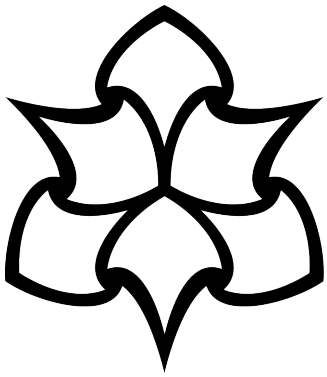

Recent advances in cholinergic imaging and cognitive decline – Revisiting the cholinergic hypothesis of dementia

Nicolaas I. Bohnen, MD, PhD[1,2,3,4]*, Michel J. Grothe PhD[5,6], Nicola J. Ray PhD[7], Martijn L.T.M. Müller PhD [1,4] & Stefan J. Teipel MD, PhD[5,6]

[1] Department of Radiology, University of Michigan, Ann Arbor, MI, USA
[2] Department of Neurology, University of Michigan, Ann Arbor, MI, USA
[3] Veterans Administration Ann Arbor Healthcare System, Ann Arbor, MI, USA
[4] Morris K. Udall Center of Excellence for Parkinson's Disease Research, University of Michigan, Ann Arbor, MI, United States
[5] German Center for Neurodegenerative Diseases (DZNE) - Rostock/Greifswald, Rostock, Germany
[6] Department of Psychosomatic Medicine, University of Rostock, Rostock, Germany
[7] Department of Psychology, Manchester Metropolitan University, Manchester, United Kingdom

*Corresponding author: N.I. Bohnen, MD, PhD; Functional Neuroimaging, Cognitive and Mobility Laboratory; University of Michigan; Domino's Farms, Lobby B, Suite 1000, Level I; 24 Frank Lloyd Wright Drive, Box 362; Ann Arbor, MI 48105-9755, USA
e-mail: nbohnen@umich.edu

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

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

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.

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 reported in Parkinson disease (PD) brains [5]. Arendt et al. found even greater forebrain neuronal loss in PD than in AD [6], suggesting that cholinergic deficits may be at least as prominent in PD as in AD. More 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 successful paradigm for the successful approval of cholinesterase inhibitors as a treatment for AD and later 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 highlight and clarify the role of the cholinergic system in cognitive impairment in the two major neurodegenerative disorders: AD and Lewy body disorders (LBD).

Imaging biomarkers and cognition

Imaging biomarkers of cognition are complex and include markers of a) proteinopathy, such as β-amyloidopathy, tauopathy or α-syncleinopathy, 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.

Neurotransmitter changes are particularly important in the setting of fluctuating cognitive symptoms. Molecular imaging methods, such as positron emission tomography (PET) or single photon computed tomography (SPECT) imaging studies allow assessment of the cholinergic neurotransmission system in the living brain. Magnetic resonance imaging (MRI) plays an important role in volumetric assessment of the cholinergic substantia innominate 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 β-amyloid plaques 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 cholinergic basal forebrain (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) provide the major cholinergic input of the hippocampus; cholinergic neurons of the horizontal limb nucleus of the diagonal band (Ch3) provide the major cholinergic input of the olfactory bulb; and cholinergic neurons of the NBM (or Ch4) provide the principal cholinergic input of the remaining cerebral cortex and amygdala [12]. The PPN, ulopontine nucleus (Ch5 cell group) and laterodorsal tegmental complex (LDTC, Ch6 cell group) supply cholinergic inputs to the cerebellum, several brainstem nuclei, thalamus, spinal cord 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 molecular imaging. Acetylcholinesterase (AChE) has been recognized since 1966 as 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. [^{123}I]IBVM and [^{18}F]FEOBV are SPECT and PET VAChT ligands, respectively. [^{11}IC]PMP and [^{11}C]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, [^{123}I]5IA and [^{18}F]flubatine are α4β2 nicotinic acetylcholine receptor (nAChR) SPECT and PET ligands, respectively. [^{123}I]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 [^{11}C]MP4A AChE PET study in healthy elderly reported that the integrity of the cholinergic system in the mesiotemporal region associated with verbal episodic memory delayed recall performance in healthy elderly [22]. The number of words forgotten after a 30 min delay period negatively correlated with AChE activity in the right posterior cingulate cortex, and frontal regions. A [^{11}C]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 the AD brain [26]. The degree of regional 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 substantia innominata, 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 basal cholinergic forebrain areas simultaneously occur 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 PD, 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 (innominatocortical), 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 acetylcholinesterase activity and about one sixth (18%) had below normal range thalamic acetylcholinesterase activity. Most patients with thalamic cholinergic hypofunction also had reduced cortical cholinergic activity implying a possible sequence effect where cholinergic losses in the forebrain NBM may precede PPN-thalamic 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 that a substantial proportion of patients with no apparent cognitive deficits, including on executive tasks, nevertheless had significant dopaminergic denervation in the setting of preserved cholinergic activity. These observation formed the basis for the 'compensatory' hypothesis [33] as also suggested by animal lesioning studies [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 (subcortical) 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 considered a key attentional mechanism that facilitates learning by focusing limited perceptual and cognitive resources on the most pertinent subset of the available sensory data. We found that thalamic cholinergic integrity predicted signal detection under perceptual challenge in PD [38]. The specific association with hits, and lack of relationship to correct rejections, supports the idea that the thalamic contributions are related to bottom-up signal salience, rather than top-down control of attentional selection. These results suggest that there are regionally-specific contributions of cholinergic function to different aspects of attention and behavior.

Cholinergic receptor imaging: Exploring brain networks

The previous discussed studies 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 have begun to unravel the heterogeneous involvement of several 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 α4β2 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 appear to decrease in healthy aging, but this decrease is accelerated in AD, with specific systems hit hardest, such as the default mode network (DMN) [43]. The DMN is generally thought to include the posterior cingulate cortex/precuneus, medial prefrontal cortex, inferior parietal lobules, lateral temporal cortices, and hippocampus [44]. It has been proposed

that activity of this network during rest is necessary for memory consolidation [45].

Alzheimer disease

A spatial covariance study of M1/M4 mAChRs in AD using [^{123}I]QNB SPECT showed concomitant decreased uptake in medial temporal, inferior frontal, basal forebrain and cingulate relative to concomitant increased uptake in frontal poles, occipital, pre-post central and precuneus/superior parietal regions [46]. The relative pattern could suggest a loss of M1/M4 receptors in the medial temporal and cholinergic rich basal forebrain, accompanied by either preservation or an increase in cortical M1/M4 receptor availability. These changes thus may reflect a compensatory response to maintain basocortical cholinergic function given that 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 α4β2 nicotinic receptors in AD using [^{123}I]5IA-85380 SPECT. They found an α4β2 spatial covariance pattern characterized by relative decreases in α4β2 binding in basal forebrain, pedunculopontine, thalamus, limbic, parietal, and frontal regions together with relative preserved or increased binding in midbrain, pallidum, cerebellum, occipital, and pre/post central gyri [48]. The covariant pattern converged on various subcortical and neocortical regions, implicating a cholinergic network that mapped onto DMN hubs, namely, medial prefrontal, posterior cingulate, precuneus, and inferior parietal [48]. This was characterized by reduced cholinergic activity. The reduced DMN activity of nAChRs was 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 node of the DMN, in patients with AD [49]. Other nAChR regions mapped onto established resting-state networks, included the anterior insula and anterior cingulate, which are key nodes of the “salience network”, for initiation of cognitive control and switching networks to aid 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, temporal, striatal, insula, and anterior cingulate together with concomitant preserved or increases in frontal and parieto-occipital areas in the patients [51]. The mAChR pattern that donepezil treatment benefits overlapped with frontoparietal and default mode networks. Covariant preservation/upregulation in regions overlapping key nodes of the DMN and frontoparietal networks could imply that a relative cholinergic maintenance of these networks may be prerequisite for cognitive remediation following cholinergic treatment in PD dementia [51]. Interestingly, a α4β2 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, insular cortex and the supplemental motor area 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 regions, 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 neurodegenerative disease [53-55] that also allow assessment of cholinergic degeneration across different cholinergic brain forebrain 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 with 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 are 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 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 therefore enables a better understanding of the role of CBFB degeneration in the cognitive sequelae of dementia syndromes [71], and could advance our knowledge of the mechanisms of cognition-enhancing cholinergic medications, 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 function [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 volumetric

measurement of the CBFB 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 AD 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 neural more extended 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 toward the cholinergic hypothesis in AD has considerably decreased over the last few decades, mostly because of the poor efficacy of the current AChE inhibitor treatments [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, novel 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 mechanism underlying dementia (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].

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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 neurodegeneration associated with

progressive declines across the spectrum of cognitive impairment in PD and typically occurs in the context of significant 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).

-- Insert Table 1 about here.

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 [82, 83].

Cholinergic systems appear to enable adaptation to injury even as they 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 acetyl transferase activity that may reflect a compensatory response to the progressive denervation of the hippocampus by lost entorhinal cortex input [84]. 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 proteineopathies 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 the loss of cholinergic system integrity and cognitive decline are intrinsically linked in AD and

LBD. It is evident that loss of cholinergic neurons enhances the severity of the symptoms 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.

Table 2 Take-home messages

- Loss of cholinergic neurons enhances the severity of the symptoms of dementia and may result from loss of cholinergic maintenance 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.

Human Rights All reported studies/experiments with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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Figure legend:

Figure 1

Diagram showing the multiple layers of pathobiological mechanisms underlying dementia. Cholinergic neurotransmitter changes occur at the neuronal level but 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 illustration 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, nevertheless had significant dopaminergic denervation in the setting of preserved cholinergic activity. In other words, 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