Cognitive functions of the basal forebrain
Mark G Baxter* and Andrea A Chiba†

Studies of the function of the basal forebrain have focused on cholinergic neurons that project to cortical and limbic structures critical for various cognitive abilities. Recent experiments suggest that these neurons serve a modulatory function in cognition, by optimizing cortical information processing and influencing attention.

Addresses
*Department of Psychology, Harvard University, 984 William James Hall, 33 Kirkland Street, Cambridge, Massachusetts 02138, USA; e-mail: mbaxter@wjh.harvard.edu
†Department of Cognitive Science, University of California – San Diego, 9500 Gilman Drive, La Jolla, California 92093-0415, USA; e-mail: chiba@cogsci.ucsd.edu

http://biomednet.com/elecref/0959438800900178
© Elsevier Science Ltd ISSN 0959-4388

Abbreviations
AMPA α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
GABA γ-aminobutyric acid
MS medial septum
nBM nucleus basalis magnocellularis of Meynert
SI substantia innominata
VOB vertical limb of the diagonal band of Broca

Introduction
The term ‘basal forebrain’ commonly refers to an extended continuum of subcortical neurons that provides projections to a variety of neocortical fields and limbic structures implicated in various aspects of cognitive function (Figure 1). Damage to the basal forebrain region can result in global cognitive impairments; for instance, aneurysms of the anterior communicating artery that injure the basal forebrain are associated with amnesia and impairments in executive function [1,2•]. Cognitive deficits in both normal aging and age-related pathological conditions have also been associated with basal forebrain dysfunction. The severity of cognitive impairment observed in Alzheimer’s disease is correlated with the extent of deterioration of cholinergic neurons in the basal forebrain [4,5]. A similar relationship between cognitive impairment and alterations in basal forebrain cholinergic neurons is seen in normal aging (for a review, see [6]). For these reasons, cholinergic neurons have been central to most explanations of the cognitive effects of basal forebrain damage. Hypotheses regarding the involvement of the basal forebrain cholinergic system in global aspects of cognitive function have been gradually revised as more and more selective lesion methods have become available for experimental studies of this region [7,8•].

Cholinergic basal forebrain neurons are intermingled with a substantial population of noncholinergic neurons that share similar projection patterns (e.g. [9]), posing a challenge to investigators seeking to determine the consequences on cognition of selective damage to basal forebrain cholinergic neurons. The development of a lesioning agent selective for basal forebrain cholinergic neurons, 192 IgG–saporin [10], has permitted direct examination of the cognitive function of basal forebrain cholinergic neurons. Methods are readily available for confirming the selectivity of lesions produced by this toxin [10,11], an important consideration in studies seeking to ascribe cognitive deficits (or the lack thereof) to the loss of basal forebrain cholinergic neurons (see discussion in [12]).

In this brief review, we will highlight recent studies of the role of the basal forebrain cholinergic neurons in attention, memory, and cortical information processing, focusing primarily on experiments using the selective cholinergic immunolesion method.

Basal forebrain and attention
Current views of basal forebrain function suggest a selective role for basal forebrain cholinergic neurons in the modulation of attention [13•]. Just as there are multiple forms of memory [14,15], investigators have defined multiple forms of attention [16•,17,18]. Selective lesions of basal forebrain cholinergic neurons produce disruptions of specific forms of attentional processing [19,20,21••,22,23,24•].

The extended neural circuitry underlying the role of corticopetal cholinergic neurons in attentional processing has recently been elaborated. For at least one domain of attention (increased attentional processing as a consequence of expectancy violation), these neurons are driven by inputs from the central nucleus of the amygdala [25••,26•]. Furthermore, it now appears that projections from the nucleus basalis magnocellularis of Meynert/substantia innominata (nBM/SI) to discrete cortical regions are responsible for modulating specific forms of attention. Restricted removal of cholinergic projections from the nBM/SI to the posterior parietal cortex also eliminates enhanced learning produced by expectancy violation [27••]. Restricted removal of cholinergic input to the frontoparietal cortex is effective at impairing sustained attention [28•].

The correspondence between the effects of neurotoxic lesions of medial prefrontal cortex and nBM/SI lesions on attention in the 5-choice serial reaction time task [29] suggests that cholinergic projections from nBM/SI to medial prefrontal cortex are involved in attentional processing in this task. The possibility that projections from the nBM/SI to different cortical areas play dissociable roles in attentional processing is worth exploring further.

Other experiments have suggested a role for septohipocampal cholinergic neurons in the modulation of some forms of attentional processing. Damage to cholinergic neurons in the medial septum/vertical limb of the diagonal
The severity of the described deficits in terms of absolute behavioral capacity is worth noting. Rats with selective lesions of basal forebrain cholinergic neurons do not simply stop attending to their environment, nor do they become unable to process any environmental stimuli. Indeed, some attentional ‘impairments’ manifest themselves as increased levels of learning [30]. Perhaps it is more accurate to characterize the ‘impairment’ following selective damage to basal forebrain cholinergic neurons not as an impairment in attention itself, but as an impairment in the ability to respond appropriately to demands placed on attention. Thus, through the modulation of specific aspects of attention, the basal forebrain cholinergic system plays a role in optimizing behavioral performance in response to specific behavioral challenges or associative histories of stimuli.

Basal forebrain and memory

A number of recent reviews have highlighted studies showing intact learning and memory following selective damage to basal forebrain cholinergic neurons [13,31]. An alternative explanation of the lack of effects of 192 IgG–saporin lesions on learning is that extremely severe (>95%) depletion of cortical cholinergic innervation is required to produce cognitive deficits following basal forebrain damage, such as that produced following intracerebroventricular administration of the immunotoxin [32–35]. However, such lesions also result in cerebellar damage, and, for example, there is currently no evidence for impairments in spatial learning in the water maze after 192 IgG–saporin lesions in the absence of additional damage to the cerebellum. Deficits in other cognitive tasks (such as the delayed nonmatching-to-position task in rats) that are relatively mild after lesions limited to basal forebrain cholinergic neurons, are much more severe after intraventricular 192 IgG–saporin lesions [36–39]. In fact, immunotoxins restricted to cerebellar neurons produce learning impairments [35]. In this context, the ability of lesions restricted to specific subpopulations of corticopetal cholinergic neurons to produce attentional deficits is particularly noteworthy [27,29], as these deficits occur with minimal loss of basal forebrain cholinergic neurons. Indeed, in situations where some memory impairment is seen following lesions of basal forebrain cholinergic neurons, these impairments may be caused by damage to a restricted set of basal forebrain projections [40].

The development of a primate cholinergic immunotoxin [41,42] has made it possible to explore the role of cholinergic basal forebrain neurons in learning and memory in an anatomical system with closer homology to the human. These initial studies reveal a very selective pattern of deficits following lesions of discrete basal forebrain nuclei. Fine et al. [42] report an impairment in perceptually difficult visual discrimination learning following apparently selective damage to rBM cholinergic neurons. Ridley et al. [43] have also shown that removal of cholinergic neurons in the VDB disrupts learning of a visuospatial conditional discrimination problem. These impairments manifest themselves against a generally spared background of stimulus–reward learning ability. The ability to address these issues in nonhuman primates...
promises further experiments that will continue to refine our understanding of the role of basal forebrain cholinergic neurons in cognitive function.

Role of the basal forebrain in cortical plasticity and information processing
On the basis of the foregoing discussion, the statement that basal forebrain cholinergic neurons subserve attention, but not learning and memory, may not adequately characterize the role of these neurons in cognitive function. Rather, cholinergic projections from the basal forebrain seem to optimize information processing and attention instead of playing a pivotal role in any global cognitive function [44,45]. Other experiments have sought to identify candidate mechanisms by which acetylcholine could exert an influence on cortical information processing. One potential mechanism is via differential suppression by acetylcholine of afferent versus intrinsic input into a particular cortical region. Hasselmo and colleagues [46–48] have demonstrated this phenomenon in hippocampal regions CA1 and CA3, and in piriform cortex. This has significant consequences on information processing in computational models of these regions, in which this modulation controls whether the network can efficiently store new patterns without interfering with previously stored ones. Sarter and Bruno [49••] postulate a more general role of acetylcholine in gating cortical information processing, such that hypo- or hyper-activity of cholinergic neurons may contribute to a broad spectrum of neuropsychiatric disorders.

Indeed, removal of cortical cholinergic input has a dramatic impact on the regulation of sensory information processing. For instance, stimulation of the nucleus basalis paired with auditory cues results in reorganization of the primary auditory cortex, an effect that appears to be attributable to the auditory cues. However, this impact on the regulation of sensory information processing, these studies emphasize the role of basal forebrain cholinergic neurons in cognitive function.

Conclusions and future directions
The ability to produce selective lesions of basal forebrain cholinergic neurons in experimental animal models has greatly advanced our knowledge of the cognitive functions of these neurons. Clearly, these neurons play a role in attention and in modulation of cortical information processing.

The behavioral work in this domain has been particularly fruitful because of the emphasis on isolating specific dynamic processes of attention. The application of this general approach to the study of learning and memory may further elucidate the role of the basal forebrain cholinergic system in these aspects of cognition. Work in this area is already being pursued, for example, in studies of reward processing after basal forebrain lesions [54•,55], and in studies of reactivity to spatial novelty after basal forebrain lesions, an important (but apparently not obligatory) component of spatial navigation ability (L. Ricceri, A. Usiello, G. Calamandrei, K. Frick, J. Berger-Sweeney, Soc. Neurosci. Abstr. 1998, 24:178).

The role of noncholinergic basal forebrain neurons in cognitive function remains relatively unexplored. These neurons are anatomically situated to regulate cortical processing directly, as well as to regulate the function of cortically projecting basal forebrain cholinergic neurons [56••]. The finding that projections from cortical areas back to the basal forebrain synapse entirely on noncholinergic neurons [56••] suggests that the intermitted neurons of these regions may function as an integrated system. Physiological studies of these neurons show that they have diverse physiological properties [57•], some of which may be shared with cholinergic neurons [58••]. The potential redundancy between cholinergic and noncholinergic basal forebrain neurons may help explain the lack of global cognitive impairment following selective lesions of basal forebrain cholinergic neurons; indeed, cholinergic and noncholinergic systems may be capable of affecting cortical information processing in similar ways [59,60••]. That cholinergic and noncholinergic neurons may cooperatively regulate cortical function is suggested by the finding that selective removal of septal cholinergic neurons renders rats more susceptible to the amnestic effects of intraventricular injections in the absence of injected drugs [61••], even though selective removal of either cholinergic [61••] or GABAergic (K. Pang, personal communication) septal neurons is without effect on spatial memory. This does not exclude the possibility that cholinergic and noncholinergic basal forebrain projections may regulate different properties of cortical information processing, which are differentially engaged in response to specific cognitive challenges, a possibility that invites future experimental studies.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as: • of special interest
** of outstanding interest


2. Abe K, Inokawa M, Kashiwagi A, Yanagihara T. Amnesia after a discrete basal forebrain lesion. J Neurol Neurosurg Psychiatry 1998, 69:126–130. The authors report a case of anterograde amnesia after a lesion apparently restricted to the nucleus of the diagonal band, accompanied by hypometabolism in the hippocampus bilaterally. This is an important contrast to previous reports (see [3]), in which the lesions were too anatomically restricted to cause damage to structures outside the basal forebrain itself could have contributed to the amnesia.
ing cholinergic lesions of the nBM/SI. Specifically, a diminished ability


45. Juliano SL:


41. Mrzljak L, Levey AI, Belcher S, Goldman-Rakic PS: Effects on learning ability following injection of the cholinergic protein does not exist uniquely as an autoreceptor in the cerebral cortex.


44. Drachman DR, Sahakian BJ: The effects of cholinergic agents on baseline hippocampal theta activity found after 192 IgG–saporin lesions. A role in generating hippocampal theta rhythm, and providing a substrate for the hippocampal theta rhythm. The number of RB neurons that rhythmically bursting neurons in rat medial septum following galanin antagonist M40 with a muscarinic M1 agonist improves delayed nonmatching to position choice accuracy in rats with cholinergic lesions. J Neurosci 1998, 18:5078-5085.


44. Drachman DR, Sahakian BJ: The effects of cholinergic agents on baseline hippocampal theta activity found after 192 IgG–saporin lesions. A role in generating hippocampal theta rhythm, and providing a substrate for the hippocampal theta rhythm. The number of RB neurons that rhythmically bursting neurons in rat medial septum following galanin antagonist M40 with a muscarinic M1 agonist improves delayed nonmatching to position choice accuracy in rats with cholinergic lesions. J Neurosci 1998, 18:5078-5085.


44. Drachman DR, Sahakian BJ: The effects of cholinergic agents on baseline hippocampal theta activity found after 192 IgG–saporin lesions. A role in generating hippocampal theta rhythm, and providing a substrate for the hippocampal theta rhythm. The number of RB neurons that rhythmically bursting neurons in rat medial septum following galanin antagonist M40 with a muscarinic M1 agonist improves delayed nonmatching to position choice accuracy in rats with cholinergic lesions. J Neurosci 1998, 18:5078-5085.


This paper demonstrates that norepinephrine and acetylcholine have similar effects on cortical information processing, selectively suppressing synaptic transmission at synapses from intrinsic but not afferent fibers. Hence, although different behavioral situations may activate these two transmitter systems, their effects on cortical information processing may be similar.


Demonstrates that selective removal of cholinergic MS/VDB neurons does not alter performance on a spatial working memory task. However, infusions into the MS/VDB of muscimol or scopolamine resulted in spatial-working-memory deficits in rats with cholinergic MS/VDB neurons, but not in control rats.