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Recent advances in cholinergic imaging and cognitive decline— Revisiting the cholinergic hypothesis of dementia

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Abstract

Purpose of review—Although the cholinergic hypothesis of dementia provided a successful paradigm for the development of new drugs for dementia, this hypothesis has waned in popularity. Cholinergic brain imaging may provide novel insights into the viability of this hypothesis.

Recent findings—Cholinergic receptor and forebrain volumetric studies suggest an important role of the cholinergic system in maintaining brain network integrity that may deteriorate with cognitive decline in Alzheimer disease (AD) and Lewy body disorders (LBD). Bidirectional changes in regional receptor expression may suggest the presence of compensatory responses to neurodegenerative injury. Cholinergic system changes are more complex in LBD because of additional subcortical degenerations compared to AD. Cholinergic-dopaminergic interactions affect attentional, verbal learning and executive functions, and impairments in these two transmitter systems may jointly increase the risk of dementia in Parkinson disease.

Summary—The cholinergic hypothesis is evolving from a primary focus on memory toward expanded cognitive functions modulated by regionally more complex and interactive brain networks. Cholinergic network adaptation may serve as a novel research target in neurodegeneration.

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Keywords

Acetylcholine; Alzheimer disease; brain network; cognition; dementia with Lewy bodies; Parkinson disease

Introduction

Current insights point to a multisystem etiology of cognitive impairment and memory loss in dementing disorders. Early studies, however, advocated the so-called 'cholinergic hypothesis' to explain cognitive and memory deficits in Alzheimer disease (AD) [1, 2]. This hypothesis resulted from observations of prominent cholinergic cell loss in the nucleus basalis of Meynert (NBM) in AD post-mortem brains [3, 4]. Significant loss of cholinergic forebrain neurons has also been found in Parkinson disease (PD) brains [5]. Findings of greater forebrain neuronal loss in PD than in AD [6] suggest that cholinergic deficits could be even more pronounced in Lewy body disorders (LBD) than in AD. Recent neuroscience research confirms the vital role of cholinergic neurotransmission in cognitive function, specifically in attention and memory encoding [7].

The cholinergic hypothesis provided a useful paradigm for the successful approval of cholinesterase inhibitor drugs as a treatment for AD and parkinsonian dementia. However, despite these advances and over four decades of research, the cholinergic hypothesis has lost some interest, in large part because of the limited effectiveness of cholinesterase inhibitor drugs in clinical practice [8] and the advance of new *in vivo* PET imaging radiotracers which highlight the role of β -amyloid, and more recently, tau proteinopathies in memory loss, at least in AD.

The goal of this review is provide an update on the recent cholinergic neuroimaging literature in an attempt to clarify the role of the cholinergic system in cognitive impairment in the two major neurodegenerative disorders: AD and LBD.

Imaging biomarkers and cognition

Imaging biomarkers of cognition are complex and include markers of a) proteinopathy, such as β -amyloidopathy, tauopathy or α -synucleinopathy, b) neurodegeneration, including neuronal loss and axonal degeneration, c) neurotransmission and d) abnormalities of brain function and connectivity [9]. Proteinopathy and other changes in subcortical projection systems may result in neurotransmitter changes [10], including cholinergic and dopaminergic systems. Molecular imaging methods, such as positron emission tomography (PET) or single photon computed tomography (SPECT) allow assessment of the cholinergic neurotransmission system in the living brain. Magnetic resonance imaging (MRI) plays a key role in volumetric assessment of the cholinergic basal forebrain (CBFB) containing the NBM.

Multi-modal imaging approaches will be of particular importance to study a more specific relationship between changes in cholinergic markers and cognition by controlling for

important cognitive disease confounders, such as the presence of proteinopathies or dopaminergic degenerations.

Cholinergic anatomy and *in vivo* imaging ligand targets

There are several sources of cholinergic projections in the brain. Magnocellular neurons of the CBFB provide widespread cholinergic input to the telencephalon [11]. Cholinergic neurons of the medial septal nucleus (also known as the Ch1 cell group) and the vertical limb nucleus of the diagonal band (Ch2) supply the major cholinergic input to the hippocampus; cholinergic neurons of the horizontal limb nucleus of the diagonal band (Ch3) supply the major cholinergic input to the olfactory bulb; and cholinergic neurons of the NBM (or Ch4) supply the main cholinergic input to the cortical mantle and amygdala [12]. The pedunculopontine nucleus (PPN, Ch5 cell group) and laterodorsal tegmental complex (LDTG, Ch6 cell group) supply cholinergic inputs to the cerebellum, thalamus, spinal cord, a number of brainstem nuclei, and some striatal fibers [13, 14]. The basal ganglia also contain a population of cholinergic interneurons [15, 16].

Several cholinergic markers have been labeled for PET or SPECT imaging. Acetylcholinesterase (AChE) is a reliable marker for brain cholinergic pathways including in the human brain [17]. The vesicular acetylcholine transporter (VACHT) is a more pure marker of presynaptic cholinergic terminal density. [¹²³I]IBVM and [¹⁸F]FEOBV are SPECT and PET VACHT ligands, respectively. [¹¹C]PMP and [¹¹C]MP4A are PET AChE ligands. Both AChE and VACHT ligands can be used to study the integrity of presynaptic cholinergic nerve terminals. Several radiotracers have also been developed for labeling of nicotinic and muscarinic cholinergic receptors. For example, [¹²³I]5IA and [¹⁸F]flubatine are $\alpha 4\beta 2$ nicotinic acetylcholine receptor (nAChR) SPECT and PET ligands, respectively. [¹²³I]QNB is a SPECT ligand to visualize muscarinic M1/M4 receptors (mAChR).

Cholinergic nerve terminal integrity imaging

Normal aging, mild cognitive impairment and Alzheimer disease

Early *in vivo* cholinergic PET and SPECT neuroimaging studies have confirmed post-mortem observations of cholinergic losses in AD. For example, cholinergic nerve terminal imaging studies have shown reduced cortical VACHT and AChE binding in AD compared to control subjects [18–20]. Thalamic AChE activity is generally spared in AD [21]. These cholinergic losses affect cognitive performance, not only in AD but also in healthy aging. For example, a recent [¹¹C]MP4A AChE PET study in healthy elderly reported that mesiotemporal cholinergic binding associated with verbal episodic memory delayed recall performance [22]. The number of words forgotten after a 30 minutes delay period negatively correlated with AChE activity in the right posterior cingulate cortex and frontal regions. A [¹¹C]MP4A AChE PET study in patients with mild cognitive impairment (MCI) found three clusters of reduced AChE activity compared to normal subjects: fronto-parietal, lateral temporal and limbic (hippocampal/amygdala) clusters [23]. AChE reductions were most prominent in the lateral temporal cluster that correlated significantly with learning, executive and language comprehension functions. We previously reported that reduced cortical AChE associated with attentional and working memory deficits in AD [24]. A recent VACHT PET

study in AD patients using the [^{18}F]FEOBV ligand found evidence of reduced cortical transporters with greatest reductions in the superior and middle temporal cortex extending in the inferior parietal lobule [25]. Severe reductions were observed also in the posterior medial cortical territory, including the posterior cingulate cortex and the precuneus. Frontal reductions, however, were less prominent. This pattern agrees with topographic findings, which suggest a caudal-rostral pattern of degeneration of the CBFB in the AD brain [26]. The degree of regional [^{18}F]FEOBV uptake reductions in patients with AD was highly variable among the different areas, ranging from 8.9% in the anterior cingulate, to 51% in the superior temporal gyrus. Cortical transporter uptake correlated robustly with global cognition in the patients [25]. No significant differences between AD patients and control subjects were found in the hippocampus, thalamus, striatum or cerebellum [25]. These observations indicate that septal nuclei and NBM, the proposed origins of the cholinergic projections to the hippocampus and neocortex, respectively, are differentially involved in AD.

Lewy body disorders

According to the Braak staging scheme of PD pathology, α -synuclein-positive inclusions in the CBFB areas occur simultaneously with nigral pathology in the early stage of PD [27]. There are more severe cholinergic losses in parkinsonian dementia compared to AD of similar degree of cognitive impairment [28]. As a consequence, there is a relatively greater clinical response to AChE inhibitor drugs in patients with LBD than AD [29]. As reductions in cholinergic nerve terminal integrity are consistently more severe in PD dementia than in AD, cholinergic dysfunction may be responsible for the transition from PD to PD with dementia [30].

A recent VAcHT [^{123}I]IBVM SPECT study investigated the integrity of the three major cholinergic pathways - the Ch1 (septohippocampal), the Ch4 (basocortical), the Ch5 (pontothalamic) cholinergic pathways and striatal cholinergic interneurons in patients with dementia with Lewy bodies (DLB) [31]. Compared to healthy subjects, VAcHT binding values for DLB patients were significantly lower in the Ch4 terminal regions of the anterior cingulate cortex (−59%), the superior (−78%) and inferior parietal cortices (−47%), in the Ch5 terminal region of the thalamus (−69%), and in the striatum (−45%). No significant reductions were seen for the hippocampus (Ch1 terminal region) illustrating differential degeneration of CBFB regions.

Cholinergic and dopaminergic interactive effects and cognition in PD: The 'compensatory' hypothesis

We recently reported heterogeneity in both cortical and subcortical (thalamic) AChE hydrolysis rates in PD patients in the absence of dementia [32]. About one third of PD patients (31%) had below normal range neocortical AChE activity and about one sixth (18%) had below normal range thalamic activity. Most patients with thalamic cholinergic hypofunction also had reduced cortical activity implying a possible sequence effect where cholinergic losses in the forebrain NBM (Ch4) may precede PPN-thalamic (Ch5) losses. We found that cortical cholinergic activity inversely correlated with verbal learning, executive and attentional functions independent from dopaminergic losses [32, 33]. Furthermore, we

found that cortical cholinergic and caudate nucleus dopaminergic denervation not only had additive but also interactive effects in their prediction of cognitive impairment in PD [33]. Interestingly, interactive or multiplicative effects were most significant for executive function deficits. Therefore, it is conceivable that loss of cholinergic nerve terminals may worsen fronto-striatal dysfunction due to loss of compensatory attentional resources [34]. As executive function impairments are a strong predictor for conversion to dementia [35], these findings may explain why cholinergic losses are consistently seen in PD dementia. Conversely, we found that a substantial proportion of patients with no apparent cognitive deficits, including on executive tasks, despite significant dopaminergic denervation, had preserved cholinergic activity. These observations formed the basis for the 'compensatory' hypothesis [33, 36]. Fronto-parietal cortical cholinergic functions associated with top-down control may be recruited (increased cholinergic activity in cortical circuits) to compensate for executive dysfunctions associated with striatal dopaminergic declines, and vice versa. Furthermore, we found that cholinergic changes have incremental contributions to cognitive decline not only independent from dopaminergic losses but also from cognitive effects of β -amyloid plaques in PD at risk of dementia [37].

Thalamic cholinergic denervation and saliency bottom-up processing in PD

We explored cognitive correlates of thalamic cholinergic hypofunction in PD patients and found evidence of a specific contribution to bottom-up saliency processing [38]. Attention can be focused volitionally by "top-down" signals derived from task demands and automatically by "bottom-up" signals from salient stimuli [39]. Saliency detection is a key attentional mechanism that promotes learning by focusing limited cognitive and perceptual resources on the most relevant subset of available sensory data. We found that thalamic cholinergic integrity is related to bottom-up signal salience, rather than top-down control of attentional selection in PD [38]. These results suggest that there are regionally specific contributions of cholinergic function to different aspects of attention.

Cholinergic receptor imaging: Exploring brain networks

The discussed studies above have examined region-specific effects of cholinergic denervation on cognition. However, to truly understand the effects of impaired cholinergic transmission on cognition it should be studied in the context of the larger networks that these specific regions encompass. Recent insights from neuroscience research provide evidence of the heterogeneous involvement of number of distinct neural networks underlying the cognitive deficits in dementia, and their modulation by neurotransmitter systems in the brain [40]. To this end, several studies have proposed network analyses of the cholinergic receptors. Cholinergic neurotransmission in the brain is mediated by ionotropic nAChR and metabotropic mAChR receptors. Previous $\alpha 4\beta 2$ nAChR studies have found significant correlations between reduced receptor binding and cognition in both AD and PD [41, 42, 35]. More recently, spatial covariance studies using nAChR or mAChR ligands have been performed to explore cholinergic networks in the brain in AD and LBD.

Connectivity and network integrity may decrease in normal aging, but this decrease is more rapid in AD, with a number of systems being more vulnerable, such as the default mode

network (DMN) [43]. The DMN is generally thought to include the posterior cingulate cortex/precuneus, inferior parietal lobules, lateral temporal cortices, medial prefrontal cortex, and hippocampus [44]. It has been proposed that activity of this network during rest is important for memory consolidation [45].

Alzheimer disease

A spatial covariance study of M1/M4 mAChRs in AD using [123 I]QNB SPECT showed concurrent decreased binding in medial temporal, basal forebrain, inferior frontal, and cingulate relative to simultaneously increased binding in the frontal poles, occipital, pre-post central, precuneus and superior parietal areas [46]. This pattern may suggest a loss of M1/M4 mAChR in the medial temporal and cholinergic rich basal forebrain, accompanied by either preservation or an increase in cortical M1/M4 mAChR binding. These bidirectional changes may reflect a compensatory process to maintain basocortical cholinergic function as loss of pre-synaptic receptors usually results in compensatory up-regulation of post-synaptic receptors [47]. The same group also reported a spatial covariance mapping study of $\alpha 4\beta 2$ nicotinic receptors in AD using [123 I]5IA-85380 SPECT. They found an $\alpha 4\beta 2$ spatial covariance pattern showing relative decreases in $\alpha 4\beta 2$ nAChR binding in basal forebrain, pedunculo-pontine, limbic, thalamus, parietal, and frontal regions together with relatively preserved or increased nAChR binding in midbrain, cerebellum, pallidum, occipital, and pre/post central gyri [48]. The pattern converged on a number of subcortical and cortical regions, implicating a cholinergic network that mapped onto DMN hubs, such as medial prefrontal, posterior cingulate, precuneus, and inferior parietal regions [48]. This was characterized by reduced cholinergic activity. The reduced DMN activity of nAChRs is consistent with the previously reported findings of reduced M1/M4 mAChR expressions within similar regions [46]. These observations highlight the potential role of both types of receptors in AD and the potentially more fundamental role of the cholinergic system in normal functioning of the DMN network. Interestingly, donepezil treatment has been reported to result in increased cerebral blood flow to the posterior cingulate cortex, a key hub of the DMN, in patients with AD [49]. Other nAChR regions mapped onto established resting-state networks, including the anterior insula and anterior cingulate, which are important nodes of the “salience network”, for initiation of cognitive control and switching networks to support access to working memory and attentional resources [50]. Therefore, cholinergic deficits mediated through nAChR and mAChR receptors underlying cognition may occur within key brain networks in AD.

Lewy body disorders

A spatial covariance pattern M1/M4 subtype mAChR brain [123 I]QNB SPECT study in cholinesterase inhibitor drug naïve PD dementia patients versus control subjects found concomitant decreases in receptor in basal forebrain, striatal, temporal, insula, and anterior cingulate together with concomitant preservation or increases in parieto-occipital and frontal areas in the patients [51]. The mAChR pattern related to donepezil treatment benefits overlapped with frontoparietal and default mode networks. Upregulated or preserved activity in regions overlapping key nodes of the DMN and frontoparietal networks may suggest that a cholinergic maintenance of these networks may be prerequisite for cognitive remediation by cholinergic treatment in PD dementia [51]. Interestingly, a $\alpha 4\beta 2$ nAChR [123 I]5IA

SPECT study found evidence of not only reduced regional receptor binding (caudate nucleus, orbitofrontal cortex, and the middle temporal gyrus) but also higher binding in the putamen, the supplemental motor area and insular cortex in cognitively normal subjects with PD [52]. Findings suggest evidence of upregulation in early stage of PD. Higher nAChR density may occur as a compensatory mechanism to maintain dopaminergic tone, in particular in the putamen and the supplemental motor areas, a key structure of the cortico-basal ganglia motor loop [52].

MRI cholinergic basal forebrain volumetry studies

Complementary to molecular imaging techniques for assessing cholinergic denervation, volumetric analysis of the CBFB on high-resolution structural MRI scans is available as an in vivo surrogate measure of cholinergic degeneration in aging and disease [53–55] allowing assessment of cholinergic degeneration across different CBFB subdivisions [56–59].

Normal aging, Alzheimer disease and Lewy body disorders: Evidence for early vulnerability of the cholinergic forebrain

In vivo MRI volumetry studies confirm the relationship between CBFB degeneration and cognitive decline in AD and LBD [53, 54, 60, 61]. Unlike autopsy studies that are usually confined to relatively advanced disease stages, MRI-based CBFB volumetry has been particularly useful for studying the role of cholinergic forebrain degeneration for the emergence of cognitive impairments during preclinical and prodromal disease stages and their distinction from the normal aging process. For example, studies show that cholinergic forebrain structure is highly vulnerable to negative effects of physiologic aging, with annual atrophy rates of the CBFB being approximately three times higher than rates of global gray matter shrinkage even in cognitively stable healthy older individuals [53, 57]. This normal age-related CBFB degeneration is further accelerated in the presence of amyloid pathology, and increased AD-related CBFB degeneration can already be detected at completely asymptomatic disease stages [62–64].

The functional implications of these CBFB changes during normal aging and preclinical AD are still incompletely understood. The data implies that neither age-related, nor initial pathological degeneration of the CBFB is linked to clinically overt cognitive deficits. In clinically normal older individuals, CBFB volumes may only indirectly relate to neuropsychological test performance via more general factors such as level of education or intelligence [65, 66]. Alternatively, more detailed neuropsychological testing may be necessary to uncover relationships between subtle changes in cognitive performance and CBFB degeneration in non-clinical older populations. Indeed, in a study that directly measured source memory, an aspect of cognitive function disproportionately affected by the aging process [67], the relationship between CBFB volumes and performance was more evident [68]. In vivo-measured CBFB degeneration was found to be robustly associated with declining cognition, particularly in the domains of memory and attentional function, in early neurodegeneration such as in MCI [59, 66, 69].

Multimodal cholinergic basal forebrain MRI volumetry and glucose metabolic PET imaging: Evidence for cholinergic mediated neural networks subserving memory and attention

The effects of CBFB degeneration on cognitive impairments are likely mediated through cortical neuronal dysfunction that arises as a consequence of cholinergic depletion in the denervated cortical target areas [7]. The relation between CBFB degeneration, cortical dysfunction, and cognitive deficits can be studied in humans by combining MRI-based CBFB volumetry with detailed neuropsychometric evaluations and additional imaging modalities such as glucose metabolic PET for the assessment of cortical synaptic function. Using such a multimodal approach, it has been shown that in vivo CBFB degeneration in MCI is coupled with neuronal dysfunction in widespread cortical networks subserving memory and attentional processes, and that this association mediates the effect of CBFB degeneration on specific deficits in the respective cognitive domains [66]. For example, the effect of CBFB degeneration on episodic memory dysfunction was fully mediated by CBFB-associated hypometabolism in a cortical “memory” network spanning the hippocampus and retrosplenial/posterior cingulate cortex [70]. On the other hand, CBFB-associated hypometabolism in a distinct fronto-temporo-parietal neocortical network accounted for the effect of CBFB degeneration on attentional control deficits. Such multimodal data enable a better understanding of the role of CBFB degeneration in dementia [71], and could advance our knowledge of the mechanisms of cognition-enhancing cholinergic drugs, thereby potentially helping to optimise their use as dementia treatments [72, 73]. For example, a randomized placebo-controlled trial of donepezil in MCI showed reduced rates of CBFB atrophy over 18 months compared with placebo. This effect was not reflected in a clinical effect of donepezil on episodic memory or executive functions [74]. It remains to be shown in independent studies if these results indicate an impact of early cholinergic therapy on cholinergic system degeneration, and if volumetric measures may be more sensitive than classical neuropsychological tests for detecting treatment effects in the grey zone between symptomatic and disease modifying therapies. The coupling of multimodal datasets with the subregional anatomical specificity provided by automated CBFB volumetry could aid in advancing our understanding of brain stimulation interventions targeting the NBM, which are currently showing early promise for the treatment of cognitive impairments in AD and LBD [75, 71]. Importantly, such interventions may depend on the precise subregional targeting of the CBFB, but very little is known about its impact on the wider brain.

Interestingly, we found that the observed structure-function-cognition relationships appeared to be independent of the presence of amyloid plaque pathology in MCI as determined by PET imaging [66], indicating that the link between CBFB degeneration, cortical dysfunction, and cognitive impairment may not be specific for the prodromal phase of AD, but may similarly extend to other neurodegenerative disorders with CBFB involvement. While in vivo correlations between CBFB degeneration and dementia severity could already be demonstrated in LBD [53, 54, 60, 61], the course of CBFB degeneration during the predementia phase of these disorders and its relevance for the emergence of initial cognitive deficits remains to be studied in more detail [55, 76]. Interestingly, a longitudinal study of PD subjects with MCI demonstrated greater cholinergic forebrain loss in those converting to PD dementia [76].

Discussion

Local neural circuits and extended brain networks

The cholinergic system plays a key role in subserving cortical circuits underlying cognitive functioning [77]. Although the cholinergic system has more typically been viewed as both spatially and functionally “diffuse” [78], more recent mapping and morphological studies of basal forebrain cholinergic neurons demonstrate that these cholinergic projection neurons can be extremely elaborate in both the extent of axonal arbors and the number of axonal branches; there is topographic, rather than diffuse, organization of basal forebrain cholinergic neurons and their target fields forming topographically distinct circuits [79].

Cholinergic receptor studies show that cortical cholinergic changes in AD and DLB are not diffuse but have topographic vulnerability that overlap with important hubs of more extended neural networks involved in various cognitive functions [46, 51, 48]. Bidirectional changes in regional cerebral cholinergic receptor expression may reflect the effects of neural function losses in some regions and compensatory responses in other brain areas. Multimodal MRI CBFB volumetry and glucose metabolic PET studies have also identified distinct neural network correlates of impaired episodic memory and attention in AD [66].

Revisiting the cholinergic hypothesis of dementia

Interest in the cholinergic hypothesis in dementia has substantially decreased over the last few decades, mostly because of the limited efficacy of the current generation of cholinergic drugs [8]. Our previous AChE PET imaging and donepezil treatment study in AD showed limited and modest donepezil-induced cerebral enzyme inhibition in AD [80]. Therefore, lack of efficacy of cholinergic augmentation therapy due to suboptimal brain effects is not a valid argument to discount the cholinergic hypothesis of dementia. Conceivably, centrally more active cholinergic pharmacotherapies may potentially result in clinically more meaningful effects. Interestingly, more recent pharmacological support for the cholinergic hypothesis of dementia comes from the accumulating evidence of striking cognitive side effects and acceleration of cognitive decline in the elderly due to anti-cholinergic side-effect burden of commonly used medications. For example, a recent study found that anti-cholinergic drug burden was associated with memory and executive function deficits, greater cortical atrophy and reduced temporal lobe cortical thickness and greater clinical decline in the elderly [81].

It is also clear that there are multiple layers of pathobiological mechanisms underlying dementia, including bidirectional changes between brain and systemic body processes [82] (Figure 1) and that a single component of this multifactorial system cannot account for the complete dementia syndrome. As such, the cholinergic system is one among others that when it fails it may exacerbate cognitive deficits and worsens the severity of dementia [7].

Recent advances in neuroimaging show that the cholinergic hypothesis is evolving from a primary focus of the effect of cholinergic loss on memory toward a more complex systems interaction with other neurodegenerations in AD and LBD. Cortical cholinergic denervation is a major process associated with worsening cognitive functions across the spectrum of cognitive impairment in PD and most often occurs in the setting of prominent caudate

nucleus dopaminergic denervation [33]. Cholinergic-dopaminergic interactions support the so-called 'compensatory' hypothesis where dual neurotransmitter system losses may aggravate cognitive, esp. executive function, deficits and jointly increase the risk of conversion to dementia in PD [33]. Conversely, fronto-parietal cortical cholinergic functions associated with top-down control may be recruited (increased cholinergic activity in cortical circuits) to compensate for executive dysfunctions associated with striatal dopaminergic declines in early stage disease (Table 1).

Cholinergic system changes are more complex in LBD because of additional subcortical cholinergic changes including the basal ganglia, thalamus and cerebellum [31] that are relatively spared in AD [21, 25]. Thalamic cholinergic hypofunction is selectively associated with bottom-up salience functions in PD [38]. Cholinergic system changes also play a role in cognition-dependent mobility functions, such as slow gait speed or falls [83, 84].

Cholinergic systems may enable adaptation to neurodegenerative injury even as they also degenerate, which has implications for functional restoration [69]. For example, a post-mortem study found evidence of cholinergic plasticity in the hippocampus in patients with MCI with a significant elevation of hippocampal choline acetyltransferase activity that may represent a compensatory reaction to the progressively denervating hippocampus by lost entorhinal cortex input [85]. Cholinergic signaling - at least in the setting of preserved cholinergic nerve terminals - may enable a compensatory effect to preserve cognitive functions in the setting of non-cholinergic pathology in dementia, like Lewy bodies or dopaminergic losses in PD or other proteinopathies in AD. Therefore, preserving the integrity of upregulated compensatory cholinergic brain regions may provide novel treatment strategies.

Conclusions

Recent neuroimaging work provides compelling evidence that cholinergic system losses and cognitive decline are intrinsically linked in AD and LBD. It is evident that loss of cholinergic neurons augments the severity of the clinical manifestation of dementia. This is supported by new insights that the integrity of cholinergic nerve terminals may modulate brain networks subserving various cognitive functions. Cholinergic system changes are more complex in LBD because of additional subcortical degenerations compared to AD, where subcortical cholinergic changes may associate with bottom-up salience attentional functions. Further elucidation of possible compensatory functions of cholinergic nerve terminals in the setting of other pathologies in neurodegeneration may have important implication for novel functional restoration approaches. Invasive and non-invasive neuromodulation stimulation approaches may selectively target cholinergic-dependent circuits or network functions. Similarly, as shown by the successful dopaminergic replacement therapy for PD, more centrally active and effective cholinergic augmentation therapy could make a substantial clinical impact and may help to revive the cholinergic hypothesis of dementia, which has become more multifaceted with regional, bidirectional and disease-specific changes. In this respect, a personalized medicine approach may be prudent to maximize enhancement and minimize impairments of cholinergic treatments.

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Abbreviations

AChE	Acetylcholinesterase
AD	Alzheimer disease
CBFB	cholinergic basal forebrain
DLB	dementia with Lewy bodies
DMN	default mode network
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
NBM	nucleus basalis of Meynert
PD	Parkinson disease
PDD	Parkinson disease with dementia
PPN	pedunculopontine nucleus
PET	Positron Emission Tomography
SPECT	Single Photon Computed Emission Tomography
VAcHT	Vesicular Acetylcholine Transporter

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Drachman DA, Leavitt J. Human memory and the cholinergic system. A relationship to aging? Arch Neurol. 1974; 30:113–21. [PubMed: 4359364]
2. Bartus RT, Dean RL 3rd, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. Science. 1982; 217(4558):408–14. [PubMed: 7046051]
3. Davies P, Maloney A. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet. 1976; II:1403.
4. Perry EK, Perry RH, Blessed G, Tomlinson BE. Necropsy evidence of central cholinergic deficits in senile dementia. Lancet. 1977; (I):189.
5. Whitehouse PJ, Hedreen JC, White CL, Price DL. Basal forebrain neurons in the dementia of Parkinson disease. Ann Neurol. 1983; 13:243–8. [PubMed: 6847136]

6. Arendt T, Bigl V, Arendt A, Tennstedt A. Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans and Korsakoff's Disease. *Acta Neuropathol (Berl)*. 1983; 61:101–8. [PubMed: 6637393]
7. Hasselmo ME, Sarter M. Modes and models of forebrain cholinergic neuromodulation of cognition. *Neuropsychopharmacology*. 2011; 36(1):52–73. DOI: 10.1038/npp.2010.104 [PubMed: 20668433]
8. Zemek F, Drtinova L, Nepovimova E, Sepsova V, Korabecny J, Klimes J, et al. Outcomes of Alzheimer's disease therapy with acetylcholinesterase inhibitors and memantine. Expert opinion on drug safety. 2014; 13(6):759–74. DOI: 10.1517/14740338.2014.914168 [PubMed: 24845946]
9. Kalia LV. Biomarkers for cognitive dysfunction in Parkinson's disease. *Parkinsonism Relat Disord*. 2017; doi: 10.1016/j.parkreldis.2017.07.023
10. Kalaitzakis ME, Pearce RK. The morbid anatomy of dementia in Parkinson's disease. *Acta Neuropathol*. 2009; 118(5):587–98. DOI: 10.1007/s00401-009-0597-x [PubMed: 19820956]
11. Mesulam MM. The systems-level organization of cholinergic innervation in the human cerebral cortex and its alterations in Alzheimer's disease. *Prog Brain Res*. 1996; 109:285–97. [PubMed: 9009717]
12. Mesulam M, Mufson E, Levy A, Wainer B. Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *J Comp Neurol*. 1983; 214:170–97. [PubMed: 6841683]
13. Mesulam MM, Mufson EJ, Wainer BH, Levy AI. Central cholinergic pathways in the rat: An overview based on an alternative nomenclature (CH1-CH-6). *Neurosci*. 1983; 10:1185–201.
14. Heckers S, Geula C, Mesulam M. Cholinergic innervation of the human thalamus: Dual origin and differential nuclear distribution. *J Comp Neurol*. 1992; 325:68–82. [PubMed: 1282919]
15. Fibiger H. The organization and some projections of cholinergic neurons of the mammalian forebrain. *Brain Res Rev*. 1982; 4:327–88.
16. Mesulam M, Mash D, Hersch L, Bothwell M, Geula C. Cholinergic innervation of the human striatum, globus pallidus, subthalamic nucleus, substantia nigra, and red nucleus. *J Comp Neurol*. 1992; 323:252–68. [PubMed: 1401259]
17. Shute CC, Lewis PR. Electron microscopy of cholinergic terminals and acetylcholinesterase-containing neurones in the hippocampal formation of the rat. *Z Zellforsch Mikrosk Anat*. 1966; 69:334–43. [PubMed: 5973099]
18. Herholz K, Weisenbach S, Zündorf G, Lenz O, Schröder H, Bauer B, et al. In vivo study of acetylcholine esterase in basal forebrain, amygdala, and cortex in mild to moderate Alzheimer disease. *Neuroimage*. 2004; 21:136–43. [PubMed: 14741650]
19. Kuhl D, Minoshima S, Fessler J, Frey K, Foster N, Ficaró E, et al. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. *Ann Neurol*. 1996; 40:399–410. [PubMed: 8797529]
20. Kuhl DE, Koeppe RA, Minoshima S, Snyder SE, Ficaró EP, Foster NL, et al. In vivo mapping of cerebral acetylcholinesterase activity in aging and Alzheimer's disease. *Neurology*. 1999; 52:691–9. [PubMed: 10078712]
21. Kotagal V, Muller ML, Kaufer DI, Koeppe RA, Bohnen NI. Thalamic cholinergic innervation is spared in Alzheimer disease compared to parkinsonian disorders. *Neurosci Lett*. 2012; 514(2): 169–72. S0304-3940(12)00309-6 [pii]. DOI: 10.1016/j.neulet.2012.02.083 [PubMed: 22414859]
- 22*. Richter N, Allendorf I, Onur OA, Kracht L, Dietlein M, Tittgemeyer M, et al. The integrity of the cholinergic system determines memory performance in healthy elderly. *Neuroimage*. 2014; 100:481–8. A MP4A-PET study highlighting the role of cholinergic system integrity for cognitive performance in the normal aging process. DOI: 10.1016/j.neuroimage.2014.06.031 [PubMed: 24952230]
23. Haense C, Kalbe E, Herholz K, Hohmann C, Neumaier B, Kraiss R, et al. Cholinergic system function and cognition in mild cognitive impairment. *Neurobiol Aging*. 2012; 33(5):867–77. DOI: 10.1016/j.neurobiolaging.2010.08.015 [PubMed: 20961662]
24. Bohnen NI, Kaufer DI, Hendrickson R, Ivanco LS, Lopresti B, Davis JG, et al. Cognitive correlates of alterations in acetylcholinesterase in Alzheimer's disease. *Neurosci Lett*. 2005; 380(1–2):127–32. [PubMed: 15854764]

25. Aghourian M, Legault-Denis C, Soucy JP, Rosa-Neto P, Gauthier S, Kostikov A, et al. Quantification of brain cholinergic denervation in Alzheimer's disease using PET imaging with [18F]-FE0BV. *Mol Psychiatry*. 2017; doi: 10.1038/mp.2017.183
26. Liu AK, Chang RC, Pearce RK, Gentleman SM. Nucleus basalis of Meynert revisited: anatomy, history and differential involvement in Alzheimer's and Parkinson's disease. *Acta Neuropathol*. 2015; 129(4):527–40. DOI: 10.1007/s00401-015-1392-5 [PubMed: 25633602]
27. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003; 24(2):197–211. [PubMed: 12498954]
28. Bohnen NI, Kaufer DI, Ivanco LS, Lopresti B, Koeppe RA, Davis JG, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Arch Neurol*. 2003; 60(12):1745–8. [PubMed: 14676050]
29. Weintraub D, Somogyi M, Meng X. Rivastigmine in Alzheimer's disease and Parkinson's disease dementia: an ADAS-cog factor analysis. *Am J Alzheimers Dis Other Dement*. 2011; 26(6):443–9. DOI: 10.1177/1533317511424892 [PubMed: 22009228]
30. Hall H, Reyes S, Landeck N, Bye C, Leanza G, Double K, et al. Hippocampal Lewy pathology and cholinergic dysfunction are associated with dementia in Parkinson's disease. *Brain*. 2014; 137(Pt 9):2493–508. DOI: 10.1093/brain/awu193 [PubMed: 25062696]
- *31. Mazere J, Lamare F, Allard M, Fernandez P, Mayo W. 123I-Iodobenzovesamicol SPECT Imaging of Cholinergic Systems in Dementia with Lewy Bodies. *J Nucl Med*. 2017; 58(1):123–8. Study demonstrating subcortical (striatal, thalamic, cerebellar) cholinergic transporters in DLB. DOI: 10.2967/jnumed.116.176180 [PubMed: 27469360]
32. Bohnen NI, Muller MLTM, Kotagal V, Koeppe RA, Kilbourn MR, Gilman S, et al. Heterogeneity of cholinergic denervation in Parkinson's disease without dementia. *Journal of Cerebral Blood Flow and Metabolism*. 2012; 32(8):1609–17. DOI: 10.1038/jcbfm.2012.60 [PubMed: 22569194]
- *33. Bohnen NI, Albin RL, Muller ML, Petrou M, Kotagal V, Koeppe RA, et al. Frequency of cholinergic and caudate nucleus dopaminergic deficits across the predemented cognitive spectrum of Parkinson disease and evidence of interaction effects. *JAMA Neurol*. 2015; 72(2): 194–200. A multitracer PET study showing both independent and interactive effects of cholinergic and dopaminergic degeneration on cognitive decline in Parkinson disease. DOI: 10.1001/jamaneurol.2014.2757 [PubMed: 25506674]
34. Sarter M, Albin RL, Kucinski A, Lustig C. Where attention falls: Increased risk of falls from the converging impact of cortical cholinergic and midbrain dopamine loss on striatal function. *Exp Neurol*. 2014; 257C:120–9. DOI: 10.1016/j.expneurol.2014.04.032
35. Ewers M, Walsh C, Trojanowski JQ, Shaw LM, Petersen RC, Jack CR Jr, et al. Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. *Neurobiol Aging*. 2012; 33(7):1203–14. DOI: 10.1016/j.neurobiolaging.2010.10.019 [PubMed: 21159408]
36. Kucinski A, Paolone G, Bradshaw M, Albin RL, Sarter M. Modeling fall propensity in Parkinson's disease: deficits in the attentional control of complex movements in rats with cortical-cholinergic and striatal-dopaminergic deafferentation. *J Neurosci*. 2013; 33(42):16522–39. 33/42/16522 [pii]. DOI: 10.1523/JNEUROSCI.2545-13.2013 [PubMed: 24133257]
37. Shah N, Frey KA, Muller MLTM, Petrou M, Kotagal V, Koeppe RA, et al. Striatal and Cortical beta-Amyloidopathy and Cognition in Parkinson's Disease. *Mov Disord*. 2016; 31(1):111–7. DOI: 10.1002/mds.26369 [PubMed: 26380951]
- *38. Kim K, Muller M, Bohnen NI, Sarter M, Lustig C. Thalamic cholinergic innervation makes a specific bottom-up contribution to signal detection: Evidence from Parkinson's disease patients with defined cholinergic losses. *Neuroimage*. 2017; 149:295–304. Multitracer PET study demonstrating a unique role of thalamic cholinergic innervation (as opposed to cortical cholinergic or midbrain dopaminergic innervation) for bottom-up salience processing in the human brain. DOI: 10.1016/j.neuroimage.2017.02.006 [PubMed: 28167350]
39. Buschman TJ, Miller EK. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science*. 2007; 315(5820):1860–2. DOI: 10.1126/science.1138071 [PubMed: 17395832]

- **40. Gratwicke J, Jahanshahi M, Foltynie T. Parkinson's disease dementia: a neural networks perspective. *Brain*. 2015; 138(Pt 6):1454–76. A comprehensive review and perspective article outlining possible links between neurotransmitter deficits, large-scale neural network dysfunction, and cognitive impairments in PD. DOI: 10.1093/brain/awv104 [PubMed: 25888551]
41. Meyer PM, Strecker K, Kendziorra K, Becker G, Hesse S, Woelpl D, et al. Reduced alpha4beta2*-nicotinic acetylcholine receptor binding and its relationship to mild cognitive and depressive symptoms in Parkinson disease. *Arch Gen Psychiatry*. 2009; 66(8):866–77. doi:66/8/866 [pii] 10.1001/archgenpsychiatry.2009.106. [PubMed: 19652126]
42. Kendziorra K, Wolf H, Meyer PM, Barthel H, Hesse S, Becker GA, et al. Decreased cerebral alpha4beta2* nicotinic acetylcholine receptor availability in patients with mild cognitive impairment and Alzheimer's disease assessed with positron emission tomography. *Eur J Nucl Med Mol Imaging*. 2011; 38(3):515–25. DOI: 10.1007/s00259-010-1644-5 [PubMed: 21069319]
43. Dennis EL, Thompson PM. Functional brain connectivity using fMRI in aging and Alzheimer's disease. *Neuropsychology review*. 2014; 24(1):49–62. DOI: 10.1007/s11065-014-9249-6 [PubMed: 24562737]
44. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A*. 2001; 98(2):676–82. DOI: 10.1073/pnas.98.2.676 [PubMed: 11209064]
45. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci*. 2007; 8(9):700–11. DOI: 10.1038/nrn2201 [PubMed: 17704812]
- *46. Colloby SJ, McKeith IG, Wyper DJ, O'Brien JT, Taylor JP. Regional covariance of muscarinic acetylcholine receptors in Alzheimer's disease using (R, R) [(123)I]-QNB SPECT. *J Neurol*. 2015; 262(9):2144–53. Study showing regional muscarinic cholinergic receptor changes overlapping with important brain networks subserving cognition in AD. DOI: 10.1007/s00415-015-7827-z [PubMed: 26122542]
47. Overk CR, Felder CC, Tu Y, Schober DA, Bales KR, Wu J, et al. Cortical M1 receptor concentration increases without a concomitant change in function in Alzheimer's disease. *J Chem Neuroanat*. 2010; 40(1):63–70. DOI: 10.1016/j.jchemneu.2010.03.005 [PubMed: 20347961]
- *48. Colloby SJ, Field RH, Wyper DJ, O'Brien JT, Taylor JP. A spatial covariance ¹²³I-5IA-85380 SPECT study of alpha4beta2 nicotinic receptors in Alzheimer's disease. *Neurobiol Aging*. 2016; 47:83–90. Study showing regional nicotinic cholinergic receptor changes overlapping with important brain networks subserving cognition in AD. DOI: 10.1016/j.neurobiolaging.2016.07.017 [PubMed: 27565302]
49. Iizuka T, Kameyama M. Cholinergic enhancement increases regional cerebral blood flow to the posterior cingulate cortex in mild Alzheimer's disease. *Geriatrics & gerontology international*. 2017; 17(6):951–8. DOI: 10.1111/ggi.12818 [PubMed: 27215917]
50. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007; 27(9):2349–56. DOI: 10.1523/JNEUROSCI.5587-06.2007 [PubMed: 17329432]
- *51. Colloby SJ, McKeith IG, Burn DJ, Wyper DJ, O'Brien JT, Taylor JP. Cholinergic and perfusion brain networks in Parkinson disease dementia. *Neurology*. 2016; 87(2):178–85. Study showing regional muscarinic cholinergic receptor changes overlapping with important brain networks subserving cognition in PD. DOI: 10.1212/WNL.0000000000002839 [PubMed: 27306636]
- *52. Isaias IU, Spiegel J, Brumberg J, Cosgrove KP, Marotta G, Oishi N, et al. Nicotinic acetylcholine receptor density in cognitively intact subjects at an early stage of Parkinson's disease. *Frontiers in aging neuroscience*. 2014; 6:213. Study showing regional upregulation of nicotinic receptors in PD. doi: 10.3389/fnagi.2014.00213 [PubMed: 25177294]
53. Hanyu H, Asano T, Sakurai H, Tanaka Y, Takasaki M, Abe K. MR analysis of the substantia innominata in normal aging, Alzheimer disease, and other types of dementia. *AJNR Am J Neuroradiol*. 2002; 23(1):27–32. [PubMed: 11827872]
54. Choi SH, Jung TM, Lee JE, Lee SK, Sohn YH, Lee PH. Volumetric analysis of the substantia innominata in patients with Parkinson's disease according to cognitive status. *Neurobiol Aging*. 2012; 33(7):1265–72. DOI: 10.1016/j.neurobiolaging.2010.11.015 [PubMed: 21220177]

55. Ziegler DA, Wonderlick JS, Ashourian P, Hansen LA, Young JC, Murphy AJ, et al. Substantia nigra volume loss before basal forebrain degeneration in early Parkinson disease. *JAMA Neurol.* 2013; 70(2):241–7. DOI: 10.1001/jamaneurol.2013.597 [PubMed: 23183921]
56. Teipel SJ, Flatz WH, Heinsen H, Bokde AL, Schoenberg SO, Stockel S, et al. Measurement of basal forebrain atrophy in Alzheimer's disease using MRI. *Brain.* 2005; 128(Pt 11):2626–44. DOI: 10.1093/brain/awh589 [PubMed: 16014654]
57. Grothe M, Heinsen H, Teipel SJ. Atrophy of the cholinergic basal forebrain over the adult age range and in early stages of Alzheimer's disease. *Biol Psychiatry.* 2012; 71(9):805–13. DOI: 10.1016/j.biopsych.2011.06.019 [PubMed: 21816388]
58. Teipel SJ, Meindl T, Grinberg L, Grothe M, Cantero JL, Reiser MF, et al. The cholinergic system in mild cognitive impairment and Alzheimer's disease: an in vivo MRI and DTI study. *Hum Brain Mapp.* 2011; 32(9):1349–62. DOI: 10.1002/hbm.21111 [PubMed: 20672311]
59. Grothe M, Zaborszky L, Atienza M, Gil-Neciga E, Rodriguez-Romero R, Teipel SJ, et al. Reduction of basal forebrain cholinergic system parallels cognitive impairment in patients at high risk of developing Alzheimer's disease. *Cereb Cortex.* 2010; 20(7):1685–95. DOI: 10.1093/cercor/bhp232 [PubMed: 19889714]
- **60. Grothe MJ, Ewers M, Krause B, Heinsen H, Teipel SJ. Basal forebrain atrophy and cortical amyloid deposition in nondemented elderly subjects. *Alzheimers Dement.* 2014; A combined MRI volumetry and amyloid-PET study demonstrating an in vivo association between cholinergic forebrain atrophy and cortical amyloid pathology in preclinical and predementia stages of AD that reproduces analogue findings from the neuropathologic literature. doi: 10.1016/j.jalz.2013.09.011
61. Whitwell JL, Weigand SD, Shiung MM, Boeve BF, Ferman TJ, Smith GE, et al. Focal atrophy in dementia with Lewy bodies on MRI: a distinct pattern from Alzheimer's disease. *Brain.* 2007; 130(Pt 3):708–19. DOI: 10.1093/brain/awl388 [PubMed: 17267521]
62. Teipel S, Heinsen H, Amaro E Jr, Grinberg LT, Krause B, Grothe M. Cholinergic basal forebrain atrophy predicts amyloid burden in Alzheimer's disease. *Neurobiol Aging.* 2014; 35(3):482–91. DOI: 10.1016/j.neurobiolaging.2013.09.029 [PubMed: 24176625]
63. Grothe MJ, Schuster C, Bauer F, Heinsen H, Prudlo J, Teipel SJ. Atrophy of the cholinergic basal forebrain in dementia with Lewy bodies and Alzheimer's disease dementia. *J Neurol.* 2014; 261(10):1939–48. DOI: 10.1007/s00415-014-7439-z [PubMed: 25059393]
- *64. Schmitz TW, Nathan Spreng R. Basal forebrain degeneration precedes and predicts the cortical spread of Alzheimer's pathology. *Nature communications.* 2016; 7:13249. A serial MRI volumetry study showing that accelerated cholinergic forebrain degeneration precedes medial temporal lobe atrophy in the preclinical stage of AD. doi: 10.1038/ncomms13249
65. Wolf D, Grothe M, Fischer FU, Heinsen H, Kilimann I, Teipel S, et al. Association of basal forebrain volumes and cognition in normal aging. *Neuropsychologia.* 2014; 53:54–63. DOI: 10.1016/j.neuropsychologia.2013.11.002 [PubMed: 24269297]
- **66. Grothe MJ, Heinsen H, Amaro E Jr, Grinberg LT, Teipel SJ. Cognitive Correlates of Basal Forebrain Atrophy and Associated Cortical Hypometabolism in Mild Cognitive Impairment. *Cereb Cortex.* 2016; 26(6):2411–26. A combined MRI volumetry and glucose metabolic PET imaging study providing in vivo lesion evidence for cholinergic mediated neural networks subserving memory and attention in the human brain. DOI: 10.1093/cercor/bhv062 [PubMed: 25840425]
67. Chalfonte BL, Johnson MK. Feature memory and binding in young and older adults. *Mem Cognit.* 1996; 24(4):403–16.
68. Butler T, Zaborszky L, Pirraglia E, Li J, Wang XH, Li Y, et al. Comparison of human septal nuclei MRI measurements using automated segmentation and a new manual protocol based on histology. *Neuroimage.* 2014; 97:245–51. DOI: 10.1016/j.neuroimage.2014.04.026 [PubMed: 24736183]
69. Ray NJ, Metzler-Baddeley C, Khondoker MR, Grothe MJ, Teipel S, Wright P, et al. Cholinergic Basal forebrain structure influences the reconfiguration of white matter connections to support residual memory in mild cognitive impairment. *J Neurosci.* 2015; 35(2):739–47. DOI: 10.1523/jneurosci.3617-14.2015 [PubMed: 25589767]
70. Ranganath C, Ritchey M. Two cortical systems for memory-guided behaviour. *Nat Rev Neurosci.* 2012; 13(10):713–26. DOI: 10.1038/nrn3338 [PubMed: 22992647]

71. Gratwicke J, Kahan J, Zrinzo L, Hariz M, Limousin P, Foltynie T, et al. The nucleus basalis of Meynert: a new target for deep brain stimulation in dementia? *Neurosci Biobehav Rev*. 2013; 37(10 Pt 2):2676–88. DOI: 10.1016/j.neubiorev.2013.09.003 [PubMed: 24035740]
72. Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *Cochrane Database Syst Rev*. 2012; 3:CD006504.doi: 10.1002/14651858.CD006504.pub2
73. Behl P, Edwards JD, Kiss A, Lanctot KL, Streiner DL, Black SE, et al. Treatment effects in multiple cognitive domains in Alzheimer's disease: a two-year cohort study. *Alzheimer's research & therapy*. 2014; 6(4):48.doi: 10.1186/alzrt280
74. Cavedo E, Grothe MJ, Colliot O, Lista S, Chupin M, Dormont D, et al. Reduced basal forebrain atrophy progression in a randomized Donepezil trial in prodromal Alzheimer's disease. *Sci Rep*. 2017; 7(1):11706.doi: 10.1038/s41598-017-09780-3 [PubMed: 28916821]
75. Kuhn J, Hardenacke K, Lenartz D, Gruendler T, Ullsperger M, Bartsch C, et al. Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. *Mol Psychiatry*. 2015; 20(3):353–60. DOI: 10.1038/mp.2014.32 [PubMed: 24798585]
- *76. Lee JE, Cho KH, Song SK, Kim HJ, Lee HS, Sohn YH, et al. Exploratory analysis of neuropsychological and neuroanatomical correlates of progressive mild cognitive impairment in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2014; 85(1):7–16. A longitudinal clinical observation study providing first in vivo evidence that MRI-measured cholinergic forebrain atrophy may predict imminent conversion to dementia in Parkinson Disease patients with MCI. DOI: 10.1136/jnnp-2013-305062 [PubMed: 23828835]
77. Berger-Sweeney J. The cholinergic basal forebrain system during development and its influence on cognitive processes: important questions and potential answers. *Neurosci Biobehav Rev*. 2003; 27(4):401–11. [PubMed: 12946692]
78. Woolf NJ. Cholinergic systems in mammalian brain and spinal cord. *Prog Neurobiol*. 1991; 37(6): 475–524. [PubMed: 1763188]
79. Ballinger EC, Ananth M, Talmage DA, Role LW. Basal Forebrain Cholinergic Circuits and Signaling in Cognition and Cognitive Decline. *Neuron*. 2016; 91(6):1199–218. DOI: 10.1016/j.neuron.2016.09.006 [PubMed: 27657448]
80. Bohnen NI, Kaufer DI, Hendrickson R, Ivanco LS, Lopresti BJ, Koeppe RA, et al. Degree of inhibition of cortical acetylcholinesterase activity and cognitive effects by donepezil treatment in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2005; 76(3):315–9. [PubMed: 15716518]
81. Risacher SL, McDonald BC, Tallman EF, West JD, Farlow MR, Unverzagt FW, et al. Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults. *JAMA Neurol*. 2016; 73(6):721–32. DOI: 10.1001/jamaneurol.2016.0580 [PubMed: 27088965]
82. Lauretani F, Meschi T, Ticinesi A, Maggio M. "Brain-muscle loop" in the fragility of older persons: from pathophysiology to new organizing models. *Aging Clin Exp Res*. 2017; doi: 10.1007/s40520-017-0729-4
83. Bohnen NI, Muller ML, Koeppe RA, Studenski SA, Kilbourn MA, Frey KA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. *Neurology*. 2009; 73(20): 1670–6. doi:73/20/1670 [pii] 10.1212/WNL.0b013e3181c1ded6. [PubMed: 19917989]
84. Bohnen NI, Frey KA, Studenski S, Kotagal V, Koeppe RA, Scott PJ, et al. Gait speed in Parkinson disease correlates with cholinergic degeneration. *Neurology*. 2013; 81(18):1611–6. doi:WNL.0b013e3182a9f558 [pii] 10.1212/WNL.0b013e3182a9f558. [PubMed: 24078735]
85. Ikonomic MD, Mufson EJ, Wu J, Cochran EJ, Bennett DA, DeKosky ST. Cholinergic plasticity in hippocampus of individuals with mild cognitive impairment: correlation with Alzheimer's neuropathology. *J Alzheimers Dis*. 2003; 5:39–48. [PubMed: 12590165]

Table 2 Take-home messages

- Loss of cholinergic neurons enhances the severity of clinical dementia symptoms and may result from loss of cholinergic control of neural networks subserving various cognitive functions.
- Vulnerability of the cholinergic forebrain may already occur in preclinical and prodromal stages of neurodegeneration
- Bidirectional changes in regional cerebral cholinergic receptor expression may reflect in part the effects of neural function losses in some regions and compensatory responses to maintain cholinergic function in other brain areas
- Multiplicative effects between cholinergic and dopaminergic losses may significantly contribute to dementia risk in PD
- Cholinergic system changes are more extensive in Lewy body disorders because of subcortical cholinergic degenerations that are relatively spared in AD.

BIOLOGICAL LAYERS OF DEMENTIA: CHOLINERGIC EFFECTS

Figure 1.

There are multiple layers of pathobiological mechanisms underlying dementia and a single layer of this multifactorial system cannot account for the complete dementia syndrome. As such, the cholinergic system is one among others that when it fails it may exacerbate cognitive deficits and worsens the severity of dementia. Although cholinergic neurotransmitter changes occur at the neuronal level, degeneration of the long axonal projections will affect regional cerebral circuits and network functions.

Table 1

Simplified model of dopaminergic and cholinergic interaction effects and cognition in PD illustrating the 'compensatory' hypothesis. This hypothesis is based on the observation that a substantial proportion of patients with no apparent cognitive deficits, including on executive tasks, despite significant dopaminergic denervation, had preserved cholinergic activity. In other words, intact fronto-parietal cortical cholinergic functions associated with top-down control may be recruited (increased cholinergic activity in cortical circuits) to compensate for executive dysfunctions associated with striatal dopaminergic declines, and vice versa.

Dopaminergic system	Cholinergic system	Cognition
↓	Preserved to increased	Attenuation or masking of cognitive deficits, esp. executive function deficits
↓	↓	Exacerbation of cognitive deficits, esp. executive function deficits