Cognitive functions of the basal forebrain

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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.

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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
VDB	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•,3]. 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 septohippocampal cholinergic neurons in the modulation of some forms of attentional processing. Damage to cholinergic neurons in the medial septum/vertical limb of the diagonal

band of Broca (MS/VDB) eliminates reductions of attentional processing while maintaining enhanced learning in response to violation of expectancy [30••]. This pattern of results is opposite that resulting from lesions of corticopetal cholinergic neurons in the nBM/SI, which produce a disruption of enhanced learning due to violation of expectancy, but no impairment in reduction of attention to predictable or irrelevant stimuli [20].

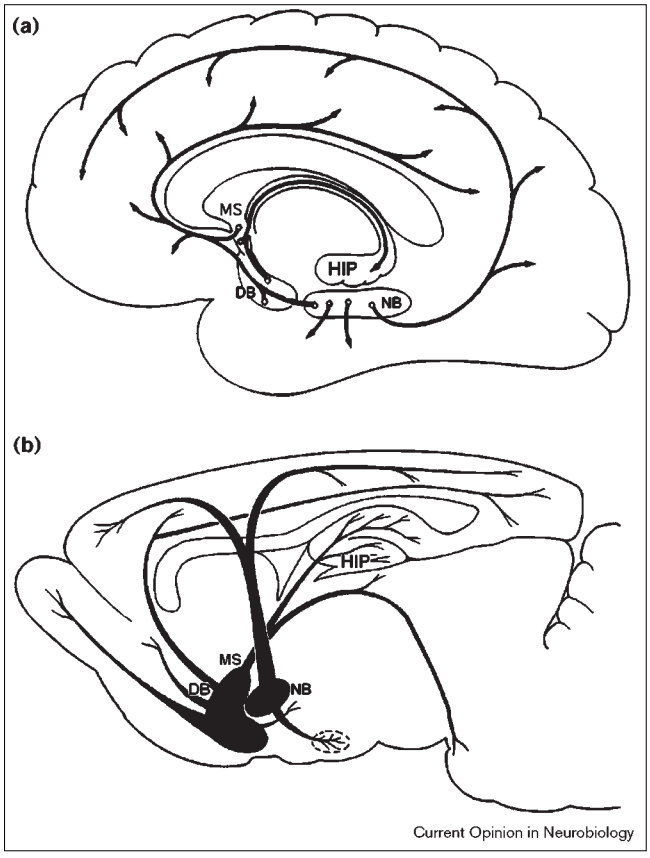
The severity of the described deficits in terms of absolute behavioral capacity is worth noting. Rats with selective lesions of basal forebrain cholinergic neurons do not simply stop attending to their environment, nor do they become unable to process any environmental stimuli. Indeed, some attentional '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, immunotoxic lesions restricted to cerebellar neurons produce learning impairments [24•]. In this context, the ability of lesions restricted to specific subpopulations of corticopetal cholinergic neurons to produce attentional deficits is particularly noteworthy [27••,28•], 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 nBM 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

Figure 1



The basal forebrain cholinergic system, schematically represented in sagittal views of the **(a)** human and **(b)** rat brain. The basal forebrain can be divided roughly into three major divisions (rostral to caudal): the medial septum (MS), projecting primarily to the hippocampus (HIP); the diagonal band (DB) nuclei, consisting of the VDB, projecting to the hippocampus and cingulate cortex, and the horizontal limb of the diagonal band of Broca, projecting to the olfactory bulb and entorhinal cortex; and the nucleus basalis (NB), projecting to neocortex and amygdala. (The projections from the NB to the amygdala are spared by the immunolesion method discussed in this review [11], so statements about the function of cholinergic basal forebrain neurons based on the effects of this toxin are limited to the cortical projections of these cells.) These cell groups share similar projection patterns in both species. In the text, we refer to the nBM/SI for this area in rats, because it forms a less discrete nucleus in the rat than in the primate, but both terms refer to the region of the basal forebrain that sends cholinergic projections to neocortex. For recent reviews of the anatomy of this region, see [8•,13•]. (a) Adapted from [62]. (b) Adapted from [13•].

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 action of basal forebrain cholinergic neurons [50••]. Basal forebrain cholinergic neurons also appear to be essential for reorganizing the somatosensory cortex in response to removal of vibrissae [51••,52,53]. That these phenomena may have behavioral consequences is suggested by a preliminary study by Juliano and colleagues (M Kossut, O Rahimi, DC Tatham, SL Juliano, *Soc Neurosci Abstr* 1998, 24:632). They have demonstrated that selective removal of basal forebrain cholinergic neurons prevents the reacquisition of a preoperatively learned challenging tactile discrimination problem. Like the studies of restricted cortical cholinergic depletion on specific forms of attentional processing, these studies emphasize the role of basal forebrain cholinergic projections in optimizing the information processing functions of their cortical targets.

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 [9,56••]. The finding that projections from cortical areas back to the basal forebrain synapse entirely on noncholinergic neurons [56••] suggests that the interspersed neurons of these region 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 intraseptal drug infusions [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

1. Diamond BJ, DeLuca J, Kelley SM: **Memory and executive functions in amnesic and non-amnesic patients with aneurysms of the anterior communicating artery.** *Brain* 1997, **120**:1015-1025.

2. • Abe K, Inokawa M, Kashiwagi A, Yanagihara T: **Amnesia after a discrete basal forebrain lesion.** *J Neurol Neurosurg Psychiatry* 1998, **65**: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 less anatomically restricted so damage to structures outside the basal forebrain itself could have contributed to the amnesia.

3. Damasio AR, Graff-Radford NR, Eslinger PJ, Damasio H, Kassell N: **Amnesia following basal forebrain lesions.** *Arch Neurol* 1985, **42**:263-271.

4. Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH, Perry RH: **Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia.** *BMJ* 1978, **2**:1457-1459.

5. Bierer LM, Haroutunian V, Gabriel S, Knott PJ, Carlin LS, Purohit DP, Perl DP, Schmeidler J, Kanof P, Davis KL: **Neurochemical correlates of dementia severity in Alzheimer's disease: relative importance of the cholinergic deficits.** *J Neurochem* 1995, **64**:749-760.

6. Gallagher M, Nagahara AH, Burwell RD: **Cognition and hippocampal systems in aging: animal models.** In *Brain and Memory: Modulation and Mediation of Neuroplasticity*. Edited by McGaugh JL, Weinberger NM, Lynch G. New York: Oxford University Press; 1995:103-126.

7. Dunnett SB, Everitt BJ, Robbins TW: **The basal forebrain-cortical cholinergic system: interpreting the functional consequences of excitotoxic lesions.** *Trends Neurosci* 1991, **14**:494-501.

8. • Wenk GL: **The nucleus basalis magnocellularis cholinergic system: one hundred years of progress.** *Neurobiol Learn Mem* 1997, **67**:85-95.
A thoughtful review and history of work aimed towards understanding the corticopetal cholinergic system. The review focuses on current electrophysiological and behavioral studies investigating the role of this system in subserving higher cognitive function.

9. Gritti I, Mainville L, Mancia M, Jones BE: **GABAergic and other noncholinergic basal forebrain neurons, together with cholinergic neurons, project to the mesocortex and isocortex in the rat.** *J Comp Neurol* 1997, **383**:163-177.

10. Wiley RG, Oeltmann TN, Lappi DA: **Immunolesioning: selective destruction of neurons using immunotoxin to rat NGF receptor.** *Brain Res* 1991, **562**:149-153.

11. Heckers S, Ohtake T, Wiley RG, Lappi DA, Geula C, Mesulam M-M: **Complete and selective cholinergic denervation of rat neocortex and hippocampus but not amygdala by an immunotoxin against the p75 NGF receptor.** *J Neurosci* 1994, **14**:1271-1289.

12. Chappell J, McMahan R, Chiba A, Gallagher M: **A re-examination of the role of basal forebrain cholinergic neurons in spatial working memory.** *Neuropharmacology* 1998, **37**:481-487.

13. • Everitt BJ, Robbins TW: **Central cholinergic systems and cognition.** *Annu Rev Psychol* 1997, **48**:649-684.
This article presents a comprehensive, authoritative review of the role of central cholinergic systems in cognitive function, including both the basal forebrain and brain stem cholinergic systems.

14. Kesner RP, Bolland BL, Dakis M: **Memory for spatial locations, motor responses, and objects: triple dissociation among the hippocampus, caudate nucleus, and extrastriate visual cortex.** *Exp Brain Res* 1993, **93**:462-470.

15. Squire LR, Zola SM: **Structure and function of declarative and nondeclarative memory systems.** *Proc Natl Acad Sci USA* 1996, **93**:13515-13522.

16. • Bushnell PJ: **Behavioral approaches to the assessment of attention in animals.** *Psychopharmacology* 1998, **138**:231-259.
An extensive review of the study of multiple forms of attention in rats. Distinctions are made between categories of attentional processing, and results implicating various neural and neurochemical systems in subserving these categories of attentional processing are synthesized.

17. Parasuraman R (Ed): *The Attentive Brain*. Cambridge, Massachusetts: MIT Press; 1998.

18. Posner MI, Petersen SE: **The attention system of the human brain.** *Annu Rev Neurosci* 1990, **13**:25-42.

19. Turchi J, Sarter M: **Cortical acetylcholine and processing capacity: effects of cortical cholinergic deafferentation on crossmodal divided attention in rats.** *Cogn Brain Res* 1997, **6**:147-158.

20. Chiba AA, Bucci DJ, Holland PC, Gallagher M: **Basal forebrain cholinergic lesions disrupt increments but not decrements in conditioned stimulus processing.** *J Neurosci* 1995, **15**:7315-7322.

21. •• Chiba AA, Bushnell PJ, Oshiro WM, Gallagher M: **Selective removal of cholinergic neurons in the basal forebrain alters cued target detection in rats.** *Neuroreport* 1998, in press.
Alterations in target detection/attention to cues was revealed in rats following cholinergic lesions of the nBM/SI. Specifically, a diminished ability (i.e. increased reaction time and decreased accuracy) to detect targets preceded by invalid cues was observed in the presence of intact ability to detect targets preceded by valid cues.

22. McGaughy J, Kaiser T, Sarter M: **Behavioral vigilance following infusions of 192 IgG-saporin into the basal forebrain: selectivity of the behavioral impairment and relation to cortical AChE-positive fiber density.** *Behav Neurosci* 1996, **110**:247-265.

23. Stoehr JD, Mobley SL, Roice D, Brooks R, Baker LM, Wiley RG, Wenk GL: **The effects of selective cholinergic basal forebrain lesions and aging upon expectancy in the rat.** *Neurobiol Learn Mem* 1997, **67**:214-227.

24. • Waite JJ, Wardlow ML, Power AE: **Deficit in selective and divided attention associated with cholinergic basal forebrain immunotoxic lesion produced by 192-saporin; motoric/sensory deficit associated with Purkinje cell immunotoxic lesion produced by OX7-saporin.** *Neurobiol Learn Mem* 1999, in press.
Intraventricular administration of 192 IgG–saporin resulted in impairments in attention in the multiple-choice reaction time task developed by Robbins and colleagues (see [29] and citations therein), similar to the effects of neurotoxic basal forebrain lesions that are not selective for cholinergic neurons.

25. •• Han J-S, Holland PC, Gallagher M: **Disconnection of amygdala central nucleus and substantia innominata/nucleus basalis disrupts increments in conditioned stimulus processing.** *Behav Neurosci* 1999, **113**:143-150.
Disconnection of the central nucleus of the amygdala (CN) and cholinergic neurons in the nBM/SI, achieved by crossed unilateral lesions, produced a disruption in incremental processing of conditioned stimuli similar to that produced by bilateral lesions of either structure. This indicates that regulation of attentional processing by CN is mediated via direct projections to cholinergic neurons in nBM/SI.

26. • Whalen PJ: **Fear, vigilance and ambiguity: initial neuroimaging studies of the human amygdala.** *Curr Directions Psychol Sci* 1998, in press.
Evidence is presented suggesting that the amygdala is activated under conditions of associative ambiguity. In addition, the author proposes that the amygdala might influence cortical sensory processing by stimulating release of acetylcholine from basal forebrain neurons that project to the cortex. In turn, the cholinergic modulation of cortical neurons might serve to lower thresholds for sensory information processing.

27. •• Bucci DJ, Holland PC, Gallagher M: **Removal of cholinergic input to rat posterior parietal cortex disrupts incremental processing of conditioned stimuli.** *J Neurosci* 1998, **18**:8038-8046.
Removal of the cholinergic input to the posterior parietal cortex was accomplished through site-specific infusions of 192 IgG–saporin into cortical regions in the rat homologous to primate posterior parietal cortex. Following removal of this relatively small number of cholinergic neurons, rats failed to increase attentional processing under conditions where expectancies regarding stimulus relationships were violated.

28. • McGaughy J, Sarter M: **Sustained attention performance in rats with intracortical infusions of 192 IgG-saporin-induced cortical cholinergic deafferentation: effects of physostigmine and FG 7142.** *Behav Neurosci* 1998, **112**:1519-1525.
Cholinergic denervation of frontoparietal cortical regions was accomplished through multiple cortical infusions of 192 IgG–saporin in rat. Subsequently, these rats demonstrated persistent impairments in sustained attention relative to control rats. These impairments were not attenuated by increasing the acetylcholine release from residual neurons through administration of physostigmine or FG 7142.

29. Muir JL, Everitt BJ, Robbins TW: **The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task.** *Cereb Cortex* 1996, **6**:470-481.

30. •• Baxter MG, Holland PC, Gallagher M: **Disruption of decrements in conditioned stimulus processing by selective removal of hippocampal cholinergic input.** *J Neurosci* 1997, **17**:5230-5236.
Injections of 192 IgG–saporin into the MS/VDB produced impairments in the ability to decrease processing of conditioned stimuli, such as a disruption of latent inhibition, similar to the effects of neurotoxic hippocampal lesions on these tasks. The rats with MS/VDB lesions had been shown previously to be unimpaired on a test of spatial learning, indicating a dissociation between spatial learning and attentional processing in the hippocampus.

31. • Baxter MG, Gallagher M: **Cognitive effects of selective loss of basal forebrain cholinergic neurons: implications for cholinergic therapies of Alzheimer's disease.** In *Pharmacological Treatment of Alzheimer's Disease: Molecular and Neurobiological Foundations*. Edited by Brioni JD, Decker MW. New York: Wiley; 1997:87-103.
A review of recent experiments using 192 IgG–saporin in rats, focused on the work leading to the hypothesis that basal forebrain cholinergic projec-

tions to both hippocampus and neocortex play a role in attentional processing, but not in learning and memory *per se*.

32. Leanza G, Nilsson OG, Wiley RG, Björklund A: **Selective lesioning of the basal forebrain cholinergic system by intraventricular 192 IgG-saporin: behavioural, biochemical and stereological studies in the rat.** *Eur J Neurosci* 1995, **7**:329-343.

33. Waite JJ, Chen AD, Wardlow ML, Wiley RG, Lappi DA, Thal LJ: **192 immunoglobulin G-saporin produces graded behavioral and biochemical changes accompanying the loss of cholinergic neurons of the basal forebrain and cerebellar Purkinje cells.** *Neuroscience* 1995, **65**:463-476.

34. Walsh TJ, Kelly RM, Dougherty KD, Stackman RW, Wiley RG, Kutscher CL: **Behavioral and neurobiological alterations induced by the immunotoxin 192-IgG-saporin: cholinergic and non-cholinergic effects following i.c.v. injection.** *Brain Res* 1995, **702**:233-245.

35. Winkler J, Thal LJ, Gage FH, Fisher LJ: **Cholinergic strategies for Alzheimer's disease.** *J Mol Med* 1998, **76**:555-567.

36. Torres EM, Perry TA, Blokland A, Wilkinson LS, Wiley RG, Lappi DA, Dunnett SB: **Behavioural, histochemical and biochemical consequences of selective immunolesions in discrete regions of the basal forebrain cholinergic system.** *Neuroscience* 1994, **63**:95-122.

37. Steckler T, Keith AB, Wiley RG, Sahgal A: **Cholinergic lesions by 192 IgG-saporin and short-term recognition memory: role of the septohippocampal pathway.** *Neuroscience* 1995, **66**:101-114.

38. Leanza G, Muir J, Nilsson OG, Wiley RG, Dunnett SB, Björklund A: **Selective immunolesioning of the basal forebrain cholinergic system disrupts short-term memory in rats.** *Eur J Neurosci* 1996, **8**:1535-1544.

39. McDonald MP, Willard LB, Wenk GL, Crawley JN: **Coadministration of 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.

40. • Dougherty KD, Turchin PI, Walsh TJ: **Septocingulate and septohippocampal cholinergic pathways: involvement in working/episodic memory.** *Brain Res* 1998, **810**:59-71.
Site-specific infusions of 192 IgG–saporin were used to selectively remove cholinergic neurons projecting to the hippocampus or those projecting to the anterior cingulate in rats. A differential pattern of deficits was demonstrated on an eight-arm radial maze task, implicating the septocingulate but not the septohippocampal cholinergic pathway in spatial working memory.

41. • Mrzljak L, Levey AI, Belcher S, Goldman-Rakic PS: **Localization of the m2 muscarinic acetylcholine receptor protein and mRNA in cortical neurons of the normal and cholinergically deafferented rhesus monkey.** *J Comp Neurol* 1998, **390**:112-132.
Using an immunotoxin targeted against the primate p75 nerve growth factor receptor (ME20.4 IgG–saporin) the authors produced selective lesions of basal forebrain cholinergic neurons in rhesus monkeys. With their preparation of toxin, cholinergic neurons were destroyed and noncholinergic neurons at the lesion site were preserved. Analysis of m2 muscarinic acetylcholine receptor immunoreactivity in cerebral cortex of monkeys with these lesions revealed sparing of m2 reactivity, indicating that this receptor protein does not exist uniquely as an autoreceptor in the cerebral cortex.

42. •• Fine A, Hoyle C, Maclean CJ, Levatte TL, Baker HF, Ridley RM: **Learning impairments following injection of a selective cholinergic immunotoxin, ME20.4 IgG-saporin, into the basal nucleus of Meynert in monkeys.** *Neuroscience* 1997, **81**:331-343.
Apparently selective lesions of cholinergic nBM neurons in marmosets produced no impairments in retention of preoperatively learned visual discriminations, but a marked impairment in learning of new perceptually difficult discrimination problems postoperatively.

43. •• Ridley RM, Barefoot H, Maclean CJ, Pugh P, Baker HF: **Different effects on learning ability following injection of the cholinergic immunotoxin ME20.4IgG-saporin into the diagonal band of Broca, basal nucleus of Meynert, or both in monkeys.** *Behav Neurosci* 1999, in press.
This study reports a double dissociation between effects of removal of cholinergic neurons in the VDB and nBM: lesions of these neurons impair both learning and retention of conditional and simple discrimination problems, respectively.

44. Drachman DR, Sahakian BJ: **The effects of cholinergic agents on human learning and memory.** In *Choline and Lecithin in Brain Disorders (Nutrition and the Brain),* vol 5. Edited by Barbeau A, Growden JH, Wurtman RJ. New York: Raven; 1979:351-366.

45. Juliano SL: **Mapping the sensory mosaic.** *Science* 1998, **279**:1653-1654.

46. Hasselmo ME, Bower JM: **Cholinergic suppression specific to intrinsic not afferent fiber synapses in rat piriform (olfactory) cortex.** *J Neurophysiol* 1992, **67**:1222-1229.

47. Hasselmo ME, Schnell E: **Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal region CA1: computational modeling and brain slice physiology.** *J Neurosci* 1994, **14**:3898-3914.

48. Hasselmo ME, Schnell E, Barkai E: **Dynamics of learning and recall at excitatory recurrent synapses and cholinergic modulation in rat hippocampal region CA3.** *J Neurosci* 1995, **15**:5249-5262.

49. • Sarter M, Bruno JP: **Abnormal regulation of corticopetal cholinergic neurons and impaired information processing in neuropsychiatric disorders.** *Trends Neurosci* 1999, **22**:67-74.
On the basis of careful anatomical, neurochemical, and behavioral considerations, this review puts forth the hypothesis that "abnormal regulation of the excitability of cortical cholinergic affronts represents a final common pathway mediating the manifestation of major neuropsychiatric disorders".

50. •• Kilgard MP, Merzenich MM: **Cortical map reorganization enabled by nucleus basalis activity.** *Science* 1998, **279**:1714-1718.
Pairing an auditory stimulus with electrical stimulation of the nucleus basalis resulted in a remapping of auditory cortex, increasing the area of auditory cortex that responded preferentially to the paired stimulus. That this effect might be cholinergically mediated was shown by pairing nBM stimulation with a tone in rats that had received 192 IgG–saporin lesions; these rats did not demonstrate remapping of auditory cortex in response to the pairing.

51. •• Baskerville KA, Schweitzer JB, Herron P: **Effects of cholinergic depletion on experience-dependent plasticity in the cortex of the rat.** *Neuroscience* 1997, **80**:1159-1169.
Removal of basal forebrain cholinergic neurons eliminated experience-dependent plasticity in somatosensory cortex in response to paired whisker stimulation. This finding directly implicates basal forebrain cholinergic neurons in the reorganizational properties of somatosensory cortex in response to sensory stimulation.

52. Sachdev RN, Lu SM, Wiley RG, Ebner FF: **Role of the basal forebrain cholinergic projection in somatosensory cortical plasticity.** *J Neurophysiol* 1998, **79**:3216-3228.

53. Zhu XO, Waite PM: **Cholinergic depletion reduces plasticity of barrel field cortex.** *Cereb Cortex* 1998, **8**:63-72.

54. • Olmstead MC, Robbins TW, Everitt BJ: **Basal forebrain cholinergic lesions enhance conditioned approach responses to stimuli predictive of food.** *Behav Neurosci* 1998, **112**:611-629.
Lesions of the nBM produced by AMPA or quinolinic acid increased locomotor responses in an environment paired with food, and enhanced responding to a lever paired with a light CS (conditioned stimulus) associated with food, without altering consummatory responses to food or sucrose. This enhancement could reflect a disruption in the balance between cortical and subcortical dopamine levels, or perhaps an impairment in attentional processing manifested by an abnormal focusing of attention on stimuli predictive of food.

55. Robledo P, Weissenborn R, Robbins TW, Everitt BJ: **Effects of lesions of the nucleus basalis magnocellularis on the acquisition of cocaine self-administration in rats.** *Eur J Neurosci* 1998, **10**:1946-1955.

56. •• Záborszky L, Gaykema RP, Swanson DJ, Cullinan WE: **Cortical input to the basal forebrain.** *Neuroscience* 1997, **79**:1051-1078.
The authors present a series of detailed anatomical studies combining tract-tracing and immunocytochemistry to identify transmitter phenotype in pre or post-synaptic elements in rats. Taken together, the data suggest that prefrontal cortical areas may exert influence on basal forebrain cholinergic neurons by way of connections with noncholinergic basal forebrain neurons.

57. • Pang K, Tepper JM, Zaborszky L: **Morphological and electrophysiological characteristics of noncholinergic basal forebrain neurons.** *J Comp Neurol* 1998, **394**:186-204.
The authors recorded extracellularly from single basal forebrain neurons, determined their electrophysiological properties, and then labeled them with biocytin for morphological analysis. The neurons recorded did not demonstrate choline acetyltransferase activity, but did demonstrate heterogeneous morphological and electrophysiological properties.

58. •• Apartis E, Poindessous-Jazat FR, Lamour YA, Bassant MH: **Loss of rhythmically bursting neurons in rat medial septum following selective lesion of septohippocampal cholinergic system.** *J Neurophysiol* 1998, **79**:1633-1642.
Rhythmically bursting (RB) neurons in the medial septum appear to be critical for the generation of the hippocampal theta rhythm. The number of RB neurons in the medial septum was dramatically reduced, but not eliminated, following intraventricular 192 IgG–saporin. The remaining RB neurons were identified as GABAergic cells, suggesting that both neurochemical classes of neurons play a role in generating hippocampal theta rhythm, and providing a substrate for the residual hippocampal theta activity found after 192 IgG–saporin lesions.

59. Tang AC, Hasselmo ME: **Selective suppression of intrinsic but not afferent fiber synaptic transmission by baclofen in the piriform (olfactory) cortex.** *Brain Res* 1994, **659**:75-81.

60. •• Hasselmo ME, Linster C, Patil M, Ma D, Cekic M: **Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio.** *J Neurophysiol* 1997, **77**:3326-3339.
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.

61. •• Pang KCH, Nocera R: **Interactions between 192-IgG saporin and intraseptal cholinergic and GABAergic drugs: role of cholinergic medial septal neurons in spatial working memory.** *Behav Neurosci* 1999, in press.
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.

62. Saper CB: **Chemical neuroanatomy of Alzheimer's disease.** In *Handbook of Psychopharmacology,* vol 20. Edited by Iversen SD, Iversen LL, Snyder SH. New York: Plenum; 1988:131-156.