEE. https://doi.org/10.1109/cne.2005.1419713

Kennedy, B. L., & Mather, M. (2019). Neural mechanisms underlying age-related changes in attentional selectivity. In G. R. Samanez-Larkin (Ed.), *The aging brain: Functional adaptation across adulthood* (pp. 45–72). Washington, DC: American Psychological Association. https://doi.org/10.31234/osf.io/ymdx3

Keren, N. I., Lozar, C. T., Harris, K. C., Morgan, P. S., & Eckert, M. A. (2009). In vivo mapping of

the human locus coeruleus. *NeuroImage*, *47*(4), 1261–1267. https://doi.org/10.1016/j.neuroimage.2009.06.012

Keren, N. I., Taheri, S., Vazey, E. M., Morgan, P. S., Granholm, A. C. E., Aston-Jones, G., & Eckert, M. A. (2015). Histologic validation of locus coeruleus MRI contrast in post-mortem tissue. *NeuroImage*, *113*, 235–245. https://doi.org/10.1016/j.neuroimage.2015.03.020

Ketz, N. A., Jensen, O., & O'Reilly, R. C. (2015). Thalamic pathways underlying prefrontal cortex-medial temporal lobe oscillatory interactions. *Trends in Neurosciences*, *38*(1), 3–12. https://doi.org/10.1016/j.tins.2014.09.007

Kievit, R. A., Brandmaier, A. M., Ziegler, G., van Harmelen, A. L., de Mooij, S. M. M., Moutoussis, M., … Dolan, R. J. (2018). Developmental cognitive neuroscience using latent change score models: A tutorial and applications. *Developmental Cognitive Neuroscience*, *33*, 99–117. https://doi.org/10.1016/j.dcn.2017.11.007

Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M.-C., … Parsey, R. V. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *NeuroImage*, *46*(3), 786–802. https://doi.org/10.1016/j.neuroimage.2008.12.037

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews*, *29*(2–3), 169–195. https://doi.org/10.1016/S0165-0173(98)00056-3

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition-timing hypothesis. *Brain Research Reviews*, *53*(1), 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003

Klinzing, J. G., Niethard, N., & Born, J. (2019). Mechanisms of systems memory consolidation during sleep. *Nature Neuroscience*, 1–13. https://doi.org/10.1038/s41593-019-0467-3

Kray, J., & Lindenberger, U. (2000). Adult age differences in task switching. *Psychology and Aging*, *15*(1), 126–147. https://doi.org/10.1037//OS82-797-U5.1.126

Lakatos, P., O'Connell, M. N., & Barczak, A. (2016). Pondering the pulvinar. *Neuron*, *89*(1), 5–7. https://doi.org/10.1016/j.neuron.2015.12.022

Langley, J., Huddleston, D. E., Liu, C. J., & Hu, X. (2017). Reproducibility of locus coeruleus and substantia nigra imaging with neuromelanin sensitive MRI. *Magnetic Resonance Materials in Physics, Biology and Medicine*, *30*(2), 121–125. https://doi.org/10.1007/s10334-016-0590-z

Lee, T.-H., Greening, S. G., Ueno, T., Clewett, D., Ponzio, A., Sakaki, M., & Mather, M. (2018). Arousal increases neural gain via the locus coeruleus–noradrenaline system in younger adults but not in older adults. *Nature Human Behaviour*, *2*(5), 356–366. https://doi.org/10.1038/s41562-018-0344-1

Leenders, M. P., Lozano-Soldevilla, D., Roberts, M. J., Jensen, O., & De Weerd, P. (2018). Diminished alpha lateralization during working memory but not during attentional cueing in older adults. *Cerebral Cortex*, *28*(1), 21–32. https://doi.org/10.1093/cercor/bhw345

Leslie, F. M., Loughlin, S. E., Sternberg, D. B., McGaugh, J. L., Young, L. E., & Zornetzer, S. F. (1985). Noradrenergic changes and memory loss in aged mice. *Brain Research*, *359*(1–2), 292–299. https://doi.org/10.1016/0006-8993(85)91439-8

Li, S.-C., & Lindenberger, U. (1999). Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems and dedifferentiation of cognitive abilities in old age. In L.-G. Nilsson & H. J. Markowitsch (Eds.), *Cognitive neuroscience of memory.* (pp. 103–146). Ashland, OH: Hogrefe & Huber Publishers.

Li, S.-C., Lindenberger, U., & Sikström, S. (2001). Aging cognition: From neuromodulation to representation. *Trends in Cognitive Sciences*, *5*(11), 479–486. https://doi.org/10.1016/s1364-6613(00)01769-1

Li, S.-C., & Rieckmann, A. (2014). Neuromodulation and aging: Implications of aging neuronal gain control on cognition. *Current Opinion in Neurobiology*, *29*, 148–158. https://doi.org/10.1016/j.conb.2014.07.009

Li, S.-C., & Sikström, S. (2002). Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation. *Neuroscience & Biobehavioral Reviews*, *26*(7), 795–808. https://doi.org/10.1016/s0149-7634(02)00066-0

Lindenberger, U. (2014). Human cognitive aging: Corriger la fortune? *Science*, *346*(6209), 572–578. https://doi.org/10.1126/science.1254403

Lindenberger, U., Li, S.-C., & Bäckman, L. (2006). Delineating brain-behavior mappings across the lifespan: Substantive and methodological advances in developmental neuroscience. *Neuroscience and Biobehavioral Reviews*, *30*(6), 713–717. https://doi.org/10.1016/j.neubiorev.2006.06.006

Lindenberger, U., Li, S.-C., Lövdén, M., & Schmiedek, F. (2007). The Center for Lifespan Psychology at the Max Planck Institute for Human Development: Overview of conceptual agenda and illustration of research activities. *International Journal of Psychology*, *42*(4), 229–242. https://doi.org/10.1080/00207590701396591

Lindenberger, U., & Mayr, U. (2014). Cognitive aging: Is there a dark side to environmental support? *Trends in Cognitive Sciences*, *18*(1), 7–15. https://doi.org/10.1016/j.tics.2013.10.006

Lindenberger, U., & von Oertzen, T. (2006). Variability in Cognitive Aging: From Taxonomy to Theory. In *Lifespan CognitionMechanisms of Change* (pp. 297–314). Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195169539.003.0021

Lindenberger, U., von Oertzen, T., Ghisletta, P., & Hertzog, C. (2011). Cross-sectional age variance extraction: What's change got to do with it? *Psychology and Aging*, *26*(1), 34–47. https://doi.org/10.1037/a0020525

Liu, K. Y., Acosta-Cabronero, J., Cardenas-Blanco, A., Loane, C., Berry, A. J., Betts, M. J., … Hämmerer, D. (2019). In vivo visualization of age-related differences in the locus coeruleus. *Neurobiology of Aging*, *74*, 101–111. https://doi.org/10.1016/j.neurobiolaging.2018.10.014

Liu, K. Y., Marijatta, F., Hämmerer, D., Acosta-Cabronero, J., Düzel, E., & Howard, R. J. (2017). Magnetic resonance imaging of the human locus coeruleus: A systematic review. *Neuroscience and Biobehavioral Reviews*, *83*, 325–355. https://doi.org/10.1016/j.neubiorev.2017.10.023

Lopes da Silva, F. (1991). Neural mechanisms underlying brain waves: From neural membranes to networks. *Electroencephalography and Clinical Neurophysiology*, *79*(2), 81–93. https://doi.org/10.1016/0013-4694(91)90044-5

Lopes da Silva, F., & Storm van Leeuwen, W. (1977). The cortical source of the alpha rhythm. *Neuroscience Letters*, *6*(2–3), 237–241. https://doi.org/10.1016/0304-3940(77)90024-6

Lopes da Silva, F., van Lierop, T. H. M. T., Schrijer, C. F., & Storm van Leeuwen, W. (1973). Organization of thalamic and cortical alpha rhythms: Spectra and coherences. *Electroencephalography and Clinical Neurophysiology*, *35*(6), 627–639. https://doi.org/10.1016/0013-4694(73)90216-2

Lőrincz, M. L., & Adamantidis, A. R. (2017). Monoaminergic control of brain states and sensory processing: Existing knowledge and recent insights obtained with optogenetics. *Progress in Neurobiology*, *151*, 237–253. https://doi.org/10.1016/j.pneurobio.2016.09.003

Lozano-Soldevilla, D. (2018). On the physiological modulation and potential mechanisms underlying parieto-occipital alpha oscillations. *Frontiers in Computational Neuroscience*, *12*: 23. https://doi.org/10.3389/fncom.2018.00023

Luo, Y., Zhou, J., Li, M. X., Wu, P. F., Hu, Z. L., Ni, L., … Wang, F. (2015). Reversal of aging-related emotional memory deficits by norepinephrine via regulating the stability of surface AMPA receptors. *Aging Cell*, *14*(2), 170–179. https://doi.org/10.1111/acel.12282

Maass, A., Berron, D., Harrison, T. M., Adams, J. N., La Joie, R., Baker, S., … Jagust, W. J. (2019). Alzheimer's pathology targets distinct memory networks in the ageing brain. *Brain*, *Advance on*. https://doi.org/10.1093/brain/awz154

Madan, C. R. (2018). Age differences in head motion and estimates of cortical morphology. *PeerJ*, *6*: e5176. https://doi.org/10.7717/peerj.5176

Manaye, K. F., McIntire, D. D., Mann, D. M. A., & German, D. C. (1995). Locus coeruleus cell loss in the aging human brain: A non-random process. *Journal of Comparative Neurology*, *358*(1), 79–87. https://doi.org/10.1002/cne.903580105

Mann, D. M. A., & Yates, P. O. (1974). Lipoprotein pigments–Their relationship to ageing in the human nervous system. II. The melanin content of pigmented nerve cells. *Brain*, *97*(3), 489–498. https://doi.org/10.1093/brain/97.3.489

Marien, M. R., Colpaert, F. C., & Rosenquist, A. C. (2004). Noradrenergic mechanisms in neurodegenerative diseases: A theory. *Brain Research Reviews*, *45*(1), 38–78. https://doi.org/10.1016/j.brainresrev.2004.02.002

Martins, A. R. O., & Froemke, R. C. (2015). Coordinated forms of noradrenergic plasticity in the locus coeruleus and primary auditory cortex. *Nature Neuroscience*, *18*(10), 1483–1492. https://doi.org/10.1038/nn.4090

Marzo, A., Totah, N. K., Neves, R. M., Logothetis, N. K., & Eschenko, O. (2014). Unilateral electrical stimulation of rat locus coeruleus elicits bilateral response of norepinephrine neurons and sustained activation of medial prefrontal cortex. *Journal of Neurophysiology*, *111*(12), 2570–2588. https://doi.org/10.1152/jn.00920.2013

Mather, M. (in press). The locus coeruleus-norepinephrine system role in cognition and how it changes with aging. In D. Poeppel, G. R. Mangun, & M. Gazzaniga (Eds.), *The cognitive neurosciences* (6th ed.). Cambridge, MA: MIT Press.

Mather, M., Clewett, D., Sakaki, M., & Harley, C. W. (2016). Norepinephrine ignites local hotspots of neuronal excitation: How arousal amplifies selectivity in perception and memory. *Behavioral and Brain Sciences*, *39*: e200. https://doi.org/10.1017/s0140525x15000667

Mather, M., & Harley, C. W. (2016). The locus coeruleus: Essential for maintaining cognitive function and the aging brain. *Trends in Cognitive Sciences*, *20*(3), 214–226. https://doi.org/10.1016/j.tics.2016.01.001

Mathewson, K. E., Gratton, G., Fabiani, M., Beck, D. M., & Ro, T. (2009). To see or not to see: Prestimulus phase predicts visual awareness. *Journal of Neuroscience*, *29*(9), 2725–2732. https://doi.org/10.1523/jneurosci.3963-08.2009

Mazaheri, A., Slagter, H. A., Thut, G., & Foxe, J. J. (2018). Orchestration of brain oscillations: principles and functions. *European Journal of Neuroscience*, *48*(7), 2385–2388. https://doi.org/10.1111/ejn.14189

McArdle, J. J. (1988). Dynamic but structural equation modeling of repeated measures data. In J. R. Nesselroade & R. B. Cattell (Eds.), *Handbook of multivariate experimental psychology* (pp. 561–

614). Boston, MA: Springer. https://doi.org/10.1007/978-1-4613-0893-5_17

McCormick, D. A. (1989). Cholinergic and noradrenergic modulation of thalamocortical processing. *Trends in Neurosciences*, *12*(6), 215–221. https://doi.org/10.1016/0166-2236(89)90125-2

McCormick, D. A., Pape, H. C., & Williamson, A. (1991). Actions of norepinephrine in the cerebral cortex and thalamus: implications for function of the central noradrenergic system. *Progress in Brain Research*, *88*, 293–305. https://doi.org/10.1016/S0079-6123(08)63817-0

McGinley, M. J., David, S. V., & McCormick, D. A. (2015). Cortical membrane potential signature of optimal states for sensory signal detection. *Neuron*, *87*(1), 179–192. https://doi.org/10.1016/j.neuron.2015.05.038

McNamara, C. G., & Dupret, D. (2017). Two sources of dopamine for the hippocampus. *Trends in Neurosciences*, *40*(7), 383–384. https://doi.org/10.1016/j.tins.2017.05.005

Meredith, W., & Teresi, J. A. (2006). An essay on measurement and factorial invariance. *Medical Care*, *44*(11), S69–S77. https://doi.org/10.1097/01.mlr.0000245438.73837.89

Mok, R. M., Myers, N. E., Wallis, G., & Nobre, A. C. (2016). Behavioral and neural markers of flexible attention over working memory in aging. *Cerebral Cortex*, *26*(4), 1831–1842. https://doi.org/10.1093/cercor/bhw011

Molenaar, P. C. M. (2004). A Manifesto on psychology as idiographic science: Bringing the person back into scientific psychology, this time forever. *Measurement: Interdisciplinary Research & Perspectives*, *2*(4), 201–218. https://doi.org/10.1207/s15366359mea0204_1

Molenaar, P. C. M., & Campbell, C. G. (2009). The new person-specific paradigm in psychology. *Current Directions in Psychological Science*, *18*(2), 112–117. https://doi.org/10.1111/j.1467-8721.2009.01619.x

Moosmann, M., Ritter, P., Krastel, I., Brink, A., Thees, S., Blankenburg, F., … Villringer, A. (2003). Correlates of alpha rhythm in functional magnetic resonance imaging and near infrared spectroscopy. *NeuroImage*, *20*(1), 145–158. https://doi.org/10.1016/S1053-8119(03)00344-6

Moruzzi, G., & Magoun, H. W. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology*, *1*(1–4), 455–473. https://doi.org/10.1016/0013-4694(49)90219-9

Mouton, P. R., Pakkenberg, B., Gundersen, H. J. G., & Price, D. L. (1994). Absolute number and size of pigmented locus coeruleus neurons in young and aged individuals. *Journal of Chemical Neuroanatomy*, *7*(3), 185–190. https://doi.org/10.1016/0891-0618(94)90028-0

Muehlroth, B. E., Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., Shing, Y. L., & Werkle-Bergner, M. (2019a). Memory quality modulates the effect of aging on memory consolidation during sleep: Reduced maintenance but intact gain. *bioRxiv*: 547448. https://doi.org/10.1101/547448

Muehlroth, B. E., Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., Shing, Y. L., & Werkle-Bergner, M. (2019b). Precise slow oscillation–spindle coupling promotes memory consolidation in younger and older adults. *Scientific Reports*, *9*(1): 1940. https://doi.org/10.1038/s41598-018-36557-z

Muehlroth, B. E., & Werkle-Bergner, M. (2019). Studying the interplay of sleep and aging: Methodological challenges. *bioRxiv*: 713552. https://doi.org/10.1101/713552

Muir, J. L. (1997). Acetylcholine, aging, and Alzheimer's disease. *Pharmacology Biochemistry and Behavior*, *56*(4), 687–696. https://doi.org/10.1016/S0091-3057(96)00431-5

Müller, V., Brehmer, Y., von Oertzen, T., Li, S.-C., & Lindenberger, U. (2008). Electrophysiological correlates of selective attention: A lifespan comparison. *BMC Neuroscience*, *9*: 18. https://doi.org/10.1186/1471-2202-9-18

Nandy, A. S., Nassi, J. J., Jadi, M. P., & Reynolds, J. H. (2019). Optogenetically induced low-frequency correlations impair perception. *ELife*, *8*. https://doi.org/10.7554/elife.35123

Nesselroade, J. R., Gerstorf, D., Hardy, S. A., & Ram, N. (2007). Focus Article: Idiographic Filters for Psychological Constructs. *Measurement: Interdisciplinary Research & Perspective*, *5*(4), 217–235. https://doi.org/10.1080/15366360701741807

Neves, R. M., van Keulen, S., Yang, M., Logothetis, N. K., & Eschenko, O. (2018). Locus coeruleus phasic discharge is essential for stimulus-induced gamma oscillations in the prefrontal cortex. *Journal of Neurophysiology*, *119*(3), 904–920. https://doi.org/10.1152/jn.00552.2017

Nieuwenhuis, S., & Jepma, M. (2011). Investigating the role of the noradrenergic system in human cognition. In M. Delgado, E. Phelps, & T. Robbins (Eds.), *Decision making, affect, and learning: Attention and performance XXIII* (1st ed., pp. 367–386). Oxford: Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199600434.003.0017

Noudoost, B., & Moore, T. (2011). The role of neuromodulators in selective attention. *Trends in Cognitive Sciences*, *15*(12), 585–591. https://doi.org/10.1016/j.tics.2011.10.006

Nunez, P. L., & Srinivasan, R. (2006). *Electric fields of the brain : The neurophysics of EEG* (2nd ed). New York: Oxford University Press.

Nyberg, L., & Lindenberger, U. (in press). Brain maintenance and cognition in old age. In D. Poeppel, M. S. Gazzaniga, & G. Mangun (Eds.), *The cognitive neurosciences* (6th ed.). Cambridge, MA: MIT Press.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences*, *16*(5), 292–305. https://doi.org/10.1016/j.tics.2012.04.005

Nyberg, L., & Pudas, S. (2019). Successful memory aging. *Annual Review of Psychology*, *70*(1), 219–243. https://doi.org/10.1146/annurev-psych-010418-103052

O'Dell, T. J., Connor, S. A., Guglietta, R., & Nguyen, P. V. (2015). β-Adrenergic receptor signaling and modulation of long-term potentiation in the mammalian hippocampus. *Learning & Memory*, *22*(9), 461–471. https://doi.org/10.1101/lm.031088.113

Ohm, T. G., Busch, C., & Bohl, J. (1997). Unbiased estimation of neuronal numbers in the human nucleus coeruleus during aging. *Neurobiology of Aging*, *18*(4), 393–399. https://doi.org/10.1016/S0197-4580(97)00034-1

Park, D. C., Polk, T. A., Mikels, J. A., Taylor, S. F., & Marshuetz, C. (2001). Cerebral aging: integration of brain and behavioral models of cognitive function. *Dialogues in Clinical Neuroscience*, *3*(3), 151–165. http://www.ncbi.nlm.nih.gov/pubmed/22034448

Passow, S., Westerhausen, R., Hugdahl, K., Wartenburger, I., Heekeren, H. R., Lindenberger, U., & Li, S.-C. (2014). Electrophysiological correlates of adult age differences in attentional control of auditory processing. *Cerebral Cortex*, *24*(1), 249–260. https://doi.org/10.1093/cercor/bhs306

Passow, S., Westerhausen, R., Wartenburger, I., Hugdahl, K., Heekeren, H. R., Lindenberger, U., & Li, S.-C. (2012). Human aging compromises attentional control of auditory perception. *Psychology and Aging*, *27*(1), 99–105. https://doi.org/10.1037/a0025667

Pfurtscheller, G., & Aranibar, A. (1977). Event-related cortical desynchronization detected by power measurements of scalp EEG. *Electroencephalography and Clinical Neurophysiology*, *42*(6),

817–826. https://doi.org/10.1016/0013-4694(77)90235-8

Pfurtscheller, G., & Lopes da Silva, F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clinical Neurophysiology*, *110*(11), 1842–1857. https://doi.org/10.1016/S1388-2457(99)00141-8

Plude, D. J., Enns, J. T., & Brodeur, D. (1994). The development of selective attention: A life-span overview. *Acta Psychologica*, *86*(2–3), 227–272. https://doi.org/10.1016/0001-6918(94)90004-3

Popov, T., Gips, B., Kastner, S., & Jensen, O. (2019). Spatial specificity of alpha oscillations in the human visual system. *Human Brain Mapping*. Advance online publication. https://doi.org/10.1002/hbm.24712

Poreh, A. (2005). Analysis of mean learning of normal participants on the Rey Auditory-Verbal Learning Test. *Psychological Assessment*, *17*(2), 191–199. https://doi.org/10.1037/1040-3590.17.2.191

Priovoulos, N., Jacobs, H. I. L., Ivanov, D., Uludag, K., Verhey, F. R. J., & Poser, B. A. (2017). High-resolution in vivo imaging of human locus coeruleus by magnetization transfer MRI at 3T and 7T. *NeuroImage*, *168*, 127–136. https://doi.org/10.1016/j.neuroimage.2017.07.045

Qian, C., & Di, X. (2011). Phase or amplitude? The relationship between ongoing and evoked neural activity. *Journal of Neuroscience*, *31*(29), 10425–10426. https://doi.org/10.1523/jneurosci.2197-11.2011

Quentin, R., & Cohen, L. G. (2019). Reversing working memory decline in the elderly. *Nature Neuroscience*, *22*, 686–688. https://doi.org/10.1038/s41593-019-0386-3

Ramos, B. P., Stark, D., Verduzco, L., van Dyck, C. H., & Arnsten, A. F. T. (2006). Alpha2A-adrenoceptor stimulation improves prefrontal cortical regulation of behavior through inhibition of cAMP signaling in aging animals. *Learning & Memory*, *13*(6), 770–776. https://doi.org/10.1101/lm.298006

Rasmussen, K., & Jacobs, B. L. (1986). Single unit activity of locus coeruleus neurons in the freely moving cat. II. Conditioning and pharmacologic studies. *Brain Research*, *371*(2), 335–344. https://doi.org/10.1016/0006-8993(86)90371-9

Raz, N., & Lindenberger, U. (2011). Only time will tell: Cross-sectional studies offer no solution to the age–brain–cognition triangle: Comment on Salthouse (2011). *Psychological Bulletin*, *137*(5), 790–795. https://doi.org/10.1037/a0024503

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., … Acker, J. D. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex*, *15*(11), 1676–1689. https://doi.org/10.1093/cercor/bhi044

Reimer, J., Froudarakis, E., Cadwell, C. R., Yatsenko, D., Denfield, G. H., & Tolias, A. S. (2014). Pupil fluctuations track fast switching of cortical states during quiet wakefulness. *Neuron*, *84*(2), 355–362. https://doi.org/10.1016/j.neuron.2014.09.033

Reimer, J., McGinley, M. J., Liu, Y., Rodenkirch, C., Wang, Q., McCormick, D. A., & Tolias, A. S. (2016). Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. *Nature Communications*, *7*(1): 13289. https://doi.org/10.1038/ncomms13289

Reinhart, R. M. G., & Nguyen, J. A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nature Neuroscience*, *22*(5), 820–827. https://doi.org/10.1038/s41593-019-0371-x

Rihs, T. A., Michel, C. M., & Thut, G. (2009). A bias for posterior α-band power suppression versus enhancement during shifting versus maintenance of spatial attention. *NeuroImage*, *44*(1), 190–

199. https://doi.org/10.1016/j.neuroimage.2008.08.022

Robbins, T. W., & Arnsten, A. F. T. (2009). The neuropsychopharmacology of fronto-executive function: Monoaminergic modulation. *Annual Review of Neuroscience*, *32*(1), 267–287. https://doi.org/10.1146/annurev.neuro.051508.135535

Rodenkirch, C., Liu, Y., Schriver, B. J., & Wang, Q. (2019). Locus coeruleus activation enhances thalamic feature selectivity via norepinephrine regulation of intrathalamic circuit dynamics. *Nature Neuroscience*, *22*(1), 120–133. https://doi.org/10.1038/s41593-018-0283-1

Rogers, C. S., Payne, L., Maharjan, S., Wingfield, A., & Sekuler, R. (2018). Older adults show impaired modulation of attentional alpha oscillations : Evidence from dichotic listening. *Psychology and Aging*, *33*(2), 246–258. https://doi.org/10.1037/pag0000238

Romei, V., Brodbeck, V., Michel, C., Amedi, A., Pascual-Leone, A., & Thut, G. (2008). Spontaneous fluctuations in posterior α-band EEG activity reflect variability in excitability of human visual areas. *Cerebral Cortex*, *18*(9), 2010–2018. https://doi.org/10.1093/cercor/bhm229

Romei, V., Gross, J., & Thut, G. (2010). On the role of prestimulus alpha rhythms over occipito-parietal areas in visual input regulation: Correlation or causation? *Journal of Neuroscience*, *30*(25), 8692–8697. https://doi.org/10.1523/jneurosci.0160-10.2010

Rougeul-Buser, A., & Buser, P. (1997). Rhythms in the alpha band in cats and their behavioural correlates. *International Journal of Psychophysiology*, *26*(1–3), 191–203. https://doi.org/10.1016/S0167-8760(97)00764-2

Rugg, M. D., & Morcom, A. M. (2004). The relationship between brain activity, cognitive performance, and aging. In R. Cabeza, L. Nyberg, & D. Park (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging* (pp. 132–154). New York: Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195156744.003.0006

Ruzzoli, M., Torralba, M., Morís Fernández, L., & Soto-Faraco, S. (2019). The relevance of alpha phase in human perception. *Cortex*, *120*, 249–268. https://doi.org/10.1016/j.cortex.2019.05.012

Saalmann, Y. B., Pinsk, M. A., Wang, L., Li, X., & Kastner, S. (2012). The pulvinar regulates information transmission between cortical areas based on attention demands. *Science*, *337*(6095), 753–756. https://doi.org/10.1126/science.1223082

Safaai, H., Neves, R., Eschenko, O., Logothetis, N. K., & Panzeri, S. (2015). Modeling the effect of locus coeruleus firing on cortical state dynamics and single-trial sensory processing. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(41), 12834–12839. https://doi.org/10.1073/pnas.1516539112

Samanez-Larkin, G. R., & D'Esposito, M. (2008). Group comparisons: imaging the aging brain. *Social Cognitive and Affective Neuroscience*, *3*(3), 290–297. https://doi.org/10.1093/scan/nsn029

Samuels, E., & Szabadi, E. (2008a). Functional neuroanatomy of the noradrenergic locus coeruleus: Its roles in the regulation of arousal and autonomic function part I: Principles of functional organisation. *Current Neuropharmacology*, *6*(3), 235–253. https://doi.org/10.2174/157015908785777229

Samuels, E., & Szabadi, E. (2008b). Functional neuroanatomy of the noradrenergic locus coeruleus: Its roles in the regulation of arousal and autonomic function part II: Physiological and pharmacological manipulations and pathological alterations of locus coeruleus activity in humans. *Current Neuropharmacology*, *6*(3), 254–285. https://doi.org/10.2174/157015908785777193

Sander, M. C., Fandakova, Y., Grandy, T. H., Shing, Y. L., & Werkle-Bergner, M. (2019). Oscillatory

mechanisms of successful memory formation in younger and older adults are related to structural integrity. *bioRxiv*: 530121. https://doi.org/10.1101/530121

Sander, M. C., Lindenberger, U., & Werkle-Bergner, M. (2012). Lifespan age differences in working memory: A two-component framework. *Neuroscience and Biobehavioral Reviews*, *36*(9), 2007–2033. https://doi.org/10.1016/j.neubiorev.2012.06.004

Sander, M. C., Werkle-Bergner, M., & Lindenberger, U. (2011). Contralateral delay activity reveals life-span age differences in top-down modulation of working memory contents. *Cerebral Cortex*, *21*(12), 2809–2819. https://doi.org/10.1093/cercor/bhr076

Sander, M. C., Werkle-Bergner, M., & Lindenberger, U. (2012). Amplitude modulations and inter-trial phase stability of alpha-oscillations differentially reflect working memory constraints across the lifespan. *NeuroImage*, *59*(1), 646–654. https://doi.org/10.1016/j.neuroimage.2011.06.092

Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews Neuroscience*, *10*(3), 211–223. https://doi.org/10.1038/nrn2573

Sara, S. J. (2015). Locus coeruleus in time with the making of memories. *Current Opinion in Neurobiology*, *35*, 87–94. https://doi.org/10.1016/j.conb.2015.07.004

Sara, S. J., & Bouret, S. (2012). Orienting and reorienting: The locus coeruleus mediates cognition through arousal. *Neuron*, *76*(1), 130–141. https://doi.org/10.1016/j.neuron.2012.09.011

Sasaki, M., Shibata, E., Kudo, K., & Tohyama, K. (2008). Neuromelanin-sensitive MRI: Basics, technique, and clinical applications. *Clinical Neuroradiology*, *18*(3), 147–153. https://doi.org/10.1007/s00062-008-8018-4

Sasaki, M., Shibata, E., Tohyama, K., Takahashi, J., Otsuka, K., Tsuchiya, K., … Sakai, A. (2006). Neuromelanin magnetic resonance imaging of locus ceruleus and substantia nigra in Parkinson's disease. *NeuroReport*, *17*(11), 1215–1218. https://doi.org/10.1097/01.wnr.0000227984.84927.a7

Satoh, A., & Iijima, K. M. (2019). Roles of tau pathology in the locus coeruleus (LC) in age-associated pathophysiology and Alzheimer's disease pathogenesis: Potential strategies to protect the LC against aging. *Brain Research*, *1702*, 17–28. https://doi.org/10.1016/j.breainres.2017.12.027

Scheeringa, R., Mazaheri, A., Bojak, I., Norris, D. G., & Kleinschmidt, A. (2011). Modulation of visually evoked cortical fMRI responses by phase of ongoing occipital alpha oscillations. *Journal of Neuroscience*, *31*(10), 3813–3820. https://doi.org/10.1523/jneurosci.4697-10.2011

Schmid, M. C., Singer, W., & Fries, P. (2012). Thalamic coordination of cortical communication. *Neuron*, *75*(4), 551–552. https://doi.org/10.1016/j.neuron.2012.08.009

Schmidt, M. (2004). *Rey Auditory Verbal Learning Test: A handbook.* Los Angeles, CA: Western Psychological Services.

Schwarz, L. A., & Luo, L. (2015). Organization of the locus coeruleus-norepinephrine system. *Current Biology*, *25*(21), R1051–R1056. https://doi.org/10.1016/j.cub.2015.09.039

Seo, D., & Bruchas, M. R. (2017). Polymorphic computation in locus coeruleus networks. *Nature Neuroscience*, *20*(11), 1517–1519. https://doi.org/10.1038/nn.4663

Servan-Schreiber, D., Printz, H., & Cohen, J. D. (1990). A network model of catecholamine effects: Gain, signal-to-noise ratio, and behavior. *Science*, *249*(4971), 892–895. https://doi.org/10.1126/science.2392679

Shibata, E., Sasaki, M., Tohyama, K., Kanbara, Y., Otsuka, K., Ehara, S., & Sakai, A. (2006). Age-related changes in locus coeruleus on neuromelanin magnetic resonance imaging at 3 Tesla.

Magnetic Resonance in Medical Sciences, *5*(4), 197–200. https://doi.org/10.2463/mrms.5.197

Shing, Y. L., Werkle-Bergner, M., Brehmer, Y., Müller, V., Li, S.-C., & Lindenberger, U. (2010). Episodic memory across the lifespan: The contributions of associative and strategic components. *Neuroscience and Biobehavioral Reviews*, *34*(7), 1080–1091. https://doi.org/10.1016/j.neubiorev.2009.11.002

Simons, J. S., & Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Reviews Neuroscience*, *4*(8), 637–648. https://doi.org/10.1038/nrn1178

Sokoliuk, R., Mayhew, S. D., Aquino, K. M., Wilson, R., Brookes, M. J., Francis, S. T., … Mullinger, K. J. (2019). Two spatially distinct posterior alpha sources fulfill different functional roles in attention. *Journal of Neuroscience*. Advance online publication. https://doi.org/10.1523/jneurosci.1993-18.2019

Sokolov, E. N. (1963). Higher nervous functions: The orienting reflex. *Annual Review of Physiology*, *25*(1), 545–580. https://doi.org/10.1146/annurev.ph.25.030163.002553

Sommer, V. R., Fandakova, Y., Grandy, T. H., Lee Shing, Y., Werkle-Bergner, M., & Sander, M. C. (2019). Neural pattern similarity differentially relates to memory performance in younger and older adults. *Journal of Neuroscience*. Advance online publication. https://doi.org/10.1523/jneurosci.0197-19.2019

Spitzer, B., & Blankenburg, F. (2012). Supramodal parametric working memory processing in humans. *Journal of Neuroscience*, *32*(10), 3287–3295. https://doi.org/10.1523/jneurosci.5280-11.2012

Staub, B., Doignon-Camus, N., Després, O., & Bonnefond, A. (2013). Sustained attention in the elderly: What do we know and what does it tell us about cognitive aging? *Ageing Research Reviews*, *12*(2), 459–468. https://doi.org/10.1016/j.arr.2012.12.001

Stitt, I., Zhou, Z. C., Radtke-Schuller, S., & Fröhlich, F. (2018). Arousal dependent modulation of thalamo-cortical functional interaction. *Nature Communications*, *9*(1): 2455. https://doi.org/10.1038/s41467-018-04785-6

Strauß, A., Wöstmann, M., & Obleser, J. (2014). Cortical alpha oscillations as a tool for auditory selective inhibition. *Frontiers in Human Neuroscience*, *8*: 350. https://doi.org/10.3389/fnhum.2014.00350

Swift, K. M., Gross, B. A., Frazer, M. A., Bauer, D. S., Clark, K. J. D., Vazey, E. M., … Poe, G. R. (2018). Abnormal locus coeruleus sleep activity alters sleep signatures of memory consolidation and impairs place cell stability and spatial memory. *Current Biology*, *28*(22), 3599–3609.e4. https://doi.org/10.1016/j.cub.2018.09.054

Szabadi, E. (2012). Modulation of physiological reflexes by pain: Role of the locus coeruleus. *Frontiers in Integrative Neuroscience*, *6*: 94. https://doi.org/10.3389/fnint.2012.00094

Szabadi, E. (2013). Functional neuroanatomy of the central noradrenergic system. *Journal of Psychopharmacology*, *27*(8), 659–693. https://doi.org/10.1177/0269881113490326

Takeuchi, T., Duszkiewicz, A. J., Sonneborn, A., Spooner, P. A., Yamasaki, M., Watanabe, M., … Morris, R. G. M. (2016). Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature*, *537*(7620), 357–362. https://doi.org/10.1038/nature19325

Theofilas, P., Ehrenberg, A. J., Dunlop, S., Di Lorenzo Alho, A. T., Nguy, A., Leite, R. E. P., … Grinberg, L. T. (2017). Locus coeruleus volume and cell population changes during Alzheimer's disease progression: A stereological study in human postmortem brains with potential implication for early-stage biomarker discovery. *Alzheimer's and Dementia*, *13*(3), 236–246.

https://doi.org/10.1016/j.jalz.2016.06.2362

Theofilas, P., Ehrenberg, A. J., Nguy, A., Thackrey, J. M., Dunlop, S., Mejia, M. B., … Grinberg, L. T. (2018). Probing the correlation of neuronal loss, neurofibrillary tangles, and cell death markers across the Alzheimer's disease Braak stages: A quantitative study in humans. *Neurobiology of Aging*, *61*, 1–12. https://doi.org/10.1016/j.neurobiolaging.2017.09.007

Thiele, A., & Bellgrove, M. A. (2018). Neuromodulation of attention. *Neuron*, *97*(4), 769–785. https://doi.org/10.1016/j.neuron.2018.01.008

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). α-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience*, *26*(37), 9494–9502. https://doi.org/10.1523/jneurosci.0875-06.2006

Tona, K. D., Keuken, M. C., de Rover, M., Lakke, E., Forstmann, B. U., Nieuwenhuis, S., & van Osch, M. J. P. (2017). In vivo visualization of the locus coeruleus in humans: Quantifying the test–retest reliability. *Brain Structure and Function*, *222*(9), 4203–4217. https://doi.org/10.1007/s00429-017-1464-5

Totah, N. K., Logothetis, N. K., & Eschenko, O. (2019). Noradrenergic ensemble-based modulation of cognition over multiple timescales. *Brain Research*, *1709*, 50–66. https://doi.org/10.1016/j.brainres.2018.12.031

Totah, N. K., Neves, R. M., Panzeri, S., Logothetis, N. K., & Eschenko, O. (2018). The locus coeruleus is a complex and differentiated neuromodulatory system. *Neuron*, *99*(5), 1055–1068.e6. https://doi.org/10.1016/j.neuron.2018.07.037

Tromp, D., Dufour, A., Lithfous, S., Pebayle, T., & Després, O. (2015). Episodic memory in normal aging and Alzheimer disease: Insights from imaging and behavioral studies. *Ageing Research Reviews*, *24*, 232–262. https://doi.org/10.1016/j.arr.2015.08.006

Trujillo, P., Summers, P. E., Ferrari, E., Zucca, F. A., Sturini, M., Mainardi, L. T., … Costa, A. (2017). Contrast mechanisms associated with neuromelanin-MRI. *Magnetic Resonance in Medicine*, *78*(5), 1790–1800. https://doi.org/10.1002/mrm.26584

Tulving, E. (1983). *Elements of episodic memory*. Oxford: Clarendon Press.

Tune, S., Wöstmann, M., & Obleser, J. (2018). Probing the limits of alpha power lateralisation as a neural marker of selective attention in middle-aged and older listeners. *European Journal of Neuroscience*, *48*(7), 2537–2550. https://doi.org/10.1111/ejn.13862

Uematsu, A., Tan, B. Z., Ycu, E. A., Cuevas, J. S., Koivumaa, J., Junyent, F., … Johansen, J. P. (2017). Modular organization of the brainstem noradrenaline system coordinates opposing learning states. *Nature Neuroscience*, *20*(11), 1602–1611. https://doi.org/10.1038/nn.4642

Vaden, R. J., Hutcheson, N. L., McCollum, L. A., Kentros, J., & Visscher, K. M. (2012). Older adults, unlike younger adults, do not modulate alpha power to suppress irrelevant information. *NeuroImage*, *63*(3), 1127–1133. https://doi.org/10.1016/j.neuroimage.2012.07.050

van der Waal, M., Farquhar, J., Fasotti, L., & Desain, P. (2017). Preserved and attenuated electrophysiological correlates of visual spatial attention in elderly subjects. *Behavioural Brain Research*, *317*, 415–423. https://doi.org/10.1016/j.bbr.2016.09.052

van der Werf, F., & Smit, A. E. (2008). The world according to blink: Blinking and aging. In C. A. P. Cavallotti & L. Cerulli (Eds.), *Age-related changes of the human eye* (pp. 319–341). Totowa, NJ: Humana Press. https://doi.org/10.1007/978-1-59745-507-7_19

van Diepen, R. M., Foxe, J. J., & Mazaheri, A. (2019). The functional role of alpha-band activity in

attentional processing: The current zeitgeist and future outlook. *Current Opinion in Psychology*. https://doi.org/10.1016/j.copsyc.2019.03.015

van Ede, F. (2018). Mnemonic and attentional roles for states of attenuated alpha oscillations in perceptual working memory: A review. *European Journal of Neuroscience*, *48*(7), 2509–2515. https://doi.org/10.1111/ejn.13759

van Gerven, P. W. M., Paas, F., van Merriënboer, J. J. G., & Schmidt, H. G. (2004). Memory load and the cognitive pupillary response in aging. *Psychophysiology*, *41*(2), 167–174. https://doi.org/10.1111/j.1469-8986.2003.00148.x

Vazey, E. M., Moorman, D. E., & Aston-Jones, G. (2018). Phasic locus coeruleus activity regulates cortical encoding of salience information. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(40), E9439–E9448. https://doi.org/10.1073/pnas.1803716115

Vinck, M., Batista-Brito, R., Knoblich, U., & Cardin, J. A. (2015). Arousal and locomotion make distinct contributions to cortical activity patterns and visual encoding. *Neuron*, *86*(3), 740–754. https://doi.org/10.1016/j.neuron.2015.03.028

von Oertzen, T., Brandmaier, A. M., & Tsang, S. (2015). Structural equation modeling with Ωnyx. *Structural Equation Modeling*, *22*(1), 148–161. https://doi.org/10.1080/10705511.2014.935842

Voytek, B., & Knight, R. T. (2015). Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. *Biological Psychiatry*, *77*(12), 1089–1097. https://doi.org/10.1016/j.biopsych.2015.04.016

Wagatsuma, A., Okuyama, T., Sun, C., Smith, L. M., Abe, K., & Tonegawa, S. (2018). Locus coeruleus input to hippocampal CA3 drives single-trial learning of a novel context. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(2), E310–E316. https://doi.org/10.1073/pnas.1714082115

Waldhauser, G. T., Dahl, M. J., Ruf-Leuschner, M., Müller-Bamouh, V., Schauer, M., Axmacher, N., … Hanslmayr, S. (2018). The neural dynamics of deficient memory control in heavily traumatized refugees. *Scientific Reports*, *8*(1): 13132. https://doi.org/10.1038/s41598-018-31400-x

Waldhauser, G. T., Johansson, M., & Hanslmayr, S. (2012). Alpha/beta oscillations indicate inhibition of interfering visual memories. *Journal of Neuroscience*, *32*(6), 1953–1961. https://doi.org/10.1523/jneurosci.4201-11.2012

Wang, M., Gamo, N. J., Yang, Y., Jin, L. E., Wang, X.-J., Laubach, M., … Arnsten, A. F. T. (2011). Neuronal basis of age-related working memory decline. *Nature*, *476*(7359), 210–213. https://doi.org/10.1038/nature10243

Watanabe, T., Tan, Z., Wang, X., Martinez-Hernandez, A., & Frahm, J. (2019). Magnetic resonance imaging of noradrenergic neurons. *Brain Structure and Function*, *224*(4), 1609–1625. https://doi.org/10.1007/s00429-019-01858-0

Wechsler, D. (1981). *WAIS-R manual: Wechsler Adult Intelligence Scale-Revised*. New York: Psychological Corporation.

Weinshenker, D. (2018). Long road to ruin: Noradrenergic dysfunction in neurodegenerative disease. *Trends in Neurosciences*, *41*(4), 211–223. https://doi.org/10.1016/j.tins.2018.01.010

Weiskopf, N., Suckling, J., Williams, G., Correia, M. M., Inkster, B., Tait, R., … Lutti, A. (2013). Quantitative multi-parameter mapping of R1, PD(*), MT, and R2(*) at 3T: A multi-center validation. *Frontiers in Neuroscience*, *7*: 95. https://doi.org/10.3389/fnins.2013.00095

Weisz, N., Hartmann, T., Müller, N., Lorenz, I., & Obleser, J. (2011). Alpha rhythms in audition:

Cognitive and clinical perspectives. *Frontiers in Psychology*, *2*: 73. https://doi.org/10.3389/fpsyg.2011.00073

Werkle-Bergner, M., Müller, V., Li, S.-C., & Lindenberger, U. (2006). Cortical EEG correlates of successful memory encoding: Implications for lifespan comparisons. *Neuroscience and Biobehavioral Reviews*, *30*(6), 839–854. https://doi.org/10.1016/j.neubiorev.2006.06.009

Westerhausen, R., Bless, J. J., Passow, S., Kompus, K., & Hugdahl, K. (2015). Cognitive control of speech perception across the lifespan: A large-scale cross-sectional dichotic listening study. *Developmental Psychology*, *51*(6), 806–815. https://doi.org/10.1037/dev0000014

Westerhausen, R., Moosmann, M., Alho, K., Medvedev, S., Hämäläinen, H., & Hugdahl, K. (2009). Top-down and bottom-up interaction: Manipulating the dichotic listening ear advantage. *Brain Research*, *1250*, 183–189. https://doi.org/10.1016/j.brainres.2008.10.070

Wilson, R. S., Nag, S., Boyle, P. A., Hizel, L. P., Yu, L., Buchman, A. S., … Bennett, D. A. (2013). Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. *Neurology*, *80*(13), 1202–1208. https://doi.org/10.1212/wnl.0b013e3182897103

Womelsdorf, T., Valiante, T. A., Sahin, N. T., Miller, K. J., & Tiesinga, P. (2014). Dynamic circuit motifs underlying rhythmic gain control, gating and integration. *Nature Neuroscience*, *17*(8), 1031–1039. https://doi.org/10.1038/nn.3764

Wöstmann, M., Alavash, M., & Obleser, J. (2019). Alpha oscillations in the human brain implement distractor suppression independent of target selection. *bioRxiv*: 721019. https://doi.org/10.1101/721019

Wöstmann, M., Herrmann, B., Maess, B., & Obleser, J. (2016). Spatiotemporal dynamics of auditory attention synchronize with speech. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(14), 3873–3878. https://doi.org/10.1073/pnas.1523357113

Wöstmann, M., Herrmann, B., Wilsch, A., & Obleser, J. (2015). Neural alpha dynamics in younger and older listeners reflect acoustic challenges and predictive benefits. *The Journal of Neuroscience*, *35*(4), 1458–1467. https://doi.org/10.1523/jneurosci.3250-14.2015

Wöstmann, M., Vosskuhl, J., Obleser, J., & Herrmann, C. S. (2018). Opposite effects of lateralised transcranial alpha versus gamma stimulation on auditory spatial attention. *Brain Stimulation*, *11*(4), 752–758. https://doi.org/10.1016/j.brs.2018.04.006

Yuval-Greenberg, S., Tomer, O., Keren, A. S., Nelken, I., & Deouell, L. Y. (2008). Transient induced gamma-band response in EEG as a manifestation of miniature saccades. *Neuron*, *58*(3), 429–441. https://doi.org/10.1016/j.neuron.2008.03.027

Zanto, T. P., Pan, P., Liu, H., Bollinger, J., Nobre, A. C., & Gazzaley, A. (2011). Age-related changes in orienting attention in time. *The Journal of Neuroscience*, *31*(35), 12461. https://doi.org/10.1523/jneurosci.1149-11.2011

Zecca, L., Stroppolo, A., Gatti, A., Tampellini, D., Toscani, M., Gallorini, M., … Zucca, F. A. (2004). The role of iron and copper molecules in the neuronal vulnerability of locus coeruleus and substantia nigra during aging. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(26), 9843–9848. https://doi.org/10.1073/pnas.0403495101

Zecca, L., Tampellini, D., Gerlach, M., Riederer, P., Fariello, R. G., & Sulzer, D. (2001). Substantia nigra neuromelanin: Structure, synthesis, and molecular behaviour. *Molecular Pathology*, *54*(6), 414–418. https://doi.org/10.1136/mp.54.6.414

Zhou, H., Schafer, R. J., & Desimone, R. (2016). Pulvinar-cortex interactions in vision and attention. *Neuron*, *89*(1), 209–220. https://doi.org/10.1016/j.neuron.2015.11.034

Zhu, Y., Zhan, G., Fenik, P., Brandes, M., Bell, P., Francois, N., … Veasey, S. (2018). Chronic Sleep Disruption Advances the Temporal Progression of Tauopathy in P301S Mutant Mice. *The Journal of Neuroscience*, *38*(48), 10255–10270. https://doi.org/10.1523/jneurosci.0275-18.2018

Zimprich, D., & Rast, P. (2009). Verbal learning changes in older adults across 18 months. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *16*(4), 461–484. https://doi.org/10.1080/13825580902785663

Zimprich, D., Rast, P., & Martin, M. (2008). Individual differences in verbal learning in old age. In S. Hofer & D. Alwin (Eds.), *Handbook of cognitive aging: Interdisciplinary perspectives* (pp. 224–243). Thousand Oaks, CA: SAGE Publications. https://doi.org/10.4135/9781412976589.n14

Original publication I

Dahl, M. J., Mather, M., Düzel, S., Bodammer, N. C., Lindenberger, U., Kühn, S., & Werkle-Bergner, M. (2019). Rostral locus coeruleus integrity is associated with better memory performance in older adults. *Nature Human Behaviour*, 3(11):1203–1214. https://doi.org/10.1038/s41562-019-0715-2

Original publication II

Dahl, M. J., Ilg, L., Li, S.-C., Passow, S., & Werkle-Bergner, M. (2019). Diminished pre-stimulus alpha-lateralization suggests compromised self-initiated attentional control of auditory processing in old age. *NeuroImage*, *197*, 414–424. https://doi.org/10.1016/j.neuroimage.2019.04.080

Original publication III

Dahl, M. J., Mather, M. M., Sander, M. C., & Werkle-Bergner, M. (2019). Noradrenergic responsiveness supports selective attention across the adult lifespan. *The Journal of Neuroscience, 40*(22), 4372–4390. https://doi.org/10.1523/jneurosci.0398-19.2020

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