Title:

Neuromodulatory systems in aging and disease

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Neuromodulators, such as acetylcholine, dopamine, and noradrenaline, are synthesized in small, subcortical nuclei (clusters of cells) and released throughout the brain via diffuse and wide-ranging projections (Lőrincz & Adamantidis, 2017). Neuromodulator release has a profound influence on brain states (McCormick, Nestvogel, & He, 2020) and higher-order cognitive functions (Cools & Arnsten, 2021; Li, Lindenberger, & Sikström, 2001; Mather & Harley, 2016). However, neuromodulatory centers are susceptible to degeneration in aging and neurodegenerative disease, which contributes to cognitive decline (Weinshenker, 2018). Specifically, postmortem research revealed that brainstem neuromodulatory centers are the first sites to accumulate abnormal tau, a hallmark of Alzheimer's disease (Braak, Thal, Ghebremedhin, & Del Tredici, 2011), and show considerable cell loss with disease progression (Lyness, Zarow, & Chui, 2003). Here, a primary focus is on the cholinergic and noradrenergic systems, as meta analyses comparing cell counts of these neuromodulator-producing nuclei in the brains of Alzheimer's patients and controls revealed evidence of strong degeneration (mean effect size $d > 2$; Lyness et al., 2003; also see Orlando et al., 2023). Moreover, the cholinergic and noradrenergic systems prominently modulate hippocampal memory processing and accordingly their decline has been associated with memory impairment, a characteristic feature of aging and age-associated diseases (Berry & Harrison, 2023; Dahl, Bachman, et al., 2023; Dahl, Kulesza, Werkle-Bergner, & Mather, 2023; Jacobs et al., 2021; Krohn et al., 2023; Orlando et al., 2023).

While in-vivo assessments of neuromodulatory centers in humans long seemed unattainable (Astafiev, Snyder, Shulman, & Corbetta, 2010; Kranz, Hahn, Savli, & Lanzenberger, 2012), recent methodological advancements shed light on their structure (Betts et al., 2019; Sulzer et al., 2018) and function (Joshi & Gold, 2020). Moreover, recent large-scale studies link anti-neuromodulatory drugs to dementia risk (Coupland et al., 2019) and clinical trials that pharmacologically manipulate neuromodulation to alter neurodegenerative disease progression are underway (Levey et al., 2021, also see David et al., 2022). Together, these advancements propel novel insights about neuromodulatory systems and their role in age- and disease-related cognitive decline.

This special issue contains a collection of reviews and meta-analyses that summarize our current understanding of neuromodulatory systems in aging and disease based on evidence from human and non-human studies using a variety of neuroscientific methods. The seven articles can be broadly grouped into those focusing more on catecholaminergic (i.e., dopaminergic and noradrenergic; Dahl et al., 2023b; Engels-Domínguez et al., 2023; Iannitelli and Weinshenker, 2023; Krohn et al., 2023) and cholinergic (Berry & Harrison, 2023; Mieling, Meier, & Bunzeck, 2023; Orlando et al., 2023) neuromodulation, with a commentary (Kim et al. (in press); Leiman et al. (*in press*) summarizing each subsection. Two of these articles take a more comparative approach, contrasting the roles of cholinergic and noradrenergic (Orlando et al., 2023) as well as noradrenergic and dopaminergic (Dahl, Kulesza, et al., 2023) neuromodulation. The following section provides an overview of each article in the special issue, before concluding by identifying common themes across submissions.

(1) First, Engels-Domínguez and colleagues (2023) provide a comprehensive methodological introduction to the special issue, primarily reviewing human neuroimaging research into neuromodulatory subcortical systems. A key motivation for this research is the involvement of several neuromodulatory nuclei in the earliest stages of neurodegenerative diseases (Braak et al., 2003, 2011). Reliable assessments of neuromodulatory changes could therefore create a crucial

window of opportunity for early disease-modifying interventions (Grinberg & Heinsen, 2017). After addressing the challenges associated with in-vivo assessments arising from these nuclei's size, location, and susceptibility to physiological noise, they provide an overview about recent additions to the neuroscience toolkit. A specific focus is on magnetic resonance imaging-derived measures (i.e., structural MRI, functional MRI, diffusion MRI), positron emission tomography (PET) and electrophysiological assessments (see Figure 2 in Engels-Domínguez et al., 2023) for an overview of available methods), promising novel insights into structural and functional changes of neuromodulatory subcortical systems with age and disease (see Table 1 in Engels-Domínguez et al., 2023 for an overview of recent findings). The authors conclude by pointing our directions for future research, including looking beyond the noradrenergic and cholinergic systems, longitudinal and multimodal studies.

(2) Next, Krohn and colleagues (2023) give a detailed overview of the noradrenergic system, beginning with an introduction of its neuroanatomical and chemical organization as well as its roles in non-cognitive and cognitive functions. They continue by contrasting changes in noradrenergic neuromodulation in healthy aging, Alzheimer's and Parkinson's disease and how these may exacerbate disease symptoms (for an overview, see Box 1, Figure 1 in Krohn et al., 2023). In particular, they point out that the early involvement of the noradrenergic system in both diseases can lead to an overlap of neuropsychiatric symptoms, such as sleep disturbances, at early stages. Beyond demonstrating links with cognitive impairment, a major focus is on noradrenergic effects on the neurovascular and neuroimmune system, reflecting the transmitter's anti-inflammatory and vasoconstrictive properties (Feinstein, Kalinin, & Braun, 2016; Heneka et al., 2010). The authors conclude their review by highlighting the potential of pharmacological and non-pharmacological interventions that modulate the noradrenergic system, such as vagus-nerve stimulation (D'Agostini et al., 2023; Hulsey et al., 2017); see Box 1, Figure 2 in Krohn et al., 2023).

(3) Turning to animal models, the article by Ianitelli and colleagues also focuses on the noradrenergic locus coeruleus and mechanisms that may trigger inflammatory processes associated with the development of neurodegenerative disease (Iannitelli & Weinshenker, 2023). A unique feature of noradrenergic and dopaminergic nuclei is their characteristic dark color, which is caused by the accumulation of neuromelanin in the bodies of locus coeruleus and substantia nigra cells. Neuromelanin is a dark insoluble pigment formed of catecholaminergic metabolites, heavy metals, protein aggregates, and oxidized lipids (see Figure 1 in Iannitelli and Weinshenker, 2023). While neuromelanin initially scavenges toxic compounds and thus fulfills neuroprotective functions, it can become toxic when it overloads the intracellular machinery or when it is released from dying catecholaminergic cells in the advent of neurodegenerative disease. Naturally occurring neuromelanin is only found in the brains of primates and some other long-living animals. However, a recently-developed viral-mediated approach allows expression of human tyrosinase, the enzyme responsible for peripheral melanin production, in noradrenergic (Iannitelli et al., 2023) and dopaminergic (Carballo-Carbajal et al., 2019) nuclei in rodents. Ianitelli and colleagues summarize initial insights that pigment expression leads to degeneration of the dopaminergic substantia nigra (Carballo-Carbajal et al., 2019) and the noradrenergic locus coeruleus, a neuroinflammatory response, and behavioral impairments reminiscent of prodromal Alzheimer's and Parkinson's symptoms (Iannitelli et al., 2023). This new approach makes it possible for the first time to

investigate the role of neuromelanin in neurodegenerative diseases in-vivo, but as the authors summarize, some open questions remain for future research.

(4) The review by Dahl and colleagues (2023) compares how dopaminergic and noradrenergic centers modulate hippocampal synaptic plasticity and memory. Specifically, dopaminergic inputs to the medial temporal lobe are known to facilitate the consolidation of salient experiences in the hippocampus (Lisman & Grace, 2005). New animal research, however, found only sparse direct projections from the dopaminergic substantia nigra–ventral tegmental area to the hippocampus, while the brainstem's locus coeruleus showed much denser connections (Kempadoo, Mosharov, Choi, Sulzer, & Kandel, 2016; Takeuchi et al., 2016). Dopamine is converted to noradrenaline in the vesicles of locus coeruleus neurons, which is why these cells can co-release *both* transmitters to modulate hippocampal processing ((Smith & Greene, 2012); see Figure 1 in Dahl et al., 2023). Summarizing recent studies using optogenetic stimulation in rodents, Dahl and colleagues reveal a crucial role of locus coeruleus–dopaminergic neuromodulation across hippocampal subfields and stages of memory processing. This sheds new light on the mechanisms of *how* the locus coeruleus contributes to long-term memory, with implications for diseases with marked locus coeruleus degeneration, such as Alzheimer's. Moreover, it informs in-vivo human research that uses novel imaging tools to track locus coeruleus and substantia nigra–ventral tegmental area decline in aging and disease and its differential effect on cognition (Dahl, Bachman, et al., 2023).

(5) Research into catecholaminergic systems has recently gained more traction, propelled by the advent of new in-vivo imaging techniques (Engels-Domínguez et al., 2023) and a renewed interest in noradrenergic drugs (David et al., 2022). But for several decades a mainstay of symptomatic pharmacological treatment for mild cognitive impairment has centered on the cholinergic system (Berry & Harrison, 2023; Orlando et al., 2023). Most often, these neuromodulatory systems are studied in isolation. In their article, Orlando and colleagues (2023) discuss the multisystem nature of neurodegenerative diseases like Alzheimer's and Parkinson's and the need to study neuromodulatory systems in tandem. They begin by pointing out shared principles across neuromodulatory systems, such as their auto-regulation, top-down modulation, and optimal mid-range level for functioning. Over the course of neurodegenerative diseases, noradrenergic and cholinergic systems show non-linear changes. That is, prodromal phases are often characterized by a compensatory *upregulation* of activity (hyperactivity) to maintain behavioral and cognitive performance, which, however, may facilitate the spread of tau pathology (Weinshenker, 2018). By contrast, cell loss and hypoactivity dominate in later disease phases. These nonlinear changes may explain neuromodulatory contributions to seemingly opposing symptoms (e.g., apathy/impulsivity) often seen in neurodegenerative disease. Despite commonalities, there are also important distinctions between cholinergic and noradrenergic systems, including their input-output organization, assumed to promote segregated vs integrated processing (Shine, 2019). Finally, interactions of the two systems (see e.g., Slater et al., 2022) arise from unidirectional projections of the locus coeruleus to the cholinergic basal forebrain but also in common terminal regions, such as at the level of the thalamus and prefrontal cortex. Better understanding the mutual interactions of these and other neuromodulatory systems will be crucial for unraveling the effects of their (nonlinear) degeneration in neurodegenerative diseases.

(6) Motivated by a resurgence of interest in the cholinergic basal forebrain in the context of neurodegenerative diseases, Berry & Harrison commence (2023) their review by providing a concise outline of the neuroanatomical and chemical organization of this transmitter system. The discovery of reduced levels of the enzyme responsible for acetylcholine synthesis in the brains of Alzheimer's patients, along with the impact of pharmacological disruptions of cholinergic functioning on attention and memory, contributed to the formulation of the *Cholinergic Hypothesis* during the 1970s and 1980s. This hypothesis placed the cholinergic basal forebrain and the center stage of Alzheimer's etiology. However, subsequent findings of modest or no effects of cholinergic drugs in some patient groups dampened the initial enthusiasm. Together with the discovery of the causal role of amyloid-modulating genetic mutations (APP, PSEN genes) in autosomal-dominant Alzheimer's, this prompted a shift to the *Amyloid Hypothesis* (see Figure 1 in Berry and Harrison, 2023). This hypothesis states that amyloid pathology promotes the cortical spread of tau pathology and thus favors neurodegeneration and cognitive decline (Jagust, 2018). The authors argue that the time is ripe for a synthesis of the *Cholinergic* and *Amyloid Hypotheses*, integrating neuromodulatory degeneration in the etiology of Alzheimer's. Specifically, there are known mechanistic interactions across systems: amyloid disrupts cholinergic basal forebrain activity which in turn triggers further amyloid pathology. The authors conclude their review by discussing how latest findings on the cholinergic system can be incorporated into current areas of Alzheimer's research.

(7) The final article in this special issue by Mieling and colleagues (2023) builds on the prominent cholinergic contribution to Alzheimer's development outlined in previous articles (Berry & Harrison, 2023; Orlando et al., 2023) and provides empirical support from in vivo imaging studies in humans. Specifically, Mieling and colleagues suggest that late-life brain changes form a continuum, with more prominent pathological changes in mild cognitive impairment and Alzheimer's than in healthy aging. Moreover, based on earlier research they propose that the cholinergic basal forebrain may show earlier atrophy as compared to medial temporal lobe regions in later life. Aggregating voxel-based morphometry MRI findings across studies yielded data of about 1,100 patients (mild cognitive impairment, Alzheimer's) and around 1,400 healthy older control participants. The authors then evaluated the degree of convergence across studies on a voxel level, contrasting different subgroups (mild cognitive impairment > healthy controls; Alzheimer's > healthy controls). The meta-analyses revealed lower volumes in several medial temporal lobe regions in patients, and in more liberal post-hoc analyses also in the cholinergic basal forebrain. The authors conclude their article with a discussion of cholinergic modulations of hippocampal memory processing and possible factors underlying basal forebrain susceptibility to degeneration in the development of Alzheimer's disease.

Taken together, in this special issue, we have explored the intricate mechanisms of neuromodulator dysregulation in aging and age-related diseases, particularly focusing on the cholinergic and noradrenergic systems in Alzheimer's and other neurodegenerative conditions. This collection of articles offers a summary of recent insights into their susceptibility to degeneration and roles in cognitive decline. From methodological advancements enabling in-vivo assessments to comparative analyses of neuromodulatory systems and their interactions, the contributions provide a nuanced understanding of the neural basis of

late-life cognitive decline. Discussions on interventions and future research directions highlight the importance of continued investigations in this field which holds promise for earlier interventions.

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