

Review

# Developmental origins of the age-related decline in cortical cholinergic function and associated cognitive abilities

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Received 23 April 2003; received in revised form 1 October 2003; accepted 14 November 2003

## Abstract

Ontogenetic abnormalities in the regulation of the cortical cholinergic input system are hypothesized to mediate early-life cognitive limitations (ECL) that later escalate, based on reciprocal interactions between a dysregulated cholinergic system and age-related neuronal and vascular processes, to mild cognitive impairment (MCI) and, subsequently, for a majority of subjects, senile dementia. This process is speculated to begin with the disruption of trophic factor support of the basal forebrain ascending cholinergic system early in life, leading to dysregulation of cortical cholinergic transmission during the initial decades of life and associated limitations in cognitive capacities. Results from neurochemical and behavioral experiments support the possibility that aging reveals the vulnerability of an abnormally regulated cortical cholinergic input system. The decline of the cholinergic system is further accelerated as a result of interactions with amyloid precursor protein metabolism and processing, and with cerebral microvascular abnormalities. The determination of the developmental variables that render the cortical cholinergic input system vulnerable to age-related processes represents an important step toward the understanding of the role of this neuronal system in the age-related decline in cognitive functions.

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*Keywords:* Aging; Cortex; Acetylcholine; Trophic factors; Ischemia; Amyloid precursor protein; Cognition

## 1. From early-life cognitive limitations to MCI and AD

Wide-ranging cognitive impairments do not represent a necessary correlate of aging (e.g., [190,191]). Rather, a subgroup of subjects whose cognitive abilities are about a standard deviation below the mean of the general population is largely responsible, in statistical terms, for the population-based effects of age on cognitive functioning. These subjects, diagnosed with “age-associated memory impairment” (AAMI; [35–38,96]), as “cognitively impaired but not demented” (CIND; [47]) or with “mild cognitive impairment” (MCI; [156]), are at least 50 years old and, depending on psychometric criteria and other inclusion criteria—which varied across studies—represent 15–35% of their age group (for a discussion of differences and similarities between these diagnostic entities see [142]). Most importantly, MCI (the diagnostic term used throughout this paper) now is increasingly accepted to be a precursor for Alzheimer’s disease (AD), as the majority of subjects with MCI progress to AD within a decade [54,64,140,143,156].

The “Nun Study” generated evidence in support of the suspicion that subjects who later develop MCI and AD exhibit cognitive limitations much earlier in life. Snowdon, Kemper and coworkers analyzed retrospectively the linguistic abilities of autobiographies completed at a mean age of 22 years and found that low idea density predicted, with high accuracy, poor cognitive performance and age-related dementia [89,191,192]. Other studies also reported evidence in support of the general idea that early cognitive status is a more valid predictor of late-life cognitive abilities than is education, occupation and life experiences [48,158]. Collectively, these data provide at least preliminary support for a scenario that conceptualizes the age-related decline in cognitive abilities as an age-related escalation of early-life cognitive limitations (ECL; see Fig. 1), therefore raising the question about the neuronal foundations of such early cognitive limitations, and the age-related neuronal processes that interact with already vulnerable neuronal systems to result in MCI and AD (below).

The scenario illustrated in Fig. 1 also suggests that correlations between levels of education, cognitive activity, and the onset and progression of age-related cognitive decline [106,186] are subject to alternative interpretation.

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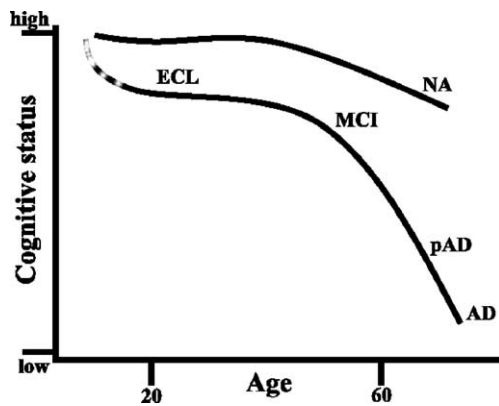


Fig. 1. Schematic illustration of a scenario that describes a progressive escalation of early-life cognitive limitations (ECL) to mild cognitive impairments (MCI), possible Alzheimer's disease (pAD) and AD. This figure was inspired by Fig. 1 in Petersen et al. [155], and was modified and extended to include ECL and to describe a non-linear progression of the age-related decline in cognitive status. The ordinate depicts "high" and "low" cognitive status with respect to each age group. ECL is hypothesized to be mediated via a suboptimal maturation and regulation of the basal forebrain ascending cholinergic system. The age-related progression of the decline in cognitive status is a result of interactions between age-related neuronal processes and the vulnerable cholinergic system (see text). The figure also shows a trace depicting the course of the cognitive status during "normal aging" (NA). Several constraints apply to comparisons between the decline during normal aging versus MCI and AD, specifically the fact that the cognitive domains affected by normal aging are largely limited to attentional capacities and related executive functions, while semantic memory and perceptual representation systems are less affected by normal aging [109,132,155,177]. Evidence in support of the distance between the traces during early and middle life are discussed in the text. Subjects with MCI typically do not differ from age-matched controls with respect to standard psychometric screening tests and global measures of cognition but exhibit impairments in measures of attentional functions and memory [20,67,153]. Thus, the trace depicting the cognitive decline in normal aging assists in illustrating the present discussion, but direct comparisons between the two traces require qualification.

In contrast to the conventional notion that high levels of education and persistent cognitive activity protect against age-related decline in cognitive functions, ECL may represent a main variable that acts to limit the likelihood of a career requiring higher education and demanding levels of cognitive activity. The biographical examples cited by Snowden ([191], pp. 100–111) impressively illustrate the dramatic differences between high and low levels of grammatical complexity and idea intensity, and they vividly exemplify the power of these measures to indicate intellectual capacity, and to predict such capacity in late life [192].

The discussion below will focus on *neuronal interactions* between age-related neuronal and vascular processes and a vulnerable cholinergic system to explain the decline in cognitive status in subjects developing MCI and AD. The escalating cognitive consequences of ECL per se may, at least in part, explain the progressive nature of cognitive impairments. Reduced grammatical complexity and idea density reflect an overall limited cognitive state, specifically

the limited processing resources available for manipulating multiple items in working memory (e.g., [138]). The escalating consequences of such limitations, in the course of five to six decades of life, may be sufficient to explain emerging weaknesses in the ability to acquire and rehearse new information and network it into long-term memory, and subsequently to recall stored information. Furthermore, and as will be discussed below, the long-term consequences of an incompletely matured basal forebrain cholinergic system, specifically for brain vascular functions, trophic mechanisms, and amyloid precursor protein (APP) processing, may represent a sufficient basis to explain the cognitive decline of MCI and early AD. This hypothesis focuses on the dynamic, life-long consequences of early abnormalities in the regulation of the cholinergic system and cognitive functions, and therefore contrasts with explanations of age-related cognitive decline that are based on more acute and abruptly emerging neuropathological processes occurring in aged subjects.

## 2. Age-related decline in cognition and the cholinergic system: matters of debate

The present discussion focuses on neuropathological and neuropsychological processes hypothesized to explain the decline in cognition in MCI and AD patients as the end result of the disruption of the development and maturation of the basal forebrain cholinergic system. Alternative hypotheses, based on evidence indicating that cortical (glutamatergic) neurons degenerate early in AD [68], or that cortical tau pathology and amyloid plaque deposition precede AD [116,120,121] eventually may be integrated, rather than contrasted, with the present hypothesis to generate a complete theory about the neuronal mechanisms mediating the transitions between intact cognitive state, MCI and AD.

The experimental and neuropathological evidence in support of the general hypothesis that decline in the basal forebrain (BF) ascending cholinergic system contributes significantly to the age-related impairments in cognitive abilities has been extensively reviewed (e.g., [11]), and thus is not summarized here. However, several main issues relevant to the present hypothesis, and which have represented the main bases for criticisms or even rejection of this hypothesis, will be discussed (see also [11] for additional discussion of related issues). This discussion centers primarily around two central questions. First, what are the exact cognitive functions mediated via the BF ascending cholinergic projections, and to what degree can the age-related decline in cognitive abilities, or even the dementia in AD, be explained sufficiently as a result of dysregulation and decline in the integrity of the basal forebrain cholinergic system? Second, what are the limitations of conclusions derived from relevant psychopharmacological research approaches? Each of these questions is addressed below.

### 2.1. Cognitive functions of cortical cholinergic inputs

Extensive evidence, ranging from experiments assessing the effects of loss of cortical cholinergic inputs on cognitive performance, to studies assessing cortical acetylcholine (ACh) release or changes in ACh-mediated neuronal activity in task-performing animals, has substantiated the general hypothesis that cortical cholinergic inputs primarily mediate attentional processes and capacities [29,49,173,176,178,212]. For example, selective loss of cortical cholinergic inputs, produced by infusions of 192 IgG-saporin into the basal forebrain or the cortex, results in impairments in a wide range of attentional abilities, ranging from sustained attention to divided attention [110,206]. Likewise, processing capacity as assessed by a span-task is disrupted by loss of cortical cholinergic inputs [207]. Studies in which cortical ACh efflux was measured while animals perform tasks taxing attentional capacities demonstrated attentional demand-associated increases in cortical ACh efflux [5,41,80]. Furthermore, distractor-induced increases in attentional demands were demonstrated to alter ACh-mediated prefrontal cortical (PFC) activity, indicating that cholinergic inputs in the PFC specifically mediate the filtering of non-signal information [62].

### 2.2. Attention and memory

Given the specific attentional functions attributed to the cortical cholinergic input system, and the limited or complete lack of effects of selective cholinergic lesions on memory performance in animals tested in conventional maze and other memory tasks (e.g., [13,204,215]), the question arises as to whether a loss of cortical cholinergic inputs is necessary, let alone sufficient, to explain age-related cognitive decline, particularly the impairments in memory in early AD. There are multiple answers to this important question.

In humans, aging is associated with decline in all aspects of attentional functions, ranging from sustained [43,61,145] to divided attentional processes and capacities [22,34,39,93,129,149,177]. The attentional abilities of subjects with MCI have not been extensively studied, except for psychometric measures (such as performance in the Digit Span subtests of the Wechsler Memory Scale) which provide only limited insight into the actual nature of the alterations in attentional processes [63,200]. However, evidence suggests that attentional impairments robustly manifest in memory-impaired, non-demented subjects or subjects with mild dementia, and they may serve as a predictor of subsequent AD [9,130,146,148,151,154,201]. Furthermore, non-demented, middle-aged carriers of the  $\epsilon 4$  allele of the APOE gene, which increases the risk for AD and is associated with decreased cortical and hippocampal ChAT activity [159], already exhibit significant deficits in visual attentional abilities that were qualitatively similar to those with AD ([74]; however, see also [33]).

Concerning AD, major disruptions in attentional performance represent an expected component of the overall cognitive deterioration. While there is evidence for the sparing of certain attentional capacities in subgroups of patients with early AD [170], impairments in attentional capacities appear to be a general cognitive characteristic of early AD, specifically with respect to attentional resources available for the division of attention. Such impairments have been hypothesized to contribute causally to the cognitive decline in these patients [9,53,73,128,146–148,151,152,162,188].

The hypothesis that early dysregulation of the activity of basal forebrain cholinergic neurons mediates early attentional impairments which later escalate to affect learning and memory remains a debated hypothesis [151]. However, limitations in the ability to select relevant stimuli (and associations) and to filter noise and irrelevant inputs, and limitations in the available processing resources or resource allocation strategies, weaken the efficacy of encoding [133,149] and rehearsal, and thus memory [2,3,179]. The relationships between attentional demands and learning and memory are complex, and conflicting results concerning the impact of age-related attentional impairments on memory [137], specifically when based on animal experiments [179], may be related to variable degrees to which attentional demands were taxed and/or to which memory tests assessed controlled, effortful processing and encoding of information. The alternative to this hypothesis is to suggest that impairments in learning and memory are unrelated to attentional dysfunctions, and that additional neuropathological processes and events are necessary to expand the spectrum of attentional impairments into the domains of learning and memory. For example, degeneration of efferent cortical and hippocampal projections, or multiple ischemic events, may be required to produce deficits in memory functions [15,75]. As will be discussed further below, such additional neuropathological processes can be described, at least in part, as secondary to the dysregulation of cortical cholinergic transmission.

Thus, in the aggregate, the question of whether the early attentional impairments that are closely associated with dysregulation in and, eventually, loss of, cortical cholinergic inputs are sufficient to explain the age-related decline in cognition, remains undecided. Tests of this hypothesis require integration of the relationships between attention and memory, and a framework that accounts for the escalating nature of persistent attentional limitations. Finally, it must be noted that the relationships between attentional processes and memory are bidirectional, because impairments in memory in turn affect knowledge-based optimization of attentional processing. Such “top-down” regulation of attentional capacities also appear to depend on the integrity of cortical cholinergic inputs, particularly of prefrontal regions, and their modulation, via cortico-cortical connections and connections via the BF, of posterior cortical regions [66,178]. Thus, more comprehensive and dynamic accounts of the cognitive consequences of dysregulation of cortical cholinergic

inputs are emerging, and such consequences include impairments in a wide range of executive functions [17,56,57,150].

### 2.3. Arguments based on psychopharmacological evidence

Another frequently raised objection against the “cholinergic hypothesis” concerns the fact that the cognitive effects of systemically administered muscarinic antagonists (scopolamine, atropine) in intact subjects do not reflect the spectrum of impairments observed in AD. However, the acute effects of these drugs do not model the mounting consequences of years and decades of dysregulation of forebrain cholinergic transmission or even cholinergic cell loss. In fact, chronic blockade of cholinergic receptors would provide a more appropriate psychopharmacological model. The robust impairments in attentional abilities and in the learning of new information that are produced already by acute cholinergic receptor blockade allows the safe prediction that chronic blockade would have devastating and comprehensive cognitive consequences, particularly in older subjects (see also [117]).

Furthermore, the limited beneficial cognitive, particularly attentional effects of cholinesterase inhibitors in patients with AD [171] may reflect the fact that the effects of these drugs do not enhance or re-instate the phasic activity that characterizes cortical cholinergic signal transmission [171,175]. Additionally, post-synaptic signaling mechanisms are also disrupted in AD [55] and may limit the efficacy of such treatments. Therefore, the restricted therapeutic usefulness of traditional cholinomimetic drugs may be considered an expected finding, rather than forming the basis for a rejection of the central contributions of abnormal cholinergic transmission to the manifestation of the cognitive impairments associated with aging and AD [199].

### 2.4. What about the septo-hippocampal cholinergic system?

The reasons why we have elected to not integrate the septo-hippocampal cholinergic system into this discussion need to be addressed. Although the available data are somewhat heterogeneous, the regulation and integrity of septo-hippocampal cholinergic projections appear to be affected by normal aging and AD, although possibly to a smaller degree than cortical cholinergic inputs [45,58,59]. However, the functions of the cholinergic septo-hippocampal projection have remained unclear as, for example, selective lesions of this system do not result in robust cognitive effects [10,25,46,82,185], including attentional performance [180]. Thus, in the absence of a specific hypothesis about the cognitive functions of septo-hippocampal cholinergic projections, it appears difficult to integrate this neuronal system into a hypothesis that relates an aging, vulnerable neuronal system to a defined decline in cognitive functions.

This discussion of critical aspects of the “cholinergic hypothesis” indicates that it entails considerable cognitive and neuropsychopharmacological complexities that have been rarely captured by the numerous recent discussions about its validity and demise. As discussed next, regulation of cholinergic neurons by trophic factors is disrupted in MCI, and this evidence corresponds with the general idea that such a disruption initiates the emergence of an imperfectly functioning basal forebrain cholinergic system and associated cognitive decline. The discussion will then focus on how a declining cholinergic system contributes to the disruption of the neurovascular regulation and the formation of amyloid plaques. These secondary consequences of an abnormally developed cholinergic system in turn contribute to the accelerating decline of the function and integrity of this neuronal system.

## 3. Dysregulation of BF cholinergic neurons in MCI

There is now ample evidence in support of the hypothesis that cholinergic neurons in MCI are not normally regulated. Mufson et al. [124,126] reported that in MCI, the number of neurons in the nucleus basalis showing immunoreactivity for trkA, the high-affinity receptor for nerve growth factor (NGF), as well as neurons immunoreactive for the low-affinity p75 NGF receptor, are significantly decreased when compared to non-cognitively impaired subjects (NCI). Moreover, the number of immunoreactive neurons in MCI was statistically similar to the low number of trkA- or p75-immunoreactive neurons counted in AD. In situ hybridization confirmed that the number of neurons expressing trkA is decreased in MCI and is indistinguishable from AD [30]. Furthermore, the number of neurons in the nucleus basalis bearing NGF receptors correlated with the cognitive status of the subjects in these reports [30,124,126].

DeKosky et al. [45] recently reported that cortical choline acetyltransferase (ChAT) activity is unchanged in subjects with MCI when compared with subjects with no cognitive impairment (NCI), and in fact is increased in hippocampal regions and the superior frontal cortex. As DeKosky et al. point out, ChAT activity does not represent the rate-limiting step in the synthesis and release of acetylcholine (ACh). Changes in ChAT activity likely indicate substantial changes in the density of presynaptic cholinergic terminals. Accordingly, in animal studies, ChAT activity changes are a poor predictor of changes in the regulation of ACh release, specifically in terms of the capacity of (residual) cholinergic neurons to respond to behavioral or pharmacological challenges (see the discussion in [174]). While DeKosky et al. consider the absence of decreases in ChAT activity in MCI an unexpected result, this result appears to be predicted by previous studies indicating no decline in the number of ChAT-immunoreactive neurons in the basal forebrain of subjects with MCI [63]. Other studies likewise did not observe significant reductions in

cortical ChAT activity in patients with mild or moderate AD [202].

Although the exact status of cholinergic transmission in the forebrain of subjects with MCI is unclear, the available data hardly challenge the cholinergic hypothesis, as suggested by Morris ([119]; see also [5]). The striking decrease in trophic receptor density indicates that trophic receptor signaling is dysfunctional, while the actual number of cholinergic neurons and cortical terminals may remain normal at this point. Emerging PET [107] or SPECT [135,136] methods to monitor cholinergic activity may provide insights into the dynamic, functional properties of cholinergic neurons in MCI.

Until such evidence arrives, we can only speculate, on the basis of experimental data, about the consequences of disrupted trophic factor support for the functions of cortical cholinergic inputs [28,91,92]. Generally, the development, differentiation and survival of cortical cholinergic inputs depend on NGF. The exact effects of NGF via p75 and trkA receptors, and their potential interactions, have remained complex (e.g., [123]), particularly in light of evidence indicating that trkA and p75-mediated signaling are mutually repressing [21]. However, transgenic mice that express a neutralizing anti-NGF recombinant antibody exhibit, as they age, extensive loss of cholinergic neurons ([26]; see also [28]). Likewise, removal of the cortical source for NGF produces atrophy of cholinergic neurons, although the degree to which the number of ChAT-positive neurons is decreased remains disputed [27,195]. Furthermore, such lesions reveal age-related vulnerabilities in the integrity of residual cholinergic system [31,196]. The attenuation of age-related effects on the integrity of the cholinergic system by exogenous NGF supply [90,92] may in part be due to NGF-induced upregulation of trkA receptors [91,98,187].

The consequences of decreases in the density of both trkA and p75 receptors, that is observed in MCI (above), are difficult to predict, specifically because of their complex, reciprocal interactions [194]. However, the overwhelming evidence indicates that trkA-mediated signaling is crucial for the development, maturation and function of cholinergic neurons. trkA protein is upregulated during critical postnatal periods for cortical plasticity [166], and this upregulation is controlled by NGF [98,218]. In trkA knockout mice, basal forebrain cholinergic neurons do not fully mature and begin to atrophy during the early weeks of postnatal life [50]. Furthermore, in mice with segmental trisomy of chromosome 16, which model major aspects of Down's syndrome, decreases in basal forebrain trkA immunoreactivity predict behavioral and cognitive impairments [72]. In contrast, the absence of p75 receptors increases the number of cholinergic neurons, supporting its role in causing cell death in development [127].

Speculations about the origin of potential early life disruption of trophic factor support in patients which subsequently develop MCI and AD remain unsubstantiated. Although cortical NGF protein levels appear strongly regulated by cholinergic

inputs themselves [169], NGF levels are not decreased in MCI or AD [51,122,125]. Thus, it is not clear whether the long-term consequences of a disruption of trophic factor support early in life are due to a possibly transient disruption of NGF supply, to a disruption in retrograde transport of trophic factors [32,94,122], or to a primary defect in the expression of trophic factor receptors by cholinergic neurons [123]. Mufson et al. [122] have proposed a scenario which begins with a defective expression of trkA receptors, a subsequent trafficking defect, and a resulting dominance of p75-mediated apoptotic cell death. This scenario is extended by the suggestion that cholinergic neurons, to use a phrase by Mufson et al. [122], are “off-trk” early in the life of patients that later develop MCI and AD. Moreover, such early limitations in the maturation of the cholinergic system are hypothesized to mediate early cognitive deficiencies (above). In addition to the potential consequences of pre- or postnatal disruption of trophic factor support, long-term organizational consequences have also been observed following other prenatal and postnatal manipulations, particularly choline deficiency and supplementation [19,76,114] or exposure to irreversible acetylcholinesterase inhibitors [160]. Collectively, these experiments support the general notion that manipulations of the development and maturation of the cholinergic system lastingly affect its structure and function. The present hypothesis suggests that, based on interactions with other neuropathological mechanisms (below), aging renders a defectively maturing cholinergic system to become increasingly dysfunctional and eventually to degenerate.

#### **4. Detrimental interactions between a declining basal forebrain cholinergic system and amyloid precursor protein (APP) processing**

The loss of cholinergic neurons is sufficient to increase expression and to reduce secretion of, and thus to increase membrane-bound, APP [77,100,167–169,214]. Furthermore, lesions of cholinergic neurons increase the cerebral deposition of the neurotoxic APP product, amyloid- $\beta$ -peptide (A $\beta$ ) [15,16,163]. The secretory processing of APP is under muscarinic receptor control [14,134,183]. A $\beta$  directly and negatively modulates cholinergic transmission, by inhibiting the rate-limiting step for ACh synthesis and high-affinity choline uptake [7,8,87,88,157], and by blocking  $\alpha$ 7-nicotinic receptor signaling [103,157]. A $\beta$  may destroy cholinergic neurons based on diverse neurotoxic mechanisms, including excitotoxic processes and lipid peroxidation [24,77]. Thus, escalating, bidirectional interactions between the disintegration of the basal forebrain system and APP metabolism and processing accelerate the decline of the cholinergic system ([205]; see Fig. 2).

The close, reciprocal and destructive interactions between A $\beta$  and the cholinergic system provide the basis for new perspectives on the long-standing question about the primary neuropathological process [65,84,131,182,190].

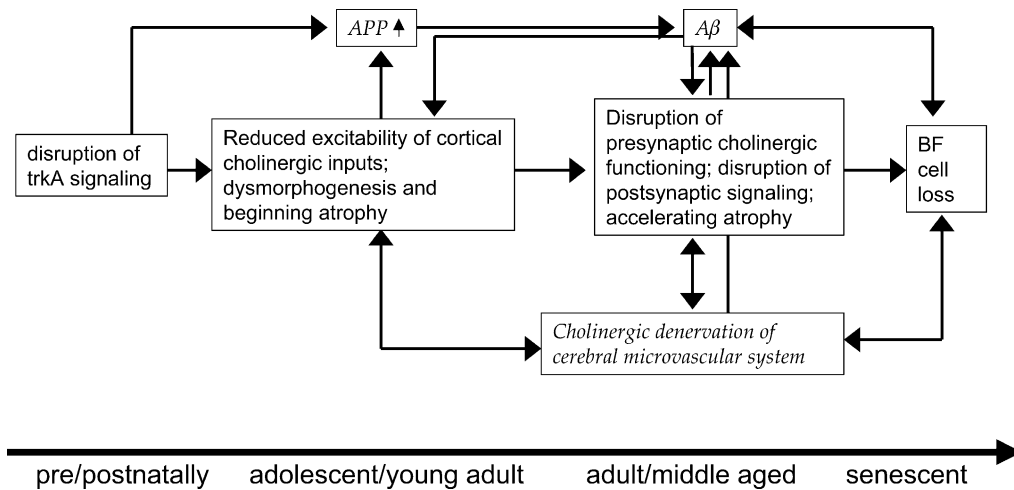


Fig. 2. Schematic summary of the main hypothesis. The diverse cellular mechanisms mediating the consequences of early-life disruption of trophic factor signaling, and the interactions between APP metabolism and processing, cholinergic denervation of the cerebral microvascular system and the declining cholinergic system, symbolized by arrows, are discussed in the main text. Furthermore, the escalation of cognitive impairments per se is discussed, as are the crucial relationships between the regulation and integrity of the cortical cholinergic input system and cognitive functions.

Early cholinergic dysfunction may be a necessary step in triggering pathological APP processing; however, in mice expressing a Swedish mutation of the human APP, cholinergic dysfunction is observed before the onset of plaque deposition [4], supporting prior reports that low concentrations of soluble A $\beta$  suffice to affect cholinergic function. Moreover, the cognitive decline in MCI and AD is most robustly and selectively predicted by decreases in cortical and hippocampal ChAT [12,141,144] as well as soluble A $\beta$  levels [111], further indicating a close relationship between these two measures (see also [15]).

This relationship becomes even more intricate in light of the accumulating evidence indicating that trkA receptor activation, possibly depending on complex interactions with p75 receptor activation, regulates APP metabolism [167]. The effects of loss of trkA receptor-mediated NGF signaling for the regulation of APP expression and secretion are not clear, but reduced secretion could be assumed to promote the production of amyloidogenic APP products. Thus, the interactions between a dysregulated and, at later stages, degenerating cholinergic system and APP processing may arise directly from an early disruption of trophic factor support of cholinergic neurons.

##### 5. Bidirectional interactions between the cholinergic denervation-induced disruption of the cerebrovascular system and ischemic events

In recent years, it has been increasingly recognized that a substantial proportion of cases with AD (60–90%), exhibit cerebrovascular pathology and thus are in fact mixed dementias ([85,189]). Furthermore, at least 1/5th of subjects with MCI develop vascular dementia [115], supporting the gen-

eral idea that the acceleration of the cognitive decline and its underlying neuropathology involve vascular dysfunction, or are even mediated by such [219]. In fact, transient ischemic attacks (TIAs), also sometimes termed “ministrokes”, have been proposed to act as a significant causal co-factor in the emergence of the cognitive decline in AD [139,193], and decreases in cortical blood flow predict the degree of the cognitive impairment [118]. The recent finding that increased plasma homocysteine levels are a profound risk factor for dementia and AD corresponds with these hypotheses [42,184].

Cerebral blood vessels are directly innervated by BF cholinergic neurons [104,105,210] and are also regulated indirectly by cholinergic neurons via nitric oxide interneurons [211]. The potency of ACh to dilate cerebral blood vessels appears to be mediated via M5 muscarinic [216] and nicotinic receptors [40,44,102,208]. BF stimulation increases cerebral blood flow [1,18,95] and, notably, aging robustly delays the stimulation-induced maximum increase in cerebral blood flow [101], possibly reflecting the reduced vasodilative capacity of the aging BF cholinergic system [209]. Immunotoxin-induced lesions of the cholinergic system produce widespread decreases in cerebral blood flow [213], although the specific contributions of the BF system to these effects remain debated [181]. Importantly, in AD, a severe cholinergic denervation of cortical microvessels has been documented, and found to be proportional to the loss of cholinergic axons in cortical regions [203]. Tong and Hamel also reported a significant increase in the luminal diameter of the denervated microvessels in AD.

An impaired capacity of the cholinergic system to dilate the cerebral microvascular system has complex consequences, ranging from inadequate increases in cerebral blood flow in response to increased cognitive activity, to limited compensatory reactions of microvessels to unusual

variations in blood flow and to ischemic events. For example, the delayed degeneration of cortical neurons following occlusion of the carotid artery is attenuated by stimulating the BF during the period of occlusion [83]. Thus, ischemic attacks would be expected to result in a substantially greater degree of ischemia-induced neuron loss in the brains of subjects with a dysfunctional BF cholinergic system.

The disruption of the integrity of the microvascular system contributes to a chain of events that leads to impaired neuronal metabolism, dysregulation of neuronal systems and loss of neurons, and cognitive failure [52]. Several scenarios have been offered to explain how TIAs or microvascular disorder yield degenerative consequences and, in the long-term AD, including the suggestion that ischemic attacks induce the accumulation of A $\beta$  and tau-like pathology. Moreover, cerebrovascular disease triggers the production of excitotoxic and inflammatory mediators and thus may directly contribute to the degenerative process in dementia [42,70,71].

Cholinergic neurons represent a neuronal population that is particularly vulnerable to ischemic events, based in part on interactions with age-related decreases in the Ca<sup>2+</sup>-buffering capacity of these neurons [4,7,60,86,205], and because of the extraordinarily high energy consumption of these neurons, specifically as required for mitochondrial acetyl-CoA synthesis [78,197]. In the spontaneously hypertensive stroke-prone rat (SHspR), TIAs have been found to affect the integrity of the basal forebrain cholinergic system. Our studies on the consequences of microsphere embolism on the integrity of the cholinergic system confirmed that such blockade of the microvascular structure results in the loss of cortical cholinergic inputs, primarily in the prefrontal cortex and the outer layers of frontoparietal regions ([108]; see also [99,198]).

The worse and more rapidly declining cognitive abilities in mixed dementias when compared to “pure” Alzheimer’s disease have been hypothesized to be due to a more severely affected and more rapidly declining cholinergic system (for review see [85]). Thus, the available data suggest escalating, reciprocal interactions between the consequences of an abnormally regulated cholinergic system for cerebral microvascular functioning and vulnerability for ischemic events, and the detrimental consequences of ischemic events for the cholinergic system. These detrimental interactions are further amplified by the accumulation of A $\beta$  (see above), because cerebral ischemia increases APP expression and facilitates the cleavage of A $\beta$  from APP, and because APP overexpression augments the effects of ischemic events [139,217,220].

## 6. Limitations of the hypothesis

The present hypothesis suggests that early disruption of trophic factor signaling results in abnormal regulation of the excitability of cholinergic neurons, triggering and amplifying neuronal and vascular pathological mechanisms that in

turn accelerate the decline in the regulation and integrity of cholinergic neurons. Furthermore, this model describes the neuronal basis of ECL, and the progression of the cognitive decline to MCI and AD. Although there is empirical substantiation for the components of this model based on data from patients with MCI and early AD, and although there is some evidence in support of ECL as an early precursor of MCI and AD, the model remains speculative with respect to the assumption that a disruption of trophic factor signaling early in life mediates ECL and, more generally, represents a trigger that is sufficient for the activation of the scheme summarized in Fig. 2. However, the evidence obtained from *trkA* knockout mice and mice with segmental trisomy of chromosome 16 (Ts65Dn) can be interpreted as indicating that loss of *trkA* receptors suffices to disrupt the maturation of cholinergic neurons and eventually to yield degenerations of BF neurons ([50,72]; see above). Furthermore, to the degree that neonatal lesions of the cholinergic system model a defective maturation of this system, their long-term consequences include a disruption of the development of cortical organization [161,164] and thus point to potentially crucial secondary effects of an abnormally regulated cholinergic system (see also [81]).

The reasons responsible for a putative, early disruption of trophic receptor expression and functioning or trophic factor trafficking are completely unclear. As this hypothesis focuses on disruption of *trkA* receptor-mediated trophic actions, it also ignores the roles of other neurotrophin gene molecules, particularly brain-derived neurotrophic factor (BDNF) and neurotrophins, and their *trk* receptors (e.g., [79,172]).

It is presently difficult to conceive how evidence indicating an early disruption of trophic factor support of cholinergic neurons in subjects which later develop MCI and AD could be generated, and thus, the heuristic significance of this hypothesis is based mainly on its usefulness in guiding animal experimental testing. For example, *trkA* receptor expression can be attenuated, using transgenic animals (above) or by lesioning of cortical neurons by the time presynaptic cholinergic terminals appear to become functional [6] and cholinergic projections make contact postnatally [69,112,113]. We have observed that multiple injections of ibotenic acid into frontal cortical regions of rats aged 4–5 weeks suppressed *trkA* receptor immunoreactivity in the basal forebrain of adult rats (Burk and Sarter, unpublished preliminary findings; see also [27,98]). Such manipulations may be useful to test hypotheses concerning the mechanisms which contribute to the escalating decline in the integrity of the cholinergic system following developmental disruption of trophic factor support (Fig. 2). Furthermore, they may be instrumental for the demonstration that attentional impairments manifest early in life as a result of such a manipulation and while the cortical cholinergic input system remains morphologically intact, and that such impairments accelerate as these animals age. We know already that a limited loss of cortical cholinergic inputs in

young-adult animals does not produce acute impairments in attentional performance but precipitates robust impairments as these animals reach 85% of the maximal life span [23]. The present hypothesis predicts that, following a postnatal disruption of *trkA* receptor expression, young-adult animals already exhibit impairments in attentional performance, at least when tested under the condition of high demands on attentional processing. Longitudinal studies assessing these animals' performance, the regulation and integrity of the cholinergic system, and APP processing and the status of the microvascular system, would begin to test the present hypothesis. Moreover, experimental manipulations of the capacity of the aging microvascular system and APP processing in the aging brain would test the bidirectional interactions between an abnormally and disintegrating cholinergic system, APP processing, and vascular capacities.

The present hypothesis assumes a developmental psychobiological perspective on research on the neuronal foundations of the decline in cognitive functions in a subset of subjects. Such perspectives have already evolved in the context of research on the neuronal foundations of schizophrenia and other brain disorders [97,165]. The determination of developmental variables may explain why only a subgroup of subjects undergoes substantial age-related impairments in cognitive function and disintegration of the basal forebrain cholinergic system. The initially rather slowly progressing consequences of abnormal maturation of the cholinergic system accelerate during aging, in part due to interactions with evolving microvascular dysregulation and the modulatory and toxic effects of amyloid peptides. In general, this perspective suggests that a better understanding of the neuronal mechanisms mediating the age-related decline in cognitive functions will be gained from animal models on age-related consequences of abnormal neurogenesis.

## Acknowledgments

The authors' research was supported by PHS grants AG10173, NS37026, MH063114, and MH057436.

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