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Cholinergic neuromodulation in the aging brain – Implications for neuropsychiatric diseases: Commentary on "neuromodulatory systems in aging and disease" special issue

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1. Introduction

The cholinergic system plays a pivotal role in both cognitive functions and affective processes. However, its significance in age-related neuropsychiatric diseases is frequently overshadowed by a predominant focus on higher-order symptoms associated with cortical pathology. Neuropsychiatric disorders encompass a wide range of symptoms affecting mood, behavior, and cognition, often without clear neurodegeneration. Neurodegenerative diseases, on the other hand, are characterized by progressive structural decline in the brain, leading to cognitive and functional decline.

Alzheimer's Disease (AD), for instance, is typically accompanied by a significant degeneration of cholinergic neurons, particularly in the basal forebrain, contributing to cognitive decline and memory impairment, specifically. Cholinergic neurodegeneration is also linked to cognitive decline in Lewy Body Dementia and is accompanied by hallucinations and other behavioral symptoms. In Parkinson's Disease Dementia, cognitive symptoms are similarly tied to cholinergic dysregulation, resulting in memory impairment and executive dysfunction.

Hence, the cholinergic system appears as a viable target for therapeutic interventions addressing not only cognitive but also neuropsychiatric symptoms. Understanding how the cholinergic system influences neuropsychiatric conditions can offer valuable insights and lead to potential avenues for novel treatments.

2. Rediscovering the relevance of neuromodulatory dynamics in age-related neuropsychiatric disorders

2.1. Cholinergic and noradrenergic treatments in the landscape of precision medicine

Although cognitive dysfunction is normally associated with cortical pathology, Orlando et al. (2023) draw attention to the important role acetylcholine and noradrenaline play in cognitive and psychiatric diseases. Given their specificity, location-dependent action, ability for self-regulation, and optimal range for function, they are exceptional targets for the development of targeted pharmacological treatments in age-related neuropsychiatric disorders. Indeed, cholinergic drugs are widely employed in the management of these disorders: the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine have been in use for the last 25 years for AD treatment. While there has been observed enhancement in cognitive function in mild to moderate AD, there hasn't been a notable alleviation in neuropsychiatric symptoms. Nonetheless, current cholinergic treatments do not seem to modify disease progression (Zhang et al., 2020). Their limited effectivity underscores the necessity for additional research, particularly to identify individual differences that could be used in neuromodulatory interventions at earlier disease stages for neuroprotective purposes. On the other hand, noradrenergic drugs have had mixed success in treating neuropsychiatric symptoms, but recent research has shown promising results that could hopefully bring them to clinical practice.

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The activation dynamics of the cholinergic and noradrenergic systems exhibit intriguing patterns that could be correlated with positive and negative neuropsychiatric symptoms in age-related diseases. For instance, hypoactivity of the locus coeruleus might be linked to apathy, while hyperactivity could result in anxious or agitated states. The varying effects on cognitive and behavioral dimensions, depending on the level of stimulation, underscore the importance of understanding the U-shaped dose-response relationship and the potential benefits of interactions between these systems. Going forward, these factors should be considered for the development of new and improved pharmacotherapies.

2.2. The basal forebrain cholinergic system in the context of the amyloid hypothesis

Berry and Harrison (2023) provide a modern reexamination of the relevance of the cholinergic system in AD. Considering the limitations of previous attempts to develop AD treatments based solely on acetylcholinesterase inhibitors, or targeting amyloid (Karran and De Strooper, 2022) the authors suggest that a combination therapy targeting both amyloid and the cholinergic system might lead to a better understanding of AD pathogenesis and etiology given the known bidirectional effects between Aβ and cholinergic integrity.

Indeed, novel methods such as PET imaging and longitudinal MRI scans, have provided further evidence on the patterns of cholinergic loss in aging and AD, as well as on the predictive capability of cholinergic system volumes for Aβ status and burden in older adults, respectively. Additionally, the development of amperometric recording for measuring transient cholinergic signaling in performing animals, as well as optogenetic studies driving behavior through phasic acetylcholine release, have been critical for redefining the cholinergic system as a system capable of modulating specific cognitive operations in a spatially and temporally discrete manner. Finally, research on tau-seeding in animals will clarify how cholinergic system projections contribute to the spread of tau disease. While these methods provide valuable insights for potential interventions and treatments, more in-depth results from AD research might also help understand the impact of cholinergic decline on cognition in other conditions such as Parkinson's Disease and Lewy Body Dementia.

2.3. The Nucleus basalis Meynert (NbM) as an early neurodegeneration biomarker

Mieling et al.' (2023) meta-analysis reveals that, compared to healthy controls, the NbM shows a significant reduction in gray matter in AD patients, but only a slight gray matter reduction in MCI patients. These differing degrees of neurodegeneration found between AD and MCI groups highlight the importance of early intervention and NbM's potential as an AD biomarker. However, at the same time, the modest gray matter change found in the NbM in MCI compared to healthy controls suggests that limitations of voxel-based morphometry, given its bias toward highly localized and linear differences among groups (Davatzikos, 2004), may render this method less suitable for detecting subtle and spatially distributed structural changes, which are often the case in AD and MCI. Also, the small size of the NbM presents a significant hurdle for its efficacy and reliability as a standalone biomarker, as current imaging techniques may not consistently detect subtle changes in such a small structure, especially in the early stages of AD where changes are minimal.

3. Overview and research prospects

The cholinergic system remains an integral yet challenging target in neurodegenerative diseases research due to its complex contribution to cognitive functions and our incomplete understanding of its susceptibility in neuropsychiatric conditions. These conditions, crucial for the cognitive decline and memory impairments characteristic of AD, places the cholinergic system at the core of understanding and potentially mitigating the disease's progression. Orlando et al. (2023), Berry and Harrison (2023), and Mieling et al. (2023) shed light on the intricate functionalities of the cholinergic system and the potential of neuromodulatory treatments targeting the cholinergic system, while outlining current gaps in knowledge and methodological approaches.

From their collective insights, the bidirectional relationship among acetylcholine, amyloid-beta, and tau protein, particularly in the context of the cholinergic system, emerges as an auspicious field for research that integrates the cholinergic and amyloid hypothesis. Future investigations should address how the cholinergic system integrity impacts and interacts with the progression and manifestation of neurodegenerative diseases such as AD, Parkinson's Disease, and Lewy Body Dementia at molecular, cellular, and system levels. The potential of the NbM in-vivo imaging as a biomarker for early pathological neurodegeneration in humans, despite being promising, calls for further critical examination due to its small size and the limitations of current imaging techniques.

These open questions lead the way for important future research avenues: The development of targeted neuroimaging and analysis techniques capable of accurately detecting structural loss by subtle, early neurodegeneration. Given the specificity and auto-regulatory function of neuromodulatory systems, together with their inverted-U relationship in cognitive modulation, require a multifaceted, translational approach to developing novel pharmacotherapies while also considering interactions with protein pathologies. Future research should focus on personalized medicine strategies, leveraging advances in neuroimaging methods and establishing biomarkers for tailoring treatments based on individual disease trajectories. In this light, while recent advancements in disease-modifying anti-amyloid therapies mark significant progress, their severe adverse risks caution us against overreliance. This conundrum emphasizes the importance of pursuing a broader therapeutic spectrum, highlighting the potential of cholinergic and noradrenergic therapies. A balanced exploration of therapeutic strategies is integral in creating a more inclusive and safer treatment regime, accommodating the diverse disease profiles and ensuring the well-being of patients and families.

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