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Review

The cholinergic hypothesis of cognitive aging revisited again: Cholinergic functional compensation

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ABSTRACT

It is now possible to reevaluate the cholinergic hypothesis of age-related cognitive dysfunction based on a synthesis of new evidence from cholinergic stimulation studies and cognitive models. We propose that a change of functional circuitry that can be observed through a combination of pharmacologic challenge and functional neuroimaging is associated with age-related changes in cholinergic system functioning. Psychopharmacological manipulations using cholinergic agonists and antagonists have been consistent in replicating patterns of aging seen in functional imaging studies. In addition, studies of anticholinesterase drugs in patients with Alzheimer's disease and mild cognitive impairment show support for the proposal that cholinergic compensation causes alterations in task-related brain activity. Thus, the cholinergic hypothesis of age-related cognitive dysfunction deserves further consideration as new methodologies for evaluating its validity are increasingly being used. Future directions for testing hypotheses generated from this model are presented.

Contents

The cholinergic system is the primary neurotransmitter system responsible for cognitive symptoms in dementia and possibly normal aging (Bartus et al., 1982). The cholinergic hypothesis of geriatric memory dysfunction proposed in 1982 by Bartus et al. (1982) hypothesizes that functional disturbances in cholinergic activity occur in the brains of healthy older adults and demented patients and that these disturbances play a role in memory loss and related cognitive problems. Thus, restoration of cholinergic function may reduce the severity of the cognitive loss. This hypothesis has been supported by the finding that cholinesterase inhibitors show positive effects on cognition in Alzheimer's disease (AD) patients (e.g., Hansen et al., 2008). Much clinical development research on cholinergic agents has followed since the initial proposal and although the overall clinical effects are limited, the cognitive enhancers used to modulate cholinergic functioning remain the most widely used medications that have been approved for use in AD.

However, since Bartus' original proposal there have been significant advances in understanding how changes in the cholinergic system affect cognition. This paper evaluates more recent attempts to enhance cognitive function with cholinergic agents and reinterprets the underlying hypothesis regarding the influence of cholinergic system on cognitive dysfunction and dementia. With the increased use of brain

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functional magnetic resonance imaging (fMRI) in combination with psychopharmacological treatments, data patterns have emerged that further define the role of the cholinergic system in cognition, aging, and dementia. First, we present the evidence for the role of the cholinergic system in cognition based on more recent pre-clinical and human-based studies. Then, we review the literature on pro-and anti-cholinergic drug effects on brain activation. Next we present a model that integrates the brain imaging data with psychopharmacological manipulations to examine the effects of aging and dementia on cholinergic functioning. We detail how this model produces testable hypotheses about the effects of cholinergic modulation on cognition and related brain activation in healthy aging and dementia. Finally, we show how this model can be used to guide imaging and drug development studies utilizing not only cholinergic strategies, but other interventions to improve cognitive aging as well as age-related disorders such as AD.

1. Cholinergic influences on human cognitive performance

Initial support for the cholinergic hypothesis came from four areas of research. First, studies by Drachman and colleagues (Drachman and Leavitt, 1974; Drachman, 1977) showed that temporary blockade of muscarinic cholinergic receptors produced impairments of learning and memory that resembled changes associated with normal aging (Ghoneim and Mewaldt, 1977; Peterson, 1977). Second, Whitehouse et al. (1982) showed that there is a loss of cholinergic neurons in the basal forebrain in Alzheimer's disease patients, thus providing anatomical evidence supporting the hypothesis that loss of cholinergic neurons is responsible for the cognitive impairments in dementia. Third, modeling with anticholinergic drugs in AD patients, normal elderly, and elderly depressed patients showed that muscarinic and nicotinic blockade reproduced substantial elements of age- and disease-related impairments in cognitive functioning (Newhouse et al., 1992, 1994, 1988; Sunderland et al., 1986). Finally, procholinergic drugs have been successful in the slowing the progression of the cognitive symptoms of AD (e.g., Davis et al., 1992).

Perhaps partly because cholinergic treatments for AD have modest effects and partly because of the limited tools accessible to study the cholinergic system, the cholinergic hypothesis of geriatric memory dysfunction has fallen out of favor since it was originally proposed in 1982. Simply enhancing cholinergic function does not stop the disease process in AD. In normal aging, procholinergic drugs such as cholinesterase inhibitors have not been successful in reversing normal age-related cognitive deficits (Drachman et al., 1982). Models of muscarinic cholinergic blockade in normal older adults did not replicate all of the cognitive deficits in AD (e.g., Beatty, 1986). Research with muscarinic and nicotinic cholinergic manipulations in healthy subjects (e.g., Newhouse et al., 2001; Warburton and Rusted, 1993) and in animals (e.g., Sarter et al., 2006) showed that the cholinergic system primarily contributes to effortful attention processes more than memory, the primary deficit in AD. Additionally, recent work has shown that age-related changes in sex hormones such as estradiol can affect cholinergic integrity and cognitive processes (Dumas et al., 2008a; Gibbs, 2009). However, with the increased use of functional neuroimaging, new data show support for the role of the cholinergic system in cognitive changes associated with aging and dementia. Below we review the role of the cholinergic system in human cognition and describe findings from imaging studies showing the effects of cholinergic modulation on brain activation patterns.

Converging evidence from psychopharmacological, neuroimaging, and psychological studies of cholinergic system functioning in humans shows that the cholinergic system has a specific modulatory role in attentional processing. Sarter et al. (2006) reviewed the prior literature examining acetylcholine efflux in animals performing attention tasks and these data support the hypothesis that a principal role of the cortical cholinergic system is to mediate attentional processes. The cortical cholinergic system is composed of projections to and from the basal forebrain and as a result of these feed forward and feedback capabilities. Sarter et al. (2005) proposed that the cholinergic system is involved in attention in two ways. First, the cholinergic system serves to optimize bottom-up, signal-driven detection processes. Second, it also optimizes top-down, knowledge-based detection of signals and the filtering of irrelevant information. Thus, depending on the task requirements and the quality of the signal, Sarter et al. (2005) proposed that the cholinergic system will be involved when attentional processes are needed because a task is difficult or relevant and irrelevant information are difficult to discriminate. In humans, the cholinergic system has been implicated in many aspects of cognition including the partitioning of attentional resources, working memory, inhibition of irrelevant information, and improved performance on effortful tasks (e.g., Newhouse et al., 2001; Warburton and Rusted, 1993). Thus, the cholinergic system will be specifically engaged in attention tasks and in memory tasks to the extent that the task is difficult and requires effortful attention for good performance.

2. Evidence for cholinergic modulation of task-related brain activity

The effects of cholinergic modulation on cognitive processing and related brain circuitry have also been revealed by neuroimaging studies (see Thiel, 2003 for a review). To preview, procholinergic and anticholinergic drugs show opposite patterns of brain activation across a range of cognitive tasks. While there are some task-specific effects of cholinergic stimulation and blockade studies, there are also task-general patterns that may be related to attentional processes that involve cholinergic system. In addition, the subject population being studied influences the patterns of results. For example, older and younger adults (e.g., Dumas et al., 2008b; Sperling et al., 2002) have different patterns of task-related brain activation as do smokers and nonsmokers (e.g., Ernst et al., 2001; Giessing et al., 2006; Lawrence et al., 2002). However, these different patterns should be interpreted with caution as the tasks in some studies were different in different populations.

Most studies examining activation after procholinergic or agonist drugs in younger adults revealed increased activation in posterior brain regions. For example, increased cortical activity while administering physostigmine, a cholinesterase inhibitor, compared to placebo produced greater activation in extrastriate and intraparietal areas during encoding but not during retrieval into working memory (Furey et al., 2000). Physostigmine administration also facilitated visual attention by increasing activity in the extrastriate cortex during a repetition priming task (Bentley et al., 2004). However, the data patterns are different in a study with older adults. Kukolja et al. (2009) examined the effects of physostigmine compared to placebo in older adults during an episodic encoding and retrieval task. They found greater activity during encoding in the right hippocampus for successfully encoded items and less activity during retrieval in the right amygdala for successfully retrieved items. Taken together the different patterns of activation for older and younger adults illustrate baseline task dependency effects of cholinergic manipulations on cognition and related brain activation.

There is a large literature on the effects of the cholinergic agonist nicotine on cognition in AD as well as normal younger adults. Overall, nicotine appears to improve attention and lessen errors in AD patients (see Newhouse et al., 2004 for a review). A recent meta-analysis by Heishman et al. (2010) of studies of nicotine in smokers and non-smokers found that nicotine improved motor responding, attention and memory after controlling for withdrawal effects in smokers. Thus, nicotine has beneficial effects on cognition in non-pathologic states as well. Below we focus on the imaging findings in an effort to evaluate the cholinergic hypothesis of geriatric memory dysfunction given recent imaging data.

Functional imaging studies examining the effects of nicotine on brain activation during attention and working memory performance have found variable results depending on whether subjects are smokers or nonsmokers. Ernst et al. (2001) examined brain activation on the 2-back condition of an N-back task of working memory in smokers and ex-smokers after nicotine and placebo gum. Results showed a laterality difference in the placebo condition for smokers who activated the right hemisphere regions while ex-smokers activated left hemisphere regions. After nicotine gum, activation was reduced in smokers and increased in ex-smokers. Hahn et al. (2009) found that nicotine reduced activation in smokers relative to placebo across tasks of stimulus detection, simple attention and complex attention. A different pattern was found in Lawrence et al. (2002) with nicotine increasing task-related brain activation in the parietal and occipital cortices as well as the thalamus and caudate nucleus during a rapid visual information processing task of attention. On an N-back task in healthy nonsmokers, nicotine increased activation in the superior frontal and parietal cortices. Giessing et al. (2006) examined attention in a cued target detection task in healthy non-smokers and found decreases in task-related brain activation in parietal regions. Thus, it seems that the effects of nicotinic stimulation are heterogeneous and dependent on the task examined and whether subjects are regular users of nicotine.

The effects of the anti-cholinergic, anti-muscarinic drug scopolamine on brain activation during an associative learning task (Sperling et al., 2002) and during encoding (Schon et al., 2005) have also been examined in younger adults. Sperling et al. (2002) found an attenuation of learning-related activity in the fusiform gyrus, inferior prefrontal cortex, and hippocampus. Schon et al. (2005) found that scopolamine challenge decreased encoding related activity in right posterior parahippocampal and mid-fusiform gyri and in the hippocampal body in younger adults. However, the patterns of activation after anti-muscarinic drugs look different in an older subject population. Dumas et al. (2010) have found that scopolamine *increased* activation in frontal brain areas during an episodic memory task relative to placebo in normal older women suggesting compensation by top-down mechanisms.

Only three studies thus far have been done utilizing the anti-nicotinic drug, mecamylamine. Dumas et al. (2008b) showed decreases in frontal regions after mecamylamine during an N-back working memory test on older women. Dumas et al. (2010) also found increased frontal and hippocampal activations and decreased occipital activation after mecamylamine challenge compared to placebo during a continuous recognition test of episodic memory also in older women. Thienel et al. (2009) found decreases in the anterior cingulate and precuneus during an attention task after mecamylamine administration in younger male subjects. Age and perhaps gender may alter the directionality of nicotinic or cholinergic effects on brain activity. The effects of cholinergic manipulations and in this case specifically nicotinic blockade may not be linearly related to age thus prolonging the differential effects of mecamylamine on brain activation patterns.

The functional imaging studies examining muscarinic and nicotinic blockade effects on younger and older adults reveal a complicated pattern of results. We suggest this pattern may be explained as a nonlinear relationship between age and responsiveness to cholinergic manipulation and its effects on brain activation with the directionality and magnitude strongly determined by baseline performance. A proposal about the nature of this relationship will be described further below.

These imaging studies show evidence for the two related functions of the cholinergic system in information processing proposed by Sarter et al. (2005). The first is that the cholinergic system modulates stimulus-specific processing of bottom-up sensory information in sensory cortical areas (Bentley et al., 2004; Furey et al., 2000). Second, brain regions involved in memory processing such as the hippocampus and frontal lobe seem to be influenced by cholinergic modulation (Dumas et al., 2010, 2008b; Schon et al., 2005; Sperling et al., 2002; Thiel, 2003). The effects of cholinergic system manipulation on sensory areas reflect the role of the cholinergic system in modulating attentional processes. Additionally, the effects on memory-related processing areas reflect a role of the cholinergic system in modulating the initial processes like attention necessary for encoding in memory. The cholinergic system seems to be involved in modulating frontal as well as posterior activation patterns in response to cognitive demands. We propose that the relationship between frontal and posterior activations is related to the integrity of the cholinergic system that is sensitive to age and disease. Below we briefly review some of the data on brain activation patterns in older and younger adults to build support for our proposed cholinergic model of task-related brain activation.

Work by Cabeza et al. (2004) has shown increased activation in the prefrontal cortex and decreased occipital activations during attention, working memory and episodic memory tasks. Cabeza et al. interpreted these findings as evidence that there are task-independent age-related changes in brain activity representing sensory decline often seen in older adults and this increased frontal activation is functional compensation for these sensory changes (posterior–anterior shift in aging, PASA) (Davis et al., 2008). Davis et al. (2008) further explored this effect to examine whether this pattern resulted as a result of task difficulty, whether it was related to compensation, and whether it generalized to activations on visual perception and episodic retrieval tasks. To investigate the difficulty explanation, Davis et al. (2008) matched older and younger adults on task performance and the PASA pattern was still observed. Frontal activations were positively correlated with improved performance while occipital deactivations were negatively correlated with performance thus providing evidence that the additional frontal activation is the result of neural compensation (Stern, 2002). Thus overall, these data patterns support the proposal that the PASA effect reflects age-related neural compensation to maintain adequate task performance. We now propose the hypothesis that age-related neural compensation is at least partly related to intact cholinergic functions.

3. Cholinergic functional compensation model of age-related cognitive dysfunction

Our model proposes that it is age-related alterations in the activity of the cholinergic system that are responsible for the PASA pattern. Early in the aging process, increases in cholinergic system activity act to compensate for age-related changes in sensory and/or executive control processes by increasing the engagement of frontal-mediated top-down processes (as represented by the middle panel in Fig. 1). Functional compensation will require the recruitment of additional frontal regions to maintain adequate performance on a task that we hypothesize is supported by cholinergic functioning. Healthy older adults will benefit from intact cholinergic functioning to assist in the recruitment of frontal networks and attentional processes to help compensate for decreasing sensory inputs. However, disease-related changes in cholinergic system activity will lead to the disruption of the ability to modulate the control of attentional resources between incoming sensory information and internally goal-directed attentional processes (right panel in Fig. 1). If cholinergic function decreases secondary to neurodegenerative disease, older adults may no longer be able to recruit cholinergic inputs for cognitive compensation. This will result in degrading of the control processes of the focus of attention that also impairs working memory and long-term memory and will thus produce quantitatively impaired performance.

Fig. 1 displays working memory as the activated portion of long-term memory and the focus of attention within working memory that

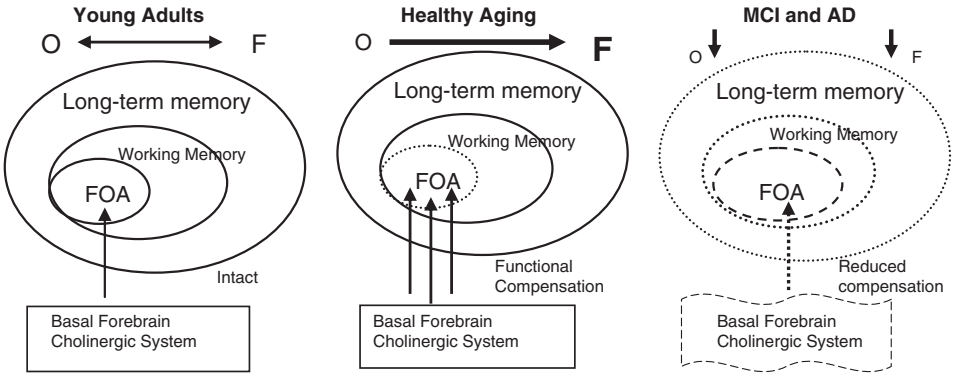

Fig. 1. Cholinergic functional compensation model of age-related cognitive dysfunction. Fig. 1 diagrams the functional compensation model illustrating the effects of aging and cholinergic dysfunction the focus of attention (FOA). Dotted and grayed lines indicate impairments. When younger adults (left panel) perform attention and memory tasks they show brain activation patterns that are balanced between occipital and frontal regions, thus allowing for a balance of bottom-up and top-down processes. Normal cognitive aging (middle panel) may degrade the control processes of the focus of attention thereby affecting working memory and long-term memory. Functional compensation will recruit the cholinergic system and associated cortical areas to maintain good performance on a task. We propose that this cholinergic recruitment will result in increases in frontal activation for older adults (PASA). Cholinergic dysfunction seen in MCI and AD (right panel) will lead to further attentional control impairments that cannot be compensated for by increased recruitment of the cholinergic system causing working memory and long-term memory processes to be impaired further. The activation patterns will show decreases in frontal and occipital regions.

can only hold a small amount of information (Cowan, 1988, 1999). Age and/or disease effects on cholinergic functioning may result in the blurring of the focus of attention or the inability of older adults to use the frontal-related central executive to control what information enters the focus of attention. Prior studies have shown that decreases in the focus of attention impair working memory (e.g., Oberauer, 2001) and episodic memory (e.g., Naveh-Benjamin et al., 2007) for older adults relative to younger adults. We propose that it is age- and disease-related changes in cholinergic functioning that are responsible for these cognitive changes. In addition, we propose that evidence for these cholinergic system changes can be observed by examining changes in brain activation patterns. Our model suggests that cholinergic system activity initially increases in response to developing age-related changes in bottom-up sensory-related (attentional) activity by increasing top-down frontal-related activity. Further, any decline in the ability of the cholinergic system to compensate for age-related cortical impairment will result in a loss of control over the manipulation of the focus of attention that also will affect working memory and episodic memory. These age- or disease-related changes will be detected in the relative activation of frontal and posterior brain regions.

The functional compensation model hypothesizes that neural compensation seen in older adults is related to increased recruitment of the cholinergic system. However, as illustrated in Fig. 2, the model predicts that the relationship between task-related brain activation and cholinergic stimulation will be modulated by neuronal or synaptic integrity and/or loss. Normal biological aging processes may not immediately have an effect on task performance because of intact cognitive reserve capacities. Brain systems of older adults with significant cognitive reserve may remain responsive to cholinergic manipulations. However when pathologic aging processes producing neuronal or synaptic loss exceed the cognitive reserve capacity, cognitive performance will decline *and* the ability to respond to cholinergic stimulation will decrease. In mild cognitive impairment (MCI) and AD neuronal integrity is no longer maintained, cognitive performance is impaired, and patients are no longer as responsive to normal levels of intrinsic cholinergic-related activation. Fig. 2 shows the proposed interaction between cholinergic activation and performance usually described as an upside-down U-shaped function with the addition of the third axis representing neuronal and synaptic integrity versus loss. This added dimension now more clearly illustrates that the ability of the cholinergic system to modulate performance is dependent on synaptic integrity. With the loss of that integrity or plasticity the dynamic range of compensation is blunted and eventually disappears. This exactly tracks the experience seen using cholinergic enhancing drugs in the treatment of AD (e.g., acetylcholinesterase inhibitors), with improvement or stabilization of cognitive performance being seen early in the disease, but with increasing neuronal degeneration, the ability of pro-cholinergic drugs to maintain or enhance performance is lost.

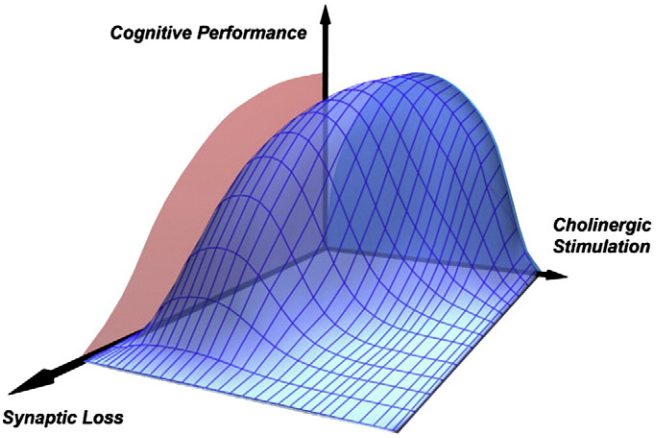

Fig. 2. The relationship between synaptic loss, cholinergic stimulation, and cognitive performance. Fig. 2 diagrams the proposed relationship between cognitive performance, cholinergic stimulation and neuronal and/or synaptic loss. The relationship between cholinergic stimulation and cognitive performance is usually described as an inverted U function with maximal cognitive performance representing an optimal degree of cholinergic stimulation. The degree to which cholinergic stimulation is necessary to maximize performance is partially a product of the initial starting point, i.e. lower performance will require more cholinergic stimulation than better performance. As cholinergic stimulation increases performance maximizes and then begins to decline with overstimulation. The two-dimensional representation of these two factors reflects real-world data on the effects of cholinesterase inhibitors and other cholinergic agonists on cognitive performance. However, with declining neuronal integrity (in this figure, neuronal or synaptic loss is represented by moving from the origin along the Z axis), the ability of cholinergic activation to improve cognitive performance declines. As neuronal or synaptic loss increases (either due to normal aging and/or neurodegenerative disease) the improvement in cognitive performance produced by cholinergic stimulation begins to get smaller and eventually disappears. Furthermore, there is a threshold-like drop off once neuronal degeneration reaches a certain point and cognitive performance may decline sharply at that point. This may represent when cognitive deficits become frankly manifest in patients with neurodegenerative disorders.

4. Potential mechanisms for the cholinergic role in functional compensation

There is a significant body of evidence that supports the role of the cholinergic system in directing and modulating cognitive operations (see Hasselmo and Sarter, 2010; Sarter et al., 2005 for reviews). What remains to be fully elucidated is how these biological processes relate the activity of the cholinergic system to patterns of brain activation in functional imaging studies and patterns of performance on tests of attention and memory. Below we make a preliminary attempt to link the hypotheses regarding the activity of the cholinergic system with the effects of cognitive aging, however a full understanding of the relevant biological mechanisms will require additional work.

As described above (Sarter et al., 2005), cholinergic activity serves to mediate both bottom-up and top-down attentional processes. Cortical cholinergic inputs appear to enhance the detection of signals (bottom-up) and are involved in the prefrontal modulation of cortical cholinergic inputs (top-down). Thus, cholinergic activity reflects the complex interaction between signal-driven and knowledge-based processes and mediates the enhancement of input and attention both to external as well as internal stimuli (Sarter et al., 2005). Furthermore, cholinergic activity appears to be required to mediate the expansion and tuning of cortical receptive fields to maintain sensory representations (bottom-up). This input appears to be necessary to augment or mediate stimulus-based responding when the situation taxes attentional processing and resources. Recent research has identified several timescales for cholinergic activity. Changes in cholinergic modulation over several seconds can occur in response to sensory events and serve to interrupt and re-direct attention and ongoing behavior. Longer time scale persistent electrical activity of neurons ("spiking") activated or sustained by cholinergic inputs may serve to maintain sensory representations and activate working memory and/or episodic memory systems (Hasselmo and Sarter, 2010). Muscarinic and nicotinic receptors may play separate roles in these processes.

With normal aging, sensory processes may deteriorate (Baltes and Lindenberger, 1997). Degraded bottom up sensory processes may increase demand on cholinergic modulation of top down processes to maintain task performance. Prefrontal cholinergic inputs act to recruit the anterior and/or dorsal attentional network based on stimulus characteristics and may provide feedback to the basal forebrain cholinergic neurons (e.g., top-down). Specifics about how the cholinergic system is involved in this feedback response have been proposed in a computational model by Yu and Dayan (2002) and are described further below.

Yu and Dayan have proposed that cortical cholinergic activity represents "top-down uncertainty", i.e. the degree to which top-down inference disagrees with the bottom-up sensory inputs and the degree to which cognitive variables governing top-down processes require adjustment (Yu and Dayan, 2002, 2005). In this model, acetylcholine signals known uncertainty between contextual information and incoming sensory information. More specifically, acetylcholine provides the ability to make an inference about sensory information and how well this information matches contextual information already in memory. Acetylcholine (along with other neurotransmitters such as norepinephrine), acts to improve inferences about relevant perceptual stimuli from competing stimuli that are both internal and external (Yu and Dayan, 2005). Cholinergic innervation and activation of prefrontal cortex is necessary to initiate cognitive mechanisms that support performance under changing task conditions, e.g., distraction. Sarter et al. (2009) have suggested that brief cholinergic transients in frontal cortex produce a processing mode "upshift" to allow attention to relevant external stimuli. Thus, as the functioning of sensory systems is affected by advancing age, incoming information will less reliably match information from memory thereby leading to poorer inferences about this information. Cholinergic systems will thus be called upon to activate more top-down, frontal-mediated processes during attention and memory encoding tasks to improve inference and subsequent decision-making.

As aging affects sensory and cognitive processes, the basal forebrain cholinergic system may at first be sufficient to modify or direct certain aspects of cortical activity during middle age. With alterations in cortical integrity that accompany normal aging as well as sensory impairments, cholinergic activity will increasingly engage frontally mediated top-down attentional processes to resolve uncertainties regarding sensory input, the contents of working memory, and material retrieved from long-term memory, as it appears that cholinergic input is critical for frontally-mediated attentional processes (Hasselmo and Sarter, 2010). This may have the effect of producing increased frontal activation that has been seen during normal task performance in healthy older individuals. Some studies have shown that this frontal increase appears necessary to maintain performance efficiency and accuracy (Mattay et al., 2006; Rypma and D'Esposito, 2000). Cholinergic deafferentation or loss (e.g., secondary to neurodegenerative diseases such as AD) will impair this activation and thus likely produce significant performance impairment especially in the presence of distractors, reflecting the dysfunctional aspects of impaired sensory-driven and top-down performance. The suggestion that cholinergic system attempts to compensate for developing cortical dysfunction is supported by the finding that some cortical cholinergic markers like choline acetyltransferase (ChAT) activity in the superior frontal cortex appear to be upregulated in MCI, the precursor condition to AD, suggesting attempts by the cholinergic system to compensate for developing cortical dysfunction (DeKosky et al., 2002).

Thus far, Yu and Dayan (2002, 2005) and Sarter et al. (2009) provide a link between the studies of the biological processes of the cholinergic system and effects of its manipulation in animal models to what is known from data patterns in human psychological and functional imaging studies. Further work is necessary to connect and test hypotheses developed from computational models and animal studies with the data patterns from human cognitive aging, psychopharmacological manipulations of cognition, and functional neuroimaging to validate these models of the cognitive and biological factors that change as a result of the interaction between cortical aging and an aging cholinergic system. This prior work on how the neurobiology of cholinergic function is related to cognition can be extended to understand why acetylcholinesterases only modestly improve cognition in AD and MCI patients.

For anticholinesterases, as the dose is increased, efficacy increases modestly, but with a relatively low therapeutic index. Side effects of acetylcholinesterase inhibitors may become a limiting factor more rapidly than loss of efficacy of these agents, with an upside down U-shaped curve describing the relationship between cholinergic stimulation and cognitive benefit (Newhouse et al., 2004; Wilkins and Newhouse, 2010). Also, due to the phasic properties of cortical acetylcholine function (Hasselmo and Sarter, 2010), it may be difficult for increased acetylcholine in the synaptic cleft to result in stimulation of post-synaptic receptors independently from pre-synaptic activity. Thus, given the phasic nature of cholinergic neurons in the cortex, medications that block cholinesterase activity may affect the dynamic range of the system but also increase noise. The ability of pre-synaptic neurons to respond to signaling may also be reduced by excessive autoreceptor stimulation (Benzi and Moretti, 1998). Thus the wide range of response to treatment seen in dementia patients may be due to variations in the cholinergic deficit.

5. Tests of the cholinergic functional compensation model of cholinergic functioning using cognitive enhancers in AD and MCI

A number of clinical trials have examined the ability of acetylcholinesterase inhibitors to modify cognitive performance in AD and MCI and these studies have been reviewed elsewhere (e.g.,

Diniz et al., 2009; Hansen et al., 2008; Wilkins and Newhouse, 2010). Briefly, most clinical trials have shown that chronic administration of acetylcholinesterase inhibitors improves scores on cognitive subscales of the Alzheimer's Disease Assessment Scale, the Mini-Mental State examination, and global scales such as the Clinical Interview-Based Impression of Change (CGIC) (Birks and Flicker, 2006; Salloway et al., 2004). These agents temporarily improve, stabilize, or reduce the rate of decline in memory and other intellectual functions relative to placebo. In a meta-analysis by Hansen et al. (2008) the effects of three major acetylcholinesterase inhibitors on behavior and cognition in 26 different studies showed modest overall benefits for stabilizing or slowing decline in cognition, function, behavior, and clinical global change. In other meta-analyses of multiple anticholinesterase trials, it was found that anticholinesterase treatment improved cognition and reduced the progression of MCI patients to dementia (Diniz et al., 2009).

A number of studies have also examined the effects of cholinergic stimulation on brain circuitry and task performance in subject populations who have dysfunctional cholinergic systems. The cholinergic functional compensation model as described above would predict that patient groups who have cholinergic dysfunction are unable to compensate for age- and disease-related processes, and will show less activation relative to controls. As suggested by Fig. 2, the ability of the cholinergic system to dynamically improve performance is reduced by neuronal loss until compensation can no longer effectively occur. By contrast, in normal aging, cholinergic stimulation will result in increases in frontal activation and similar activation patterns as those seen in healthy older subjects. A number of prior studies have investigated the brain stimulation effects of cholinesterase inhibitors on patients with MCI and AD. The results from these studies are heterogeneous across a variety of cognitive tasks, dosing regimens, cholinesterase drugs and patient populations. However, some broad conclusions can be drawn.

Cholinergic stimulation results in increases in activation in MCI and AD patients in brain regions that are relevant to the task being performed while decreasing activation in task-independent brain regions. For example, in tasks of face processing, cholinesterase medications caused increases in activation in the fusiform gyrus (Bentley et al., 2008). In working memory tasks, increases in activation were seen in frontal regions (Goekoop et al., 2004; Rombouts et al., 2002; Saykin et al., 2004). Interestingly, increases in frontal activation during memory tasks following long-term anticholinesterase treatment parallels a decline in frontal activation in subjects treated with placebo (Petrella et al., 2009).

Some studies show increased similarities between patient and control groups after treatment. In Shanks et al. (2007) patients and controls activated different brain regions in a semantic association task before treatment. After 20 weeks of rivastigmine, differences between controls and AD patients were lessened relative to baseline. However, Goekoop et al. (2006) showed decreases in MCI subjects after 5 days of galantamine treatment in posterior cingulate and bilateral frontal regions during face recognition and decreases in AD patients in the hippocampus during face encoding. These decreases in activation may be the result of increased efficiency of information in these task relevant areas in situations where performance was improved as a result of the medications. The relationship between decreases in activation and processing efficiency has been demonstrated in a study by Silver et al. (2008) who showed that an acute dose of physostigmine decreased in the spread of activation in the visual cortex in response to being presented with a checkerboard pattern in normal subjects.

Thus, in patients who have cholinergic impairments secondary to MCI and AD, cholinergic stimulation via acetylcholinesterase blockade resulted in increases in brain activation that were related to task processing. Decreases were seen in task irrelevant regions indicating an increase in processing efficiency. Decreases in activation differences between patients and controls were also seen indicating greater normalization of processing in patient groups. These three patterns indicate a nonlinear relationship between cholinergic stimulation that depends on integrity of the cholinergic system secondary to disease severity. Taken together, these studies support the proposal that the relationship between cognitive performance, brain activation, and cholinergic stimulation is modulated by neuronal integrity as illustrated in Fig. 2. Neuronal integrity in turn is modulated by age and disease severity. In addition, long-term cholinesterase treatment increased frontal activation while frontal activation decreased for the placebo group thus providing support for the cholinergic functional compensation model described in Fig. 1.

6. Are there inconsistencies with the functional compensation hypothesis?

There are some studies in the prior literature described above that may not be entirely consistent with the cholinergic functional compensation hypothesis as proposed here. First, not all studies of older and younger adults show the expected PASA pattern (Grady et al., 1995; Iidaka et al., 2001; Milham et al., 2002; Stebbins et al., 2002). These studies do not demonstrate increased frontal activation for older adults and this discrepancy may have to do with specifics related to the tasks used or subject selection. It is possible that depending on the composition of the older sample because groups of older adults may be at different points along the function describing neuronal integrity, different patterns may emerge (see Fig. 2). Secondly, not all studies of cholinergic manipulations fit into this model. Some studies of MCI and AD patients find increases in task related activation after cholinergic stimulation while other studies find decreases. This is likely due to differences in task-related baseline performance, as during good performance, cholinergic stimulation may reduce activity and during suboptimal performance, cholinergic stimulation may increase task-specific cortical activity.

7. Recommendations for future studies

Future studies may be able to capitalize on the use of cholinergic-related brain activity as a biomarker of treatment response. The effects of cholinergic stimulation and blockade in younger and older adults as well as in MCI and AD patients need further study to more fully understand the relationship between synaptic integrity, cholinergic function, and brain circuitry involved in memory and attention processes. Other neuroimaging modalities such as PET may be utilized to examine the effects of age directly on receptor status or how amyloid deposition affects cholinergic function. Numerous strategies are being proposed and tested to maintain cognitive processing in the face of normal aging such as practice and training, exercise, antioxidant supplements, etc. Future studies should examine how these manipulations affect cholinergic system integrity in an effort to bridge what is known about effective strategies to mitigate cognitive aging and how they relate to the underlying neurobiological processes. Cholinergic function may represent the function of a general brain system that is age-sensitive. The “health” of this system may be assessed after various manipulations, i.e. to what extent do processes designed to improve or minimize cognitive aging improve non-cholinergic processes and what strategies affect cholinergic systems directly or indirectly.

In an effort to draw more definitive conclusions across different patient groups after different drug challenges, similar tasks should be used across studies. We have presented evidence that tasks that require attentional control will be the most sensitive to cholinergic manipulations and will be the most useful for drawing conclusions across a range of subject groups and drug treatments.

The cholinergic hypothesis should also be tested against and perhaps integrated with other hypotheses of neurotransmitter

function and dysfunction in aging. Braver and Barch (2002) hypothesized that dopamine projections to the frontal cortex are impaired with aging and result in a loss of the ability to represent, maintain and update contextual information in memory. The relationship between age-related dopaminergic and cholinergic changes and the effects of this change on cognition should be evaluated to further describe the neurobiology of aging. The hypothesis that neural compensation in aging is partly related to dopaminergic pathogenesis should also be evaluated.

Prior studies found that age-related changes in dopamine activity using positron emission tomography (PET). Volkow et al. (1998) showed in a sample of adults aged 24–86 that there was a decline in D_2 receptor availability in the caudate and putamen with increased age. Backman et al. (2000) also examined D_2 receptor availability and found that it decreased with increased age as did performance on tests of perceptual speed and episodic memory. When they statistically controlled for the D_2 binding, age differences in cognitive performance disappeared. However, when controlling for age, changes in D_2 binding remained. They concluded that D_2 receptor binding is more important for explaining changes in cognition than chronological age. The age-related changes in dopamine receptor availability in the caudate and putamen imply that age changes in dopamine may be related to age changes in cognition and specifically in cognitive processes that rely on the striatum for good performance. As there are connections between the striatum and the frontal cortex, dopamine has been implicated in higher order cognitive processes such as working memory, episodic memory and aspects of fluid intelligence (Backman et al., 2006). While these relationships are impressive, there is no direct causal relationship of changes in dopaminergic functioning that has been shown to be responsible for cognitive aging. Furthermore, dopaminergic replacement does not correct general cognitive deficits and in fact excess dopamine may worsen cognition (Weintraub and Potenza, 2006). Future studies should examine the psychopharmacological manipulation of dopaminergic systems and the effects on attention and memory in healthy older adults in an effort to better evaluate the independent and combined roles of the dopaminergic and cholinergic systems in age-related cognition. Additionally, cholinergic and specifically nicotinic receptor systems have modulatory control over dopamine release and thus there may be direct cholinergic–dopaminergic interactions in cognitive aging that could be tested.

8. Summary

Research on cholinergic modulation of cognition in aging and dementia has flourished in recent years. There have been a number of neuroimaging studies utilizing psychopharmacological manipulations to examine the effects of aging and dementia on brain circuitry. However, there has been no neurobiological model proposed to integrate the effects of age on cognitive performance and the imaging data thus far. We propose that the cholinergic changes that occur with aging may be one explanation for the common pattern of brain activation seen in older adults compared to younger adults as well as in patients with MCI and AD after treatment with cholinergic medications. We have shown some preliminary support for this model and further direct testing of this hypothesis is necessary to provide further evidence for the link between aging of the cholinergic system, cognitive aging, and dementia.

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