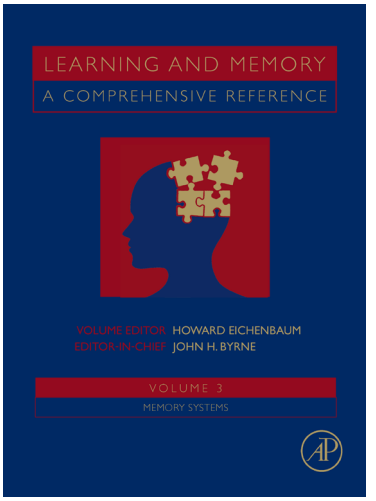




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# 3.15 Basal Forebrain and Memory

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## 3.15.1 Introduction

The basal forebrain is an aggregate of heterogeneous structures coursing along the ventral rostrocaudal extent of the brain. The anatomical connectivity of this collective allows it access to virtually the entire cortical mantle and to other subcortical structures thought to be essential to learning and memory. Often characterized by its large cholinergic projection neurons, the basal forebrain is home to a host of cell types and is regulated by a rich neurochemical background. The link between the basal forebrain and memory is frequently based on the decline of this structure in Alzheimer's disease. Yet, as in the medial temporal lobe system, there exists a characteristic amnestic syndrome associated with widespread damage to the basal forebrain. Animal models have been extensively used in an attempt to determine the role of this collective or of its subdivisions in memory and in other cognitive and behavioral functions. Further, the electrophysiological and rhythmic properties of the subdivisions of the basal forebrain are indicative of its extensive potential to function in a neuromodulatory capacity. Whereas analyses of the differential contribution of anatomical subdivisions of the basal forebrain to memory have been fruitful, further understanding of the organizational principles and functional properties of this region is likely to reveal additional clues to its role in memory and cognition.

## 3.15.2 Basal Forebrain Amnesia

A diversity of amnestic syndromes has been observed following insults to numerous loci in the neural system. As a result, a variety of neural circuits have been heavily implicated in underlying different aspects of memory, mostly indicated by the form of amnesia following disruption of the circuit. The circuits to which damage is traditionally observed to result in an amnestic syndrome are those including the prefrontal cortex, the cingulate cortices, the hippocampus, the rhinal cortices, multimodal cortical regions, and diencephalic regions (see Tranel et al., 2002; Milner, 2005; Frankland and Bontempi, 2006, for

review). Subregions of the basal forebrain share projections with each of these regions and are known for their neuromodulatory influence on these sites. Thus, not surprisingly, discrete lesions of the basal forebrain have also been observed to result in a profound amnestic syndrome. This basal forebrain amnestic syndrome shares many common features of the various forms of amnesia induced by damage to its projection sites.

Still, the manifestation of basal forebrain amnesia is dissociable from other amnestic syndromes based on a few hallmark features. In patients with basal forebrain lesions, severe anterograde amnesia for episodic memory is described as roughly equivalent to that of medial temporal and diencephalic patients. Yet, in basal forebrain amnesics, recognition of those episodic memories remains intact, demonstrating preserved function relative to medial temporal patients (Wais et al., 2006). This is illustrated by a case study, of patient JS, in which discrete damage to the basal forebrain resulted in a form of profound amnesia (Osimani et al., 2006). JS demonstrated severe anterograde amnesia, including diminished new learning and rapid forgetting, with relatively preserved recognition of episodic information. Also observed was temporally graded retrograde amnesia for episodic memory spanning several years in the face of preserved semantic and procedural memory. The general form of the amnestic syndrome described for patient JS thus overlaps with that of hippocampal and diencephalic amnesiacs who show impaired capacity for new declarative memory but preserved semantic and procedural memory. While each form of amnesia includes temporally graded retrograde amnesia, the temporal span of the retrograde amnesia in patient JS appears intermediate to that of medial temporal amnesiacs and diencephalic amnesiacs.

A further distinction between basal forebrain amnesiacs and medial temporal amnesiacs is a disproportionate deficit in their ability to determine the temporal distribution of episodic memories relative to their memories for those events. A study examining memory for episodes in contrast to memory for episodic timelines concluded that basal forebrain–damaged patients possess an equivalent deficit to medial temporal patients in knowing 'what' or retrieving information from autobiographical memories, but they have a disproportionate deficit in knowing 'when' or appropriate chronological placement of autobiographical memories (Tranel and Jones, 2006). Temporal knowledge is also disproportionately impaired in amnesiacs with retrosplenial or posterior cingulate damage who demonstrate profound impairments in the ability to remember the temporal order of recent events yet show spared order memory of remote events (Valenstein et al., 1987; Bowers et al., 1988). Thus, basal forebrain amnesiacs share the temporal disorientation of those enduring damage to cingulate cortices.

The most common source of basal forebrain damage is rupture and repair of aneurysms of the anterior communicating, the anterior cerebral, or the pericallosal artery (Myers et al., 2002). A comparison of subjects with basal forebrain damage resulting from anterior communicating artery aneurysms with those with hippocampal/medial temporal damage resulting from hypoxia demonstrated a double dissociation between medial temporal amnesics and basal forebrain amnesics in the ability to perform and reverse a conditional discrimination. The discrimination was a simple conditioning task in which subjects learned to associate a correct directional response (right or left) with a particular background color (light or dark). Hippocampal amnesiacs learned this conditional discrimination far better than did basal forebrain amnesiacs. When subjects were required to reverse the associations (direction to background color) in order to achieve a correct response, basal forebrain amnesiacs were able to reverse the contingencies, whereas hippocampal amnesiacs were rigid in their inability to perform such reversals (Myers et al., 2005). Thus, some of the most visible dissociations between medial temporal lobe amnesiacs and basal forebrain amnesiacs emerge in nondeclarative memory tasks (Myers et al., 2002).

The results put forth in this section reveal that there is a distinct amnestic syndrome that arises from damage to the basal forebrain. However, basal forebrain amnesia generally shares features of amnestic phenomena involved in damage to many other cortical and subcortical brain regions. This is most likely due to the vast anatomical connectivity in which the basal forebrain participates. The widespread influence of the basal forebrain on other regions involved in mnemonic processing suggests an integrated role of the basal forebrain and its associated structures in the determination of distinct memory dysfunction.

### 3.15.3 The Basal Forebrain and Alzheimer's Disease

The primary source of a role for the basal forebrain in memory is derived from years of research on

Alzheimer's disease (AD) (Perry et al., 1978; Bartus et al., 1982; Wenk, 1997; Francis, 2005). The cognitive signature of AD is progressive memory decline, whereas a striking neuroanatomical marker of AD is degeneration of the magnocellular cholinergic neurons in the basal forebrain (Wu et al., 2005; Wenk, 2006). In general, the observed deficits in AD parallel those of basal forebrain amnesia. There exists a deficit in explicit memory, a partial deficit for implicit memory, and preserved procedural memory (for review see Carlesimo and Oscar-Berman, 1992). An additional common feature is the recent finding of relatively preserved familiarity-based recognition memory in AD patients and intact familiarity-based recognition memory in patients with mild cognitive impairment (MCI) (Westerberg et al., 2006).

Pathology of the cholinergic basal forebrain is likely to occur in early stages of AD (Bowen et al., 1982), as is hypofunction of particular cortical target regions, including the posterior cingulate and entorhinal cortices (Huang et al., 2002; deToledo-Morrell et al., 2004; Pennanen et al., 2004; Borroni et al., 2006). Concomitant with posterior cingulate hypofunction in patients with MCI and in those with AD is a temporal disorientation that is manifested by temporal order or sequential processing problems (Hirono et al., 1998; deToledo-Morrell et al., 2001; Nestor et al., 2003). Entorhinal cortex hypofunction correlates with MCI, whereas the addition of further hippocampal dysfunction best correlates with a progression to AD (Pennanen et al., 2004). A postmortem study of individuals with AD and those with MCI demonstrates a reduction in (both groups) of P75 neurotrophin receptor (NTR) binding in the basal forebrain, indicating a reduced functional presence of the basal forebrain cholinergic neurons that bear this receptor in the brains of these individuals. This reduction is of particular interest, as the number of P75 (NTR) immunoreactive neurons in the basal forebrain is significantly correlated with tests of working memory and attention (Mufson et al., 2002). Thus, early indicators of memory decline include the basal forebrain and its projection sites. A recent clinical effort is aimed toward preserving the basal forebrain in an attempt to arrest the cognitive decline associated with AD. This effort involved the implantation of autologous fibroblasts genetically modified to express NGF directly into the basal forebrain of patients with early AD. The results are promising, as implanted patients show widespread increases in brain metabolism and markedly slower rates of cognitive decline (Tuszynski et al., 2005).

Despite the preponderance of research aimed at the cholinergic system, other transmitter systems demonstrate altered function in AD and may shed light on the role of the basal forebrain and its constituent circuits in memory (Gsell et al., 2004). For example, successful therapeutic efforts are currently being targeted at excitatory amino acid neurotransmission (for review see Wenk, 2006; also see Francis, 2005). Capitalizing on more recent anatomical findings that GABAergic neurons in the basal forebrain follow similar trajectories as cholinergic neurons may also provide an opportunity for delineating the status of GABAergic neurons in the basal forebrain of AD patients and their role in memory (McKinney and Jacksonville, 2005).

## 3.15.4 Basal Forebrain Anatomy

The basal forebrain is a group of heterogeneous clusters whose anatomical complexity and organization are constantly unraveling as new techniques are developed and applied to its study (for review see Zaborszky, 2002; also see Zahm et al., 2006). The basal forebrain is parsed into groups of functional anatomical subdivisions based on projection patterns, cell types, and transmitter content (for review see Alheid and Heimer, 1988). Historically, the striking loss of cholinergic function in AD led to extensive study of the basal forebrain cholinergic system and its role in memory. Thus, a large number of the anatomical subdivisions of this system are based on the distribution of cholinergic projection neurons. More recent investigations indicate that GABAergic and perhaps glutamatergic projection neurons also comprise this structure (Jones and Mühlethaler, 1999; Zaborszky et al., 1999).

The basal forebrain neurons are generally organized along a rostrocaudal axis, such that cholinergic nuclei are somewhat contiguous in nature (Semba et al., 1988; Zaborszky et al., 2005; see **Figure 1**). The majority of behavioral and anatomical studies subdivide the basal forebrain into primary subdivisions based on their differential projection systems. The differential projection patterns show a large degree of conservation from primate to rodent and have, thus, been heavily examined across multiple species.

The human basal forebrain has been subdivided and mapped according to the magnocellular projection neurons that reside as groups within the aggregate. The designation of subdivisions is based on cholinergic projection neurons, and the

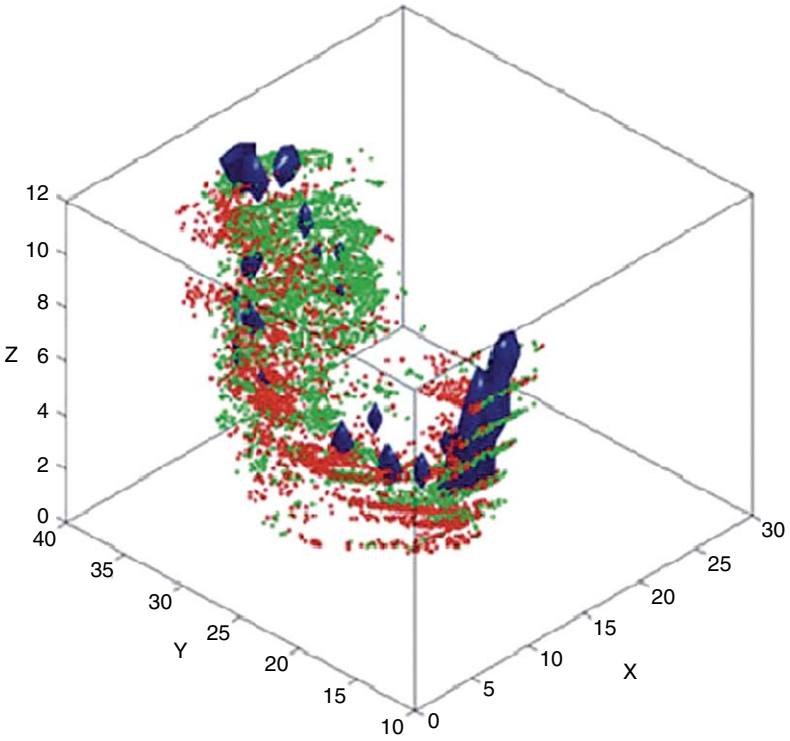


**Figure 1** Scatter plots of both cholinergic (red) and parvalbumin (green) cells superimposed on the iso-relational surface (gradient of density changes) shows the relative cell density of the two neuronal types. From Zaborszky L (2002) The modular organization of brain systems. Basal forebrain: the last frontier. *Prog. Brain Res.* 136: 359–372.

subdivisions are referred to as Ch1-4 (for reviews see Mesulam et al., 2004; also see Zaborszky et al., 1999). These Ch subdivisions correspond to designated anatomical subdivisions in the rodent and primate. The Ch1 and Ch2 regions in the human correspond to the medial septum and ventral diagonal band complex (MS/VDB). The Ch3 region corresponds to the horizontal limb of the diagonal band of Broca (HDB), and the Ch4 region corresponds to the nucleus basalis of Meynert (nBM). Ch4 can be subdivided into six spatially distinct regions: Ch4am (anteromedial), Ch4ai (anterointermediate), Ch4id (intermediodorsal), Ch4al (anterolateral), Ch4iv (intermedioventral), and Ch4p (posterior). The Ch1 and Ch2 (MS/VDB) neurons provide the primary cholinergic input to the hippocampus. The Ch3 (HDB) neurons provide primary input to the olfactory bulb. The Ch4am provides the primary cholinergic input to medial cortical areas including the cingulate gyrus, whereas the Ch4al provides the primary input to frontoparietal, opercular areas, and the amygdala. Ch4i provides projections to lateral, frontal, posterior parietal, peristriate, inferotemporal, parahippocampal, and orbitoinsular regions, whereas Ch4p provides input to superior temporal and temporopolar regions (see Mesulam, 2004, for review; also see Zaborszky et al., 1999).

Much of the basal forebrain anatomy has been conserved in the rodent, and the bulk of recent anatomy has focused on the rodent system. Three primary subdivisions are most often referred to as the functional components of the basal forebrain: the medial septal nucleus in combination with the vertical limb of the diagonal band of Broca (MS/VDB), the horizontal limb of the diagonal band of Broca in combination with portions of the magnocellular preoptic area (HDB/MCPOA), and the corticopetal basal forebrain including the nucleus basalis magnocellularis (NBM), the substantia innominata (SI), and portions of the ventral pallidum (hereafter included in NMB/SI). Neurons within the MS/VDB complex provide the major cholinergic innervation of the hippocampus, cingulate cortex, and subiculum, with a projection to the entorhinal cortex. Cells within the HDB/MCPOA project primarily to the olfactory bulb and entorhinal cortex, with additional projections to the occipital cortex and the amygdala. The NBM/SI contains a continuum of

projection neurons that provides the major source of cholinergic input and some noncholinergic input (mostly GABAergic) to nearly all neocortical regions. Additionally, it provides a primary input to the basolateral amygdala and to the reticular nucleus of the thalamus (for a detailed review see Zaborszky, 2002).

The NBM/SI region serves to regulate cortex and, at the same time, receives input from nonisocortical paralimbic cortical areas (orbitofrontal-prefrontal, temporopolar, insular, parahippocampal, and cingulate), the amygdala, the hypothalamus, and various brain stem cell groups. As there is no evidence of direct thalamic projections to the basal forebrain, sensory information must reach the basal forebrain through either the prefrontal cortex or the central nucleus of the amygdala, although other unreported pathways cannot be discarded. Additionally, the basal forebrain makes reciprocal connections with the central nucleus of the amygdala, ventral tegmental area, locus ceruleus, and pedunculopontine tegmental nucleus (PPT) (a brainstem cholinergic nucleus that also projects to the thalamus).

By virtue of a convergence of afferent brainstem projections to the basal forebrain, diverse neurochemical systems can heavily modulate the basal forebrain and its constituent cortical targets. Dopaminergic influence can occur through projections arising from the ventral tegmental area (VTA) or by projections arising directly from the substantia nigra pars compacta, substantia nigra pars reticulata, or retrorubral field (Semba et al., 1988). Serotonergic influence gains access to the basal forebrain by way of dense projections arising from the dorsal raphe nucleus, lighter projections from the median raphe nucleus, or sparse projections directly from the raphe magnus (Semba et al., 1988; Gasbarri et al., 1999). The basal forebrain can receive noradrenergic influence either from the locus ceruleus or from the nucleus of the solitary tract (Semba et al., 1988; Espana and Berridge, 2006). Finally, the brain stem cholinergic system, which is also referred to as the pontomesencephalic cholinergic system (Shute and Lewis, 1967; Woolf, 1991), provides cholinergic input to the basal forebrain primarily by receipt of projections from the laterodorsal tegmental nucleus (LDT) (Satoh and Fibiger, 1986; Woolf and Butcher, 1986; Semba et al., 1988) and also from the PPT (Semba et al., 1988).

Thus, the NBM/SI corticopetal region is well positioned to exert influence on the cortex, providing a primary source of acetylcholine and other neurotransmitters in a regionally independent manner and in the service of other neural systems. Such a system is well suited to play a role in a variety of cognitive functions, including memory.

### 3.15.5 Basal Forebrain Cell Types

The ability to produce selective neurotoxic lesions of only the cholinergic neurons within the basal forebrain has led to a strong emphasis being placed on discovering the function of these cells, especially given their role in AD and in attentional processing. However, the cholinergic cells constitute only a portion of the cell population in the region. Several other cell types, including GABAergic, peptidergic, and most likely glutamatergic cells also reside within the basal forebrain (Jones and Mühlethaler, 1999; Zaborszky et al., 1999).The characterization of these noncholinergic cell populations is an important route of exploration. While the precise role of these other cell types is unknown, the anatomical localization of these cells within the cholinergic basal forebrain system and their projection patterns indicate that they provide a very important contribution to the functionality of the basal forebrain.

In an elegant series of studies, Zaborszky's group (Zaborszky, 2002; Gritti et al., 2003; Zaborszky et al., 2005) has found noncholinergic cells that contain the different calcium-binding proteins – calbindin, calretinin, and parvalbumin – and has determined the three-dimensional structure and clustering patterns of the four cell types within the entirety of the basal forebrain. These neuronal types form sheets or bands that are twisted and attached to each other and that are not randomly distributed but show location-dependent density profiles (see **Figure 1**). In almost all basal forebrain regions that contain large cholinergic neurons, the other cell types are interspersed in this manner.

There has been some discrepancy on the percentage of basal forebrain neurons that are cholinergic as opposed to containing other neurotransmitters. Zaborszky et al. (2005) found high ratios of GABAergic to cholinergic cells that varied according to structure, with higher ratios in the globus pallidus and SI than in the MS/VDB, HDB, ventral pallidum, and the internal capsule. While it is unclear what proportion of these GABAergic cells are cortically projecting, other studies (Gritti et al., 1997; Sarter and Bruno, 2002) found that there are roughly equal amounts of GABAergic and cholinergic cells that project to cortex. Additionally, Jones

and colleagues (Manns et al., 2001, 2003) found a large subset of cells that were neither GABAergic nor cholinergic but, rather, putatively glutamatergic. These cells also project to cortical regions. In a new study by this group using unbiased stereological estimates in rat, it was found that only a small minority of cells within the BF (5%) are capable of synthesizing acetylcholine, while 35% are capable of synthesizing GABA, and a vast majority (90%) are capable of synthesizing glutamate (Gritti et al., 2006).

The heterogeneity of cell types, and the interesting structural patterning they manifest, reveals a rich organization within the basal forebrain. The structure may consist of functionally distinct circuits constituted by basal forebrain subsections and their connected cortical regions. Further understanding of the organizational principles of this system and the role of GABAergic and glutamatergic, in addition to cholinergic, cells is likely to provide clues regarding the way in which the system may subserve aspects of cognition and memory.

### 3.15.6 Medial Septum/Vertical Limb of the Diagonal Band Electrophysiology and Memory

The MS/VDB is most well known for its role in the generation and maintenance of hippocampal oscillatory activity, especially the theta and gamma rhythms found therein (Petsche and Stumpf, 1962; Stewart and Fox, 1990a,b; Vinogradova, 1995). Initial evidence for this role came from studies that showed that lesions of the MS/VDB result in abolition of the hippocampal theta rhythm, whereas stimulation of the MS/VDB produces theta in the hippocampus (Lee et al., 1994; Jackson and Bland, 2006). Additionally, cells in the MS/VDB show oscillatory activity that correlates with the hippocampal theta rhythm. Ford et al. (1989) found that the majority of cells in the MS/VDB were theta-related and classified them as theta-on or theta-off cells. Dragoi et al. (1999) also found several types of theta-related neurons in the MS/VDB: rhythmic neurons phase-locked to theta, nonrhythmic but phase-locked cells, and a smaller group of cells that were neither rhythmic nor phase-locked to the hippocampal theta oscillation (see also Gaztelu and Buno, 1982; Alonso et al., 1987; King et al., 1998). The determination of which type of cells these were was not undertaken, and there is still some controversy over the role of different types of MS/VDB neurons on hippocampal theta. Given that there is a strong reciprocal connection from hippocampal interneurons to MS/VDB GABAergic neurons, and that hippocampal cells also show intrinsic theta rhythmic firing, it may be important to think of theta generation as a system-wide phenomenon involving several cell types and depending upon the reciprocal interrelationship between the MS/VDB and hippocampus.

Evidence for a role in hippocampal theta generation and maintenance by cholinergic MS/VDB cells is mainly indirect. Selective lesions of the cholinergic cells in the MS/VDB lead to a severe reduction of rhythmically bursting neurons within the MS/VDB (Apartis et al., 1998). Additionally, Lee et al. (1994) selectively lesioned the cholinergic MS/VDB cells and found a reduction in theta power in the hippocampus. However, a definite theta peak during active wake and rapid eye movement (REM) sleep remains in the face of an absence of cholinergic input, leading to the suggestion that GABAergic neurons could play a prominent role in theta rhythm generation. In a study in which only the noncholinergic cells in the MS/VDB were lesioned (Yoder and Pang, 2005), an attenuation of hippocampal theta was found, confirming this hypothesis. Additionally, juxtacellular labeling techniques have revealed parvalbumin (PV)-positive neurons exhibiting highly regular bursting activity correlated to either the peak or trough of hippocampal theta waves. Subsequent studies have shown that MS/VDB GABAergic cells have the intrinsic propensity to oscillate at theta frequency (Serafin et al., 1996). Furthermore, some of these neurons had an intraburst frequency in the gamma range (Manns et al., 2000a,b; Borhegyi et al., 2004), allowing for entraining of both theta and gamma rhythmicity in the hippocampus. These findings indicate that the septohippocampal GABAergic projection may be sufficient to maintain some hippocampal theta activity, while the cholinergic cells may have a role in determining the magnitude of hippocampal theta.

The MS/VDB's role in memory may be mainly through its role in theta generation, as there is considerable evidence that theta rhythm plays a vital role in information processing and memory formation (Winson, 1972; Givens and Olton, 1994; O'Keefe and Burgess, 1999; Seager et al., 2002). The role of theta in learning and memory has been a topic of interest since the finding that MS/VDB lesions that eliminated theta in the hippocampus produced severe memory deficits (Winson, 1978). A plausible mechanism by which theta rhythmicity could affect

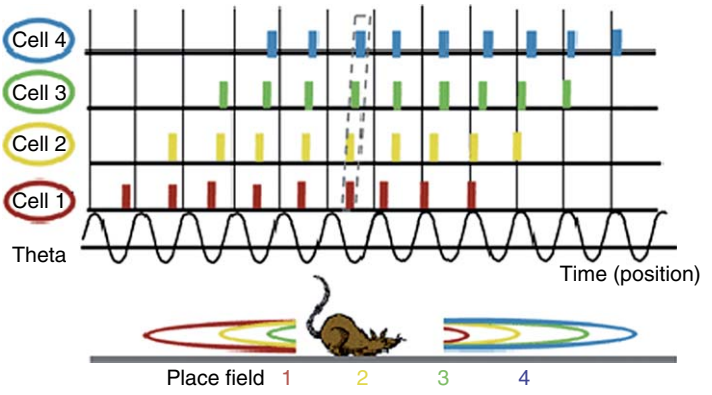


**Figure 2** Theta phase precession observed in the place cells of the rat hippocampus. When the rat runs to the right, the phase shift in firing within each theta rhythm cycle occurs in place cells 1–4, which are activated sequentially. The phase is arranged in order of firing within one phase cycle (an example is represented by gray lines). The rat running environment is expressed in compressed form in each theta cycle. From Dr. Yoko Yamaguchi, Laboratory for Dynamics of Emergent Intelligence.

information-processing and memory is for it to act as a substrate for long-term potentiation (LTP) and long-term depotentiation (LTD). In fact, studies have indicated a faster decay of LTP with MS/VDB lesions and prolonged LTP maintenance with MS/VDB stimulation (Rashidy-Pour et al., 1996; Frey et al., 2003). While the role of LTP and LTD in learning and memory is still incompletely understood, there is mounting evidence for such a role (Moser et al., 1993; Rogan et al., 1997; Wilson and Tonegawa, 1997; but see Barnes, 1995, for a critique of this view). It is revealing that several studies have indicated that LTP occurs at the peak of the theta rhythm (Pavlides et al., 1988) and that stimulation at the peak of theta induces LTP, while stimulation at the negative phase of theta rhythm depotentiates previously potentiated synapses (Holscher et al., 1997). These findings have led to the construction of a model in which the two phases, the peak and trough of local theta, correspond to memory encoding and retrieval, respectively (Hasselmo et al., 2002).

Adding to the general idea that theta has a role in memory through its action on LTP and LTD is an intriguing finding concerning the nature of place-specific cells and their firing patterns with respect to the theta rhythm. Principal (pyramidal) cells in the hippocampus show location-specific discharge during exploration (place fields). O'Keefe and Recce (1993) found that the phase of the theta cycle at which such cells fire advances gradually as the animal passes through the cell's place field; that is, the initial spiking occurs at a particular phase of theta, but each successive spike moves to an earlier location on the theta wave (see **Figure 2**). This phenomenon has been called phase precession and has been postulated to result in the compression of temporal sequences of place cell firing, which could facilitate synaptic plasticity (Skaggs et al., 1996) and perhaps act as a neural substrate of path integration and episodic memory (Dragoi and Buzsaki, 2006).

The MS/VDB's effect on hippocampal rhythmicity is thus a well-studied and robust phenomenon. Additionally, through its effect on synaptic plasticity in the form of LTP and LTD, the MS/VDB can strongly affect the way in which hippocampal processes underlying learning and memory function.

### 3.15.7 The Nucleus Basalis Magnocellularis/Substantia Innominata Electrophysiology and Memory

The NBM/SI possesses interesting electrophysiological properties that render it highly important for cortical processing. It is involved in the general role of activation or desynchronization of cortex but also plays a more specific role in learning and memory, as single-unit, field potential, and stimulation studies have revealed. While some progress has been made in determining the electrophysiological properties of NBM/SI neurons and their role in learning and memory, there is still much to be done to fully explicate these properties.

There is an abundance of evidence indicating that the NBM/SI region of the basal forebrain is involved

in the activation or desynchronization of the cortical EEG, a state that corresponds to active, exploratory, and attentive behaviors. This capacity is dependent upon both cholinergic and GABAergic projections to cortex, although much of the initial evidence for this role came from studies on acetylcholine and its role in cortical activity. The first such study (Longo, 1966) blocked cortical acetylcholine through a muscarinic receptor antagonist, which resulted in an increase in slow-wave activity much like that found in non-REM sleep. Since this initial study, many others have corroborated a role for acetylcholine on the activation of cortex (Dringenberg and Vanderwolf, 1997; McCormick and Bal, 1997; Detari et al., 1999; Cape et al., 2000; Detari, 2000; Manns et al., 2000a; Linster and Hasselmo, 2001).

Further studies showed that lesions of the NBM/SI result in a marked reduction of cortical activation, leading to the conclusion the NBM/SI is necessary for such activation. While there is some evidence that selectively lesioning just the cholinergic cells in the NBM/SI results in an attenuation of cortical desynchrony (Berntson et al., 2002), more evidence points to a combinatorial action, with GABAergic and other transmitter types such as glutamate also being involved in this capacity. Given that an equal number of GABAergic and cholinergic neurons within the NBM/SI project to cortex (Walker et al., 1989; Gritti et al., 1997; Zaborszky et al., 1999), this is not surprising. Furthermore, as stimulation of NBM/SI GABAergic corticopetal projection neurons inhibits cortical GABAergic interneurons, this can in turn increase cortical disinhibition, resulting in increased cortical activation ( Jones and Mühlethaler, 1999; Manns et al., 2001; Sarter and Bruno, 2002).

Single-unit studies have provided further evidence that the NBM/SI is involved in activating cortex. For example, enhancement of single-unit responses in the cortex occurs through stimulation of cholinergic cells (Metherate and Ashe, 1993; Herron and Schweitzer, 2000; Berntson et al., 2003). Additionally, many basal forebrain neurons show elevated discharge rates and a bursting pattern of firing during active wake and REM sleep (Cape et al., 2000; Manns et al., 2000a; Szymusiak et al., 2000). While many of these cells increase their firing rates during cortical desynchronization, some decrease their firing rates during this time. By utilizing simultaneous labeling and recording studies, Duque et al. (2000) discovered that both cholinergic and PV-labeled (GABAergic) neurons increased activity with cortical activation, while those that were labeled as neuropeptide Y (NPY), which are most likely local interneurons, decreased rates. These data lend support for a major GABAergic component to cortical activation. It is clear from the above that the basal forebrain has a complex effect on the cortex, with different neuronal types contributing differently to activation or desynchrony.

While the effect on cortical arousal is interesting in itself, there is also neurophysiological evidence supporting a more specific role for NBM/SI activity in learning and memory. This evidence originated with Kanai and Szerbs' work in 1965 on acetylcholine release in the cortex (Kanai and Szerb, 1965). They found that there were two distinct mechanisms of release in the cortex, one related to general arousal and another, more specific, function related to sensory stimuli that have obtained significance for the animal. Later work showed that stimulation of the NBM/SI increases the responsiveness of cortical neurons to sensory stimuli (Metherate and Ashe, 1991) and that Ach applied to cortical sensory neurons increases responses to sensory stimuli (Sillito and Kemp, 1983; Metherate et al., 1987), while lesions reduce the responsiveness of neurons in visual cortex to visual stimuli (Sato et al., 1987).

In addition to general increases in responsiveness, several studies have shown that NBM/SI neurons respond to particular associations formed during learning, as they respond to the learned significance of task events as well as to the novelty, familiarity, or recency of presentation of stimuli (Wilson and Rolls, 1990a,b; Whalen et al., 1994; Wilson, and Ma, 2004). Many studies have shown that stimulation of basal forebrain neurons also results in changes in the cortex that correspond to improvements in learning and increased plasticity (Metherate and Ashe, 1991; Edeline et al., 1994; Kilgard and Merzenich, 1998; Weinberger and Bakin, 1998; Rasmusson, 2000; Miasnikov et al., 2001; Kilgard, 2003). Conversely, lesions of the NBM/SI result in a reduction in such learning and plasticity (Conner et al., 2003, 2005). These changes may be subserved by the long-term enhancement of evoked potentials and the facilitation of multiunit activity that is also seen with stimulation of the region. One major remaining question is the determination of cell types that respond in these ways. To date, no study on the responses of NBM/SI neurons during behavioral tasks has determined the neurotransmitter type (cholinergic, GABAergic, or other) of the cells that have been recorded.

Cortical oscillations in the theta, beta, and gamma ranges are implicated in learning and memory.

Several studies have shown that cells within the NBM/SI are intrinsically oscillatory and that the NBM/SI can induce oscillatory activity in the cortex. Lee et al. (2004) showed that cholinergic neurons within the NBM/SI discharge in bursts at maximal rates during active waking and REM sleep, which is correlated with theta oscillations. They also found that subgroups of GABAergic neurons had very regular high-frequency tonic spiking within a gamma EEG frequency range and rhythmic bursting at theta-frequency range during cortical activation. In addition to these single-unit studies on oscillatory activity, Quinn et al. (2002) showed that local field potential recordings within the NBM/SI of freely behaving animals reveal rhythmic activity at the theta, beta, and gamma frequency ranges. Given its wide projection pattern to numerous cortical regions, oscillatory activity in the BF can have wide-ranging effects on the patterning of activity in cortex.

## 3.15.8 Animal Models of Memory

A characterization of the role of the basal forebrain and its subregions in memory has been provided through the utilization of primate and rodent models in which all or part of the basal forebrain has been removed and the resultant behavioral capabilities of the animal analyzed. A variety of techniques have been used for removal of this region, including electrolytic lesions, neurotoxic lesions, and more recently, immunotoxic lesions. Historically, observed deficits following removal of the basal forebrain were attributed to the cholinergic denervation of target structures of the basal forebrain, but with the advent of an immunolesion technique, reinterpretation of these results became necessary.

Direct investigation of the role of cholinergic neurons in memory became possible in the early 1990s, when a new immunotoxin, 192 IgG-saporin, was developed (Wiley et al., 1991). Delivery of 192 IgG-saporin directly into the basal forebrain results in selective destruction of cholinergic neurons, whereas neighboring noncholinergic neurons are left intact. This selective destruction is accomplished by taking advantage of the receptor profile of basal forebrain cholinergic neurons. Cholinergic neurons bear the P75 neurotrophin receptor that is absent from neighboring neurons. Preferentially binding to the P75 receptor, 192 IgG is an immunoglobulin that effectively delivers a cytotoxin (saporin) to the cell body, accomplishing selective destruction of the cholinergic neurons in the basal forebrain. Here it is important to note that a small subpopulation of neurons in the cholinergic basal forebrain do not bear the P75 neurotrophin receptor. This subpopulation of neurons projects primarily to amygdaloid nuclei, resulting in residual cholinergic innervation of various amygdaloid nuclei (including the basolateral nucleus) (Hecker and Mesulam, 1994).

A large body of work using this immunolesion technique has served to revise the role of the basal forebrain cholinergic system in various aspects of memory, as many of the deficits found with complete lesions have not been found with targeted removal of only cholinergic neurons. (see Baxter, 2001, for review). The basal forebrain contains several other neuromodulatory cell types, including GABAergic and glutamatergic cells, which together comprise a high percentage of the totality of neurons found in the region. Understanding the role of these and other neuromodulators is of great importance to fully explicate the role of the basal forebrain in memory.

## 3.15.9 The Medial Septum/Vertical Limb of the Diagonal Band and Memory

Total removal of MS/VDB neurons in rodents leads to profound deficits in spatial learning and memory tasks alongside an increase in reactive behavior (Gage and Olton, 1975; Mitchel et al., 1982; Dunnett et al., 1987; Hagan et al., 1988; Kelsey and Landry, 1988; Kesner et al., 1988). For example, on several spatial memory tasks that are classically disrupted by hippocampal lesions, including the Morris water maze and radial eight-arm maze, deficits in the ability to recall spatial locations following full lesions of the MS/VDB are robust. Additionally, temporary inactivation of the MS/VDB results in drastic memory deficits along with a reduction in hippocampal theta rhythm, which is important for memory (Mizumori et al., 1990; Givens and Olton, 1994; Hasselmo et al., 2002) Thus, historically, such deficits were thought to be a result of cholinergic denervation of the hippocampus and other structures to which the intact MS/VDB provides cholinergic input, building on a cholinergic hypothesis of memory. However, with the advent of selective lesioning techniques, the cholinergic basis of these deficits has been called into question.

### 3.15.10 Selective Cholinergic and GABAergic Lesions of the Medial Septum/Vertical Limb of the Diagonal Band: Implications for Attention, Learning, and Memory

A more recent body of work, in which discrete removal of the cholinergic neurons is accomplished by direct infusion of 192IgG-saporin into the MS/VDB complex, demonstrates that rodents maintain the ability to do standard spatial memory tasks, including various versions of the Morris water maze (Baxter et al., 1995, 1999a); McMahan et al., 1997). Rats with these lesions are also able to perform a standard radial maze task, even when long delays are inserted between training and testing (Chappell et al., 1998). Interestingly, selective lesions of just GABAergic cells within the MS/VDB also do not affect rats' ability to perform normally on the same tasks (Pang et al., 2001). Since neither type of lesion alone results in impairments on standard spatial memory tasks, it may be concluded that most spatial memory impairments found with lesions of the MS/VDB require at the least a depletion of both the cholinergic and GABAergic neurons within the region.

Whereas impairments in spatial memory are either mild or absent in rats who have sustained selective cholinergic lesions of the MS/VDB, a separate body of work indicates that these rats have memory deficits in tasks that emphasize other behavioral or sensory domains. Rats with selective cholinergic MS/VDB lesions demonstrate impairments on a social transmission of food preference task, a task that is dependent on olfactory associative memory (Berger-Sweeney et al., 2001; Vale-Martinez et al., 2002). Specifically, these rats demonstrate a deficit in delayed recall of a food preference learned prior to surgery, indicating a retrograde memory deficit. These data are taken to mean that the cholinergic projection to the hippocampus is involved in retrieval of social memories related to food preference.

Another arena in which rats with selective lesions of the MS/VDB demonstrate memory deficits is when they are presented with more than one potentially relevant feature. Rats were tested on a conditional associative learning task, termed environment-spatial conditional learning. In this task, the correct location of a spatial response depended on the array of local environmental cues. Rats with cholinergic lesions of the MS/VDB were impaired when the two parts of the conditional problem were presented concurrently, but not when one spatial environment was learned prior to the other. (Janisiewicz and Baxter, 2003).

These same lesions reliably produced impairments in tasks requiring that the rat learn to decrement attention to irrelevant stimuli, indicating that this system is critical for reducing attention to irrelevant stimuli and perhaps to reducing interference from irrelevant features in the environment. Although these functions do not directly address memory functions, they certainly come to bear on effective learning and memory. (Baxter et al., 1997, 1999b). Such changes in attentional processing are also evident in selective lesions of projection sites of the MS/VDB area. Discrete cholinergic denervation of the anterior cingulate, a projection region of this system, led to an increase in interference from distracting background flashes in a target detection task. This same manipulation also reduced a characteristic increase in the firing rate of medial prefrontal neurons to the distracting flashes (Gill et al., 2000), indicating that such firing works in the service of reducing processing of the flash and allowing salient information to be processed and remembered.

Discrete cholinergic lesions of the MS/VDB also impair various tasks that involve strategy selection or adaptively changing strategies or behavioral sets across both spatial (Cahill and Baxter, 2001; Bizon et al., 2003) and nonspatial (Baxter, 2001) memory tasks. This function of learning enables optimal performance in learning and memory tasks.

Selective cholinergic lesions of the MS/VDB produce domain-specific deficits in learning and memory that are insufficient to account for the sort of amnesia observed in humans but are sufficient to hamper the sort of optimal learning on which memory relies. Additionally, some very convincing studies have emphasized the importance of the GABAergic system not just as a modulator of the cholinergic system but as another primary projection system of the basal forebrain. Combined cholinergic and GABAergic lesions lead to global spatial memory impairments. This is a strong indicator that the conjoint activity of the system is essential to memory function.

### 3.15.11 The Nucleus Basalis Magnocellularis/Substantia Innominata and Memory

Complete lesions of the nucleus basalis/substantia innominata (NBM/SI) region of the basal forebrain

reveals similar learning and memory deficits to those of the MS/VDB region, despite the very different projection patterns of the two regions. Lesioning either region leads to difficulty on spatial discrimination tasks (Hepler et al., 1985) and spatial working memory tasks, including standard water maze and radial maze tasks (Bartus et al., 1985; Connor et al., 1991; Matsuoka et al., 1991). Thus, earlier studies viewed these two basal forebrain systems as having somewhat redundant memory functions while emphasizing a role for the total system in working rather than reference memory (Knowlton et al., 1985).

On nonspatial tasks, investigations have revealed differential disturbances of temporal memory between the MS/VDB and the NBM, indicating that rats with NBM lesions share deficits in temporal memory with those having frontal cortex lesions, rather than with those having MS/VDB lesions (Meck et al., 1987). The role of the NBM in aspects of temporal memory has also been explored through direct comparisons of the performance of rodents with NBM lesions to that of patients with AD on order memory tasks. Such comparisons revealed that complete lesions of the NBM result in order memory deficits that parallel those observed in patients with AD (Kesner et al., 1987).

With the development of a broader variety of neurotoxic lesion techniques, further studies indicated that, as with the MS/VDB, the substantive spatial working memory deficits observed in rodents with NBM lesions were most highly correlated with maximal destruction of basal forebrain neurons, but not with maximal depletion of acetylcholine (Wenk et al., 1989; Markowska et al., 1990). A direct comparison of different types of memory tasks across different neurotoxic lesions of the NBM indicated that maximal destruction of the NBM (in the absence of maximal depletion of cortical acetylcholine) led to spatial working memory deficits in the water maze and delayed match-to-position tasks. These lesions also impaired an attention-based serial reaction time and a passive avoidance task.

NBM lesions that maximally depleted cortical acetylcholine resulted in preserved performance on spatial working memory tasks. However, cortical acetylcholine depletion did result in impaired performance on the serial reaction task (Dunnett et al., 1990). These findings combined with contemporary findings from pharmacological studies, led to the proposal that the NBM may be preferentially involved in attentional processes rather than memory processes (Dunnett et al., 1990; Muir et al., 1993; Pang et al., 1993). One hypothesis set forth to explain the stark behavioral contrast between the substantive working memory deficits following total destruction of the NBM as opposed to the absent or mild working memory deficits following partial destruction of the NBM was the idea that the substantive memory deficits were a result of damage to the globus pallidus that included disruption of corticostriatal output pathways (for review see Dunnett et al., 1990; Muir et al., 1993). Alternatively, the mild deficits were taken to be a result of depleting cortical acetylcholine and thereby disrupting basic attentional processes (for review see Muir et al., 1993).

### 3.15.12 Selective Cholinergic Lesions of the Nucleus Basalis Magnocellularis/Substantia Innominata: Implications for Attention, Learning, and Memory

The advent of a selective immunolesion technique (192-IgG saporin) has allowed a thorough assessment of the necessity of the SI/NBM corticopetal cholinergic system in various aspects of attention as well as memory.

Behavioral and neurobiological data concur that cholinergic neurons in the basal forebrain help to fluidly and appropriately regulate attention to relevant stimuli (for review see Baxter and Chiba, 1999; McGaughy et al., 2000). The integrity of NBM/SI cholinergic neurons is also required for the typical facilitation in processing stimuli whose outcomes are uncertain (Chiba et al., 1995; Bucci et al., 1998), a strategy that has been proposed to underlie the learning of effective predictive associations between stimuli (Pearce and Hall, 1980; Holland and Gallagher, 1993). This facilitated learning of, or increasing of attention to, surprising events that are typical of intact rats but are absent in rats with NBM/SI cholinergic lesions. In addition, the integrity of NBM/SI cholinergic neurons has been found to contribute to the fluid allocation of visuospatial attention, perhaps by reducing the behavioral influence of misleading stimulus expectations from visuospatial cues. This was revealed in an experiment in which rats with NBM/SI cholinergic lesions demonstrated poorer performance than control rats on trials in which misleading cues were presented (Chiba et al., 1999). The integrity of the NBM/SI cholinergic system may also be essential for adequate detection, selection, vigilance, and processing of stimulus associations, in

addition to the proper allocation of processing to these attentional functions. This is indicated by a large literature in which NBM/SI cholinergic lesions selectively impair aspects of these functions. (for review see Sarter et al., 1999; McGaughy et al., 2000, 2002; Baxter, 2001).

Many of the described attentional deficits have been replicated by utilizing cortical infusions of 192IgG saporin to remove only those NBM/SI neurons that innervate particular cortical sites involved in these aspects of attention. Specifically, vigilance or sustained attention deficits have been replicated in animals with frontoparietal deafferentation (McGaughy et al., 1998), whereas failure to increase attention to surprising events and deficits in conditioned responding were replicated by posterior parietal deafferentation (Bucci et al., 1998; Bucci and Chess, 2005). Thus, there exists a large body of literature, based on this selective immunolesion technique, implying a role for the cholinergic NBM/SI and its cortical targets in various aspects of attention.

A large number of studies indicate that the classic working memory deficits observed in rats with total NBM/SI lesions are not observed in rats with selective cholinergic lesions of this system (for review see Baxter and Gallagher, 1996; Everitt and Robbins, 1997; Wenk, 1997; Baxter and Chiba, 1999; Baxter, 2001). For example, neither a deficit in water maze performance nor a deficit in radial maze performance (even with very long delays) was evident in these rats (Baxter et al., 1995; Chappell et al., 1998; Galani et al., 2002). Additionally, neither passive avoidance nor delayed alternation was impaired in rats with these lesions (Wenk et al., 1994). In order to eliminate the possibility that the MS/VDB neurons exert a compensatory function when the NBM/SI is lesioned, it was also important to examine the behavioral effects of combined lesions of the MS/VDB and NBM/SI cholinergic neurons on behavior. An investigation utilizing a cholinergic immunotoxin to create a combined lesion of MS/VDB, SI/NBM, and HDB indicated that, even in the face of removing this entire system, spatial working memory (as measured by performance in a standard water maze task) remained intact (Vuckovich et al., 2004). The aggregate of the NBM neurotoxic lesion work and the large body of work utilizing the selective cholinergic immunotoxin, 192 IgG saporin, refuted the long-standing hypothesis that basal forebrain cholinergic projections to the cortical mantle are essential to support classic working memory tasks.

Here it is important to note that the NBM/SI provides cholinergic innervation to the cortical mantle and also to the amygdala. The cholinergic immunotoxin, 192 IgG saporin, depletes the preponderance of cortical acetylcholine while sparing a large portion of the cholinergic innervation of the amygdala. Selected studies examining the importance of the NBM/SI projections to amygdala in memory highlight the potential importance of this basal forebrain axis in subserving aspects of memory. If the NMB/SI cholinergic neurons are lesioned simultaneously with either lesioning or cholinergic blockade of the amygdala, substantive working memory and/or emotional memory deficits are incurred, including aspects of memory consolidation and enhancement of emotional memory (see Beninger et al., 2001; Power et al., 2002). Further examination of the basal forebrain amygdalopetal pathway is likely to provide insight regarding an important role for basal forebrain cholinergic neurons in additional aspects of memory.

In light of the reliance of many of the classic working memory tasks on spatial information, a further set of studies set out to examine the role of the NBM/SI cholinergic projections in supporting forms of associative memory that rely on nonspatial sensory associations. The studies revealed that NBM/SI cholinergic lesions produce a deficit in social transmission of food preference on both immediate and 24-h retention intervals (Berger-Sweeney et al., 2000; Vale-Martinez et al., 2002), indicating a deficit in encoding new sensory associations. Another study assessing a form of configural associative memory, negative patterning, indicates that rats with NBM/SI cholinergic lesions demonstrated a deficit in this form of sensory associative learning (lights and tones) (Butt et al., 2002). These results were taken to indicate that the rats either were unable to attend to multiple sensory stimuli concurrently or were unable to cope with the different response strategies required by the task. In order to address the potential issue of cognitive flexibility, an additional study examined the ability of NBM/SI cholinergic lesioned rats to learn and reverse sensory associations. The results of this study indicate that NBM/SI lesioned rats were able to learn a simple discrimination (between two stimuli of different sensory modalities) but that they were impaired at learning multiple reversals (Cabrera et al., 2006). This is indicative of a general lack of cognitive flexibility, a function that is also impaired in primates with similar lesions. Thus, the NBM/SI appears to

play an important role in the learning, memory, and flexible use of sensory associations. Further clarity of this role will arise from additional investigation (*See* Chapter 3.11).

### 3.15.13 The Role of the Basal Forebrain in Regulating Cortical Targets

Behavioral learning and memory that depend on the formation and utilization of complex sensory associations have been shown to rely upon intact basal forebrain cholinergic projections to cortical regions. This is consistent with a large body of literature indicating that cortically projecting cholinergic neurons in the basal forebrain promote activity and plasticity in the cortex in response to sensory stimuli or actions that predict significant events in the environment (Wilson and Rolls, 1990a; Whalen et al., 1994; Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998; Mercado et al., 2001; Conner et al., 2003, 2005; Oldford et al., 2003; Berg et al., 2005). The ability of the NBM/SI to promote plasticity in very restricted cortical regions (see Weinberger, 2003; Kilgard, 2003, for review) provides anatomical support for the idea that such associative learning deficits may rely on the basal forebrain cholinergic projections to the cortical targets that preferentially support a particular type of learning.

Further support for this hypothesis comes from studies showing that selective removal of only those cholinergic neurons that project to a particular target cortical region disrupts aspects of sensory learning or memory. For example, selective removal of the cholinergic innervation of the orbitofrontal cortex (OFC) in rats is sufficient to replicate the learning and memory deficits in social transmission of food preference observed in NBM/SI lesioned rats (Ross et al., 2005). This finding is in accordance with the strong anatomical olfactory inputs to OFC and the importance of the OFC in supporting various aspects of olfactory learning and memory (see Eichenbaum, 1998, for review). Removal of the HDB cholinergic neurons eliminated acetylcholine in the olfactory system (including cortical targets and the olfactory bulb), thereby decreasing a rat's ability to discriminate between perceptually similar odorants (Linster et al., 2001).

Whereas the aforementioned studies focus on the role of acetylcholine in permitting sensory associations and discriminations, other studies examining selective destruction of basal forebrain cholinergic neurons that project to multimodal cortical regions indicate that such lesions disrupt learning and memory of novel stimuli, but not familiar stimuli. For example, cholinergic deafferentation of the entorhinal cortex results in impaired working memory, as measured by a delayed nonmatch-to-sample task, for novel but not for familiar odorants (McGaughy et al., 2005). Cholinergic deafferentation of the perirhinal cortex disrupts object recognition memory for novel objects, a process that is also disrupted by complete lesions of the perirhinal cortex (Winters and Bussey, 2005). Interestingly, these cortical target structures receive cholinergic information from two or more of the basal forebrain regions, indicating redundancy of cholinergic input and an opportunity for convergence of basal forebrain input at these cortical sites. Taken together, investigations utilizing selective cortical deafferentation indicate that these selective lesions replicate impairments incurred by lesions to their cortical regions. This indicates that basal forebrain cholinergic modulation is basic to effective cortical function under conditions of learning, memory, and attention.

### 3.15.14 The Effects of Basal Forebrain Lesions in the Nonhuman Primate

The effect of basal forebrain lesions on learning and memory delineated above was gleaned primarily from rodent studies. Nonhuman primate studies utilizing neurotoxic lesion techniques that removed the majority of NBM cell bodies have revealed selective performance deficits that differ somewhat from those found in rodents. In general, unlike complete lesions in rodents, only mild or transient memory deficits ensued, whereas, as in the rodent studies, impairments in learning and attention persisted. A study of monkeys with restricted NBM lesions found a lack of memory impairment on a recognition memory test (Aigner et al., 1987). A study of visual discrimination learning in marmoset monkeys with neurotoxic lesions of the nucleus basalis indicated a transient impairment for retention (lasting only 1 week after lesion), with a persistent impairment in new learning (Roberts et al., 1990). An additional study, testing other aspects of learning and memory, demonstrated that marmoset monkeys were able to selectively attend to stimulus features in an intra- and extradimensional set shifting task. Still, they demonstrated a

transient impairment for new learning and were incapable of serial reversal learning, demonstrating a sort of cognitive inflexibility (Roberts et al., 1992). An additional study, examining the role of the basal forebrain in cynomolgus monkeys, employed neurotoxic lesion techniques targeted at both MS/VDB and NBM (with the end result being substantial damage to the NBM with lesser damage to the MS/VDB). These basal forebrain lesioned monkeys were tested on a variety of memory tasks and on aspects of attention such as orienting and target detection. The resultant data strongly indicate a role for this region in allocating visuospatial attention, in the absence of any distinct memory impairments (Voytko et al., 1994).

An immunotoxin (with similar action to 192-IgG saporin, described above) targeting cholinergic neurons in the primate was used to independently lesion the projections to hippocampus (MS/VDB) and to the majority of cortex (NBM) in the marmoset monkey. Monkeys with MS/VDB cholinergic lesions demonstrate intact performance on a simple visual discrimination task, with a persistent deficit in a visuospatial conditional discrimination task. Monkeys with NBM cholinergic lesions demonstrate intact visuospatial conditional discrimination learning, with a transient deficit in simple visuospatial learning (Ridley et al., 1999a).

Further studies indicate that combined cholinergic lesions of the MS/VDB and NBM led to persistent deficits in both of these tasks (Ridley et al., 1999b, 2005). Thus, cholinergic depletion of the primate basal forebrain appears to produce a persistent effect on new learning.

## 3.15.15 Behavior Summary

Certainly, the variety of work done on the basal forebrain indicates that it plays an important role in aspects of attention and in aspects of learning and memory. The role of the system in memory may rely, in part, on the fact that the integrity of the basal forebrain is essential in order for experience to exert change on fundamental stimulus representations (*See* Chapter 3.11). Although this sort of memory is distinct from the classic form of declarative memory to which people typically refer when discussing memory deficits, it remains a form of memory that can substantively affect many aspects of cognition, including working memory. Another way in which the system may play a role in memory is through facilitating acquisition and encoding of selected aspects of memories (see Hasselmo, 2006, for review). Thus, the basal forebrain is an essential structure in allowing new information to be fully sustained and flexibly used by the neural system.

## 3.15.16 A Comment on Theoretical Models of Basal Forebrain Function

A multitude of experiments across behavioral domains and species have been conducted in order to shed light on the essential role of the basal forebrain and memory. Anatomical work provides the rich neurochemical landscape and potential of this region to regulate target structures and serve as a pathway to cortical modulation. Electrophysiological recording provides clues to the timing functions of this structure, in addition to its potential to modulate brain dynamics under various behavioral states. Animal models present the potential for this structure to subserve various aspects of learning, memory, and attention. Disease states provide clues to the impoverished world in which subjects with damaged basal forebrains must exist. Despite the convergent evidence that multiple fields of study lend to the behavioral function of this region, reconstruction of this work into a unified framework has posed a difficult problem. Promising attempts to unify and concatenate these data into a formal structure have recently been attempted through theoretical modeling.

The important, but often contested, roles of the basal forebrain in supporting learning and memory have inspired formal theories of the computations performed by this region and the role of such computations in regulating aspects of neuromodulation and/or neural transmission in target structures. These theories hold promise in that they provide testable hypotheses and a means by which a multitude of data can be reconstructed into a larger theoretical framework. Of the many computational models that exist, those of Hasselmo and colleagues (see Hasselmo, 2006, for review; Linster and Hasselmo, 2001) and those of Dayan, Yu, and colleagues (Yu and Dayan, 2005) are particularly relevant to the behavioral work presented in this chapter. Among other things, models by Hasselmo and colleagues provide an account of how encoding might be enhanced in various target structures of basal forebrain neurons. Models by Dayan, Yu, and colleagues provide an account of how learning is

facilitated by basal forebrain influences on cortex, revealing the way in which stimulus uncertainty augments cortical processing according to prior expectations. Full explication of such models is beyond the scope of this chapter but bears high relevance to the role of the basal forebrain in learning and memory and provides a compelling direction for future investigation.

## 3.15.17 Conclusion

Given its widespread anatomical connectivity and provocative neurophysiological properties, the sphere of influence enjoyed by the basal forebrain is undoubtedly extensive. Accessing nearly all regions of cortex and subcortex through distinct subregions, each holding a rich and diverse compilation of cells and neurochemicals, the basal forebrain is in a position to affect neuronal function across the brain. The complexities and intricacies of this heterogeneous region have only begun to be discovered, but the knowledge already gleaned has provided us with insight into some of its functions. Many of the structures to which the basal forebrain is most highly connected are essential to learning and memory, and thus the basal forebrain is naturally positioned to have a large effect on mnemonic function. Evidence provided through behavioral, lesional, and electrophysiological methods has revealed just such an effect. Through further examination of the entirety of the basal forebrain, including the different cell types and their neuromodulatory action, and through continuing examination of the vast nexus of connectivity to cortical and subcortical areas involved in memory, subtleties concerning the exact role in mnemonic processing will most likely be revealed.

## References


Aigner TG, Mitchell SJ, Aggleton JP, et al. (1987) Effects of scopolamine and physostigmine on recognition memory in monkeys with ibotenic-acid lesions of the nucleus basalis of Meynert. *Psychopharmacology (Berl)* 92(3): 292–300.

Alheid GF and Heimer L (1988) New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: The striatopallidal, amygdaloid, and corticopetal components of substantia innominata. *Neuroscience* 27(1): 1–39.

Alonso A, Gaztelu JM, Buno W Jr, and Garcia-Austt E (1987) Cross-correlation analysis of septohippocampal neurons during theta-rhythm. *Brain Res.* 413(1): 135–146.

Apartis E, Poindessous-Jazat FR, Lamour YA, and Bassant MH (1998) Loss of rhythmically bursting neurons in rat medial septum following selective lesion of septohippocampal cholinergic system. *J. Neurophysiol.* 79(4): 1633–1642.

Apparsundaram S, Martinez V, Parikh V, Kozak R, and Sarter M (2005) Increased capacity and density of choline transporters situated in synaptic membranes of the right medial prefrontal cortex of attentional task-performing rats. *J. Neurosci.* 25(15): 3851–3856.

Bakin J and Weinberger N (1996) Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. *Proc. Natl. Acad. Sci. USA* 93(20): 11219–11224.

Barnes CA (1995) Involvement of LTP in memory: Are we ''searching under the street light''? *Neuron* 15(4): 751–754.

Bartus RT, Dean RL 3rd, Beer B, and Lippa AS (1982) The cholinergic hypothesis of geriatric memory dysfunction. *Science* 217(4558): 408–414.

Bartus RT, Flicker C, Dean RL, Pontecorvo M, Figueiredo JC, and Fisher SK (1985) Selective memory loss following nucleus basalis lesions: Long-term behavioral recovery despite persistent cholinergic deficiencies. *Pharmacol. Biochem. Behav.* 23(1): 125–135.

Baxter MG (2001) Effects of selective immunotoxic lesions on learning and memory. *Methods Mol. Biol.* 166: 249–265.

Baxter MG, Bucci DJ, Gorman LK, Wiley RG, and Gallagher M (1995) Selective immunotoxic lesions of basal forebrain cholinergic cells: Effects on learning and memory in rats. *Behav. Neurosci.* 109(4): 714–722.

Baxter MG, Bucci DJ, Holland PC, and Gallagher M (1999a) Impairments in conditioned stimulus processing and conditioned responding after combined selective removal of hippocampal and neocortical cholinergic input. *Behav. Neurosci.* 113(3): 486–495.

Baxter MG, Bucci DJ, Sobel TJ, Williams MJ, Gorman LK, and Gallagher M (1996) Intact spatial learning following lesions of basal forebrain cholinergic neurons. *Neuroreport* 7(8): 1417–1420.

Baxter MG and Chiba AA (1999) Cognitive functions of the basal forebrain. *Curr. Opin. Neurobiol.* 9: 178–183.

Baxter MG and Gallagher M (1996) Intact spatial learning in both young and aged rats following selective removal of hippocampal cholinergic input. *Behav. Neurosci.* 110(3): 460–467.

Baxter MG, Gallagher M, and Holland PC (1999b) Blocking can occur without losses in attention in rats with selective removal of hippocampal cholinergic input. *Behav. Neurosci.* 113(5): 881–890.

Baxter MG, Holland PC, and Gallagher M (1997) Disruption of decrements in conditioned stimulus processing by selective removal of hippocampal cholinergic input. *J. Neurosci.* 17(13): 5230–5236.

Beninger RJ, Dringenberg HC, Boegman RJ, and Jhamandas K (2001) Cognitive effects of neurotoxic lesions of the nucleus basalis magnocellularis in rats: Differential roles for corticopetal versus amygdalopetal projections. *Neurotox. Res.* 3(1): 7–21.

Berg RW, Friedman B, Schroeder LF, and Kleinfeld D (2005) Activation of nucleus basalis facilitates cortical control of a brain stem motor program. *J. Neurophysiol.* 94(1): 699–711.

Berger-Sweeney J, Stearns NA, Frick KM, Beard B, and Baxter MG (2000) Cholinergic basal forebrain is critical for social transmission of food preferences. *Hippocampus* 10(6): 729–738.

Berger-Sweeney J, Stearns NA, Murg SL, Floerke-Nashner LR, Lappi DA, and Baxter MG (2001) Selective immunolesions of cholinergic neurons in mice: Effects on neuroanatomy, neurochemistry, and behavior. *J. Neurosci.* 21(20): 8164–8173.

Berntson GG, Shafi R, and Sarter M (2002) Specific contributions of the basal forebrain corticopetal cholinergic system to electroencephalographic activity and sleep/waking behaviour. *Eur. J. Neurosci.* 16(12): 2453–2461.

Berntson GG, Shafi R, Knox D, and Sarter M (2003) Blockade of epinephrine priming of the cerebral auditory evoked response by cortical cholinergic deafferentation. *Neuroscience* 116(1): 179–186.

Bizon JL, Han JS, Hudon C, and Gallagher M (2003) Effects of hippocampal cholinergic deafferentation on learning strategy selection in a visible platform version of the water maze. *Hippocampus* 13(6): 676–684.

Blake TM, Varnhagen CK, and Parent MB (2001) Emotionally arousing pictures increase blood glucose levels and enhance recall. *Neurobiol. Learn. Mem.* 75(3): 262–273.

Borhegyi Z, Varga V, Szilagyi N, Fabo D, and Freund TF (2004) Phase segregation of medial septal GABAergic neurons during hippocampal theta activity. *J. Neurosci.* 24(39): 8470–8479.

Borroni B, Anchisi D, Paghera B, et al. (2006) Combined 99mTc-ECD SPECT and neuropsychological studies in MCI for the assessment of conversion to AD. *Neurobiol. Aging* 27(1): 24–31.

Bowen DM, Benton JS, Spillane JA, Smith CC, and Allen SJ (1982) Choline acetyltransferase activity and histopathology of frontal neocortex from biopsies of demented patients. *J. Neurol. Sci.* 57(2–3): 191–202.

Bowers D, Verfaellie M, Valenstein E, and Heilman KM (1988) Impaired acquisition of temporal information in retrosplenial amnesia. *Brain Cogn.* 8(1): 47–66.

Bucci DJ and Chess AC (2005) Specific changes in conditioned responding following. neurotoxic damage to the posterior parietal cortex. *Behav. Neurosci.* 119(6): 1580–1587.

Bucci DJ, Holland PC, and Gallagher M (1998) Removal of cholinergic input to rat posterior parietal cortex disrupts incremental processing of conditioned stimuli. *J. Neurosci.* 18(19): 8038–8046.

Butt AE, Noble MM, Rogers JL, and Rea TE (2002) Impairments in negative patterning, but not simple discrimination learning, in rats with 192 IgG-saporin lesions of the nucleus basalis magnocellularis. *Behav. Neurosci.* 116(2): 241–255.

Cabrera SM, Chavez CM, Corley SR, Kitto MR, and Butt AE (2006) Selective lesions of the nucleus basalis magnocellularis impair cognitive flexibility. *Behav. Neurosci.* 120(2): 298–306.

Cahill JF and Baxter MG (2001) Cholinergic and noncholinergic septal neurons modulate strategy selection in spatial learning. *Eur. J. Neurosci.* 14(11): 1856–1864.

Cape EG, Manns ID, Alonso A, Beaudet A, and Jones BE (2000) Neurotensin-induced bursting of cholinergic basal forebrain neurons promotes gamma and theta cortical activity together with waking and paradoxical sleep. *J. Neurosci.* 20(22): 8452–8461.

Carlesimo GA and Oscar-Berman M (1992) Memory deficits in Alzheimer's patients: A comprehensive review. *Neuropsychol. Rev.* 3(2): 119–169.

Chappell J, McMahan R, Chiba A, and Gallagher M (1998) A re-examination of the role of basal forebrain cholinergic neurons in spatial working memory. *Neuropharmacology* 37(4–5): 481–487.

Chen KC, Baxter MG, and Rodefer JS (2004) Central blockade of muscarinic cholinergic receptors disrupts affective and attentional set-shifting. *Eur. J. Neurosci.* 20(4): 1081–1088.

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

Chiba AA, Bushnell PJ, Oshiro WM, and Gallagher M (1999) Selective removal of cholinergic neurons in the basal forebrain alters cued target detection. *Neuroreport* 10(14): 3119–3123.

Conner JM, Culberson A, Packowski C, Chiba AA, and Tuszynski MH (2003) Lesions of the basal forebrain cholinergic system impair task acquisition and abolish cortical plasticity associated with motor skill learning. *Neuron* 38(5): 819–829.

Conner JM, Chiba AA, and Tuszynski MH (2005) The basal forebrain cholinergic system is essential for cortical plasticity and functional recovery following brain injury. *Neuron* 46(2): 173–179.

Connor DJ, Langlais PJ, and Thal LJ (1991) Behavioral impairments after lesions of the nucleus basalis by ibotenic acid and quisqualic acid. *Brain Res.* 555(1): 84–90.

Crowder NA, Lehmann H, Parent MB, and Wylie DR (2002) The accessory optic system contributes to the spatio-temporal tuning of motion-sensitive pretectal neurons. *J. Neurophysiol.* 90(2): 1140–1151.

Dalley JW, McGaughy J, O'Connell MT, Cardinal RN, Levita L, and Robbins TW (2001) Distinct changes in cortical acetylcholine and noradrenaline efflux during contingent and noncontingent performance of a visual attentional task. *J. Neurosci.* 21(13): 4908–4914.

Dayan P, Kakade S, and Montague PR (2000) Learning and selective attention. *Nat. Neurosci.* 3(supplement): 1218–1223.

De Rosa E, Hasselmo ME, and Baxter MG (2001) Contribution of the cholinergic basal forebrain to proactive interference from stored odor memories during associative learning in rats. *Behav. Neurosci.* 115(2): 314–327.

Degroot A and Parent MB (2000) Increasing acetylcholine levels in the hippocampus or entorhinal cortex reverses the impairing effects of septal GABA receptor activation on spontaneous alternation. *Learn. Mem.* 7(5): 293–302.

Degroot A and Parent MB (2001) Infusions of physostigmine into the hippocampus or the entorhinal cortex attenuate avoidance retention deficits produced by intra-septal infusions of the GABA agonist muscimol. *Brain Res.* 920(1–2): 10–18.

Degroot A, Kornecook T, Quirion R, DeBow S, and Parent MB (2003) Glucose increases hippocampal extracellular acetylcholine levels upon activation of septal GABA receptors. *Brain Res.* 979(1–2): 71–77.

Detari L (2000) Tonic and phasic influence of basal forebrain unit activity on the cortical EEG. *Behav. Brain Res.* 115(2): 159–170.

Detari L, Rasmusson DD, and Semba K (1999) The role of basal forebrain neurons in tonic and phasic activation of the cerebral cortex. *Prog. Neurobiol.* 58(3): 249–277.

deToledo-Morrell L, Bulgakova M, Stoub T, et al. (2001) Differential prediction of memory performance in two tasks with MRI derived brain volumetry. *Soc. Neurosci. Abst.* 27: 858.

deToledo-Morrell L, Stoub TR, Bulgakova M, et al. (2004) MRI-derived entorhinal volume is a good predictor of conversion from MCI to AD. *Neurobiol. Aging* 25(9): 1197–1203.

Dragoi G and Buzsaki G (2006) Temporal encoding of place sequences by hippocampal cell assemblies. *Neuron* 50(1): 145–157.

Dragoi G, Carpi D, Recce M, Csicsvari J, and Buzsaki G (1999) Interactions between hippocampus and medial septum during sharp waves and theta oscillation in the behaving rat. *J. Neurosci.* 19(14): 6191–6199.

Dringenberg HC and Vanderwolf CH (1997) Neocortical activation: modulation by multiple pathways acting on central cholinergic and serotonergic systems. *Exp. Brain Res.* 116(1): 160–174.

Dunnett SB, Everitt BJ, and Robbins TW (1991) The basal forebrain-cortical cholinergic system: interpreting the functional consequences of excitotoxic lesions. *Trends Neurosci.* 14(11): 494–501.

Dunnett SB, Whishaw IQ, Jones GH, and Bunch ST (1987) Behavioural, biochemical and histochemical effects of

different neurotoxic amino acids injected into nucleus basalis magnocellularis of rats. *Neuroscience* 20(2): 653–669.
Duque A, Balatoni B, Detari L, and Zaborszky L (2000) EEG correlation of the discharge properties of identified neurons in the basal forebrain. *J. Neurophysiol.* 84(3): 1627–1635.
Edeline JM, Hars B, Maho C, and Hennevin E (1994) Transient and prolonged facilitation of tone-evoked responses induced by basal forebrain stimulations in the rat auditory cortex. *Exp. Brain Res.* 97(3): 373–386.
Eichenbaum H (1998) Using olfaction to study memory. *Ann. NY Acad. Sci.* 855: 657–669.
Erickson EJ, Watts KD, and Parent MB (2006) Septal co-infusions of glucose with a GABAB agonist impair memory. *Neurobiol. Learn. Mem.* 85(1): 66–70.
Espana RA and Berridge CW (2006) Organization of noradrenergic efferents to arousal-related basal forebrain structures. *J. Comp. Neurol.* 496(5): 668–683.
Everitt BJ and Robbins TW (1997) Central cholinergic systems and cognition. *Annu. Rev. Psychol.* 48: 649–684.
Fischer W, Wictorin K, Isacson O, and Bjorklund A (1988) Trophic effects on cholinergic striatal interneurons by submaxillary gland transplants. *Prog. Brain Res.* 78: 409–412.
Ford RD, Colom LV, and Bland BH (1989) The classification of medial septum-diagonal band cells as theta-on or theta-off in relation to hippocampal EEG states. *Brain Res.* 493(2): 269–282.
Fox MT, Barense MD, and Baxter MG (2003) Perceptual attentional set-shifting is impaired in rats with neurotoxic lesions of posterior parietal cortex. *J. Neurosci.* 23(2): 676–681.
Francis PT (2005) The interplay of neurotransmitters in Alzheimer's disease. *CNS Spectr.* 10–11(supplement 18): 6–9.
Frankland PW and Bontempi B (2006) Fast track to the medial prefrontal cortex. *Proc. Natl. Acad. Sci. USA* 103(3): 509–510.
Frey S, Bergado JA, and Frey JU (2003) Modulation of late phases of long-term potentiation in rat dentate gyrus by stimulation of the medial septum. *Neuroscience* 118(4): 1055–1062.
Frick KM, Kim JJ, and Baxter MG (2004) Effects of complete immunotoxin lesions of the cholinergic basal forebrain on fear conditioning and spatial learning. *Hippocampus* 14(2): 244–254.
Gage FH and Olton DS (1975) Hippocampal influence on hyperreactivity induced by septal lesions. *Brain Res.* 98(2): 311–325.
Galani R, Lehmann O, Bolmont T, et al. (2002) Selective immunolesions of CH4 cholinergic neurons do not disrupt spatial memory in rats. *Physiol. Behav.* 76(1): 75–90.
Gasbarri A, Sulli A, Pacitti C, and McGaugh JL (1999) Serotonergic input to cholinergic neurons in the substantia innominata and nucleus basalis magnocellularis in the rat. *Neuroscience* 91(3): 1129–1142.
Gaztelu JM and Buno W Jr (1982) Septo-hippocampal relationships during EEG theta rhythm. *Electroencephalogr. Clin. Neurophysiol.* 54(4): 375–387.
Gill TM, Sarter M, and Givens B (2000) Sustained visual attention performance-associated prefrontal neuronal activity: Evidence for cholinergic modulation. *J. Neurosci.* 20(12): 4745–4757.
Givens B and Olton DS (1994) Local modulation of basal forebrain: effects on working and reference memory. *J. Neurosci.* 14(6): 3578–3587.
Gritti I, Mainville L, Mancia M, and Jones BE (1997) GABAergic and other noncholinergic basal forebrain neurons, together with cholinergic neurons, project to the mesocortex and isocortex in the rat. *J. Comp. Neurol.* 383(2): 163–177.
Gritti I, Manns ID, Mainville L, and Jones BE (2003) Parvalbumin, calbindin, or calretinin in cortically projecting and GABAergic, cholinergic, or glutamatergic basal forebrain neurons of the rat. *J. Comp. Neurol.* 458(1): 11–31.
Gritti I, Henry P, Gallioni F, Mainville L, Mariotti M, and Jones BE (2006) Stereological estimates of the basal forebrain cell population in the rat, including neurons containing choline acetyltransferase, glutamic acid decarboxylase or phosphate-activated glutaminase and colocalizing vesicular glutamate transporters. *Neuroscience* 143(4): 1051–1064.
Gsell W, Jungkunz G, and Riederer P (2004) Functional neurochemistry of Alzheimer's disease. *Curr. Pharm. Des.* 10(3): 265–293.
Hagan JJ, Salamone JD, Simpson J, Iversen SD, and Morris RG (1988) Place navigation in rats is impaired by lesions of medial septum and diagonal band but not nucleus basalis magnocellularis. *Behav. Brain Res.* 27(1): 9–20.
Hasselmo ME (2006) The role of acetylcholine in learning and memory. *Curr. Opin. Neurobiol.* 16(6): 710–715.
Hasselmo ME and McGaughy J (2004) High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. *Prog. Brain Res.* 145: 207–231.
Hasselmo ME, Bodelon C, and Wyble BP (2002) A proposed function for hippocampal theta rhythm: Separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Comput.* 14(4): 793–817.
Hecker S and Mesulam MM (1994) Two types of cholinergic projections to the rat amygdala. *Neuroscience* 60(2): 383–397.
Hepler DJ, Olton DS, Wenk GL, and Coyle JT (1985) Lesions in nucleus basalis magnocellularis and medial septal area of rats produce qualitatively similar memory impairments. *J. Neurosci.* 5(4): 866–873.
Herron P and Schweitzer JB (2000) Effects of cholinergic depletion on neural activity in different laminae of the rat barrel cortex. *Brain Res.* 872(1–2): 71–76.
Hirono N, Mori E, Ishii K, et al. (1998) Hypofunction in the posterior cingulate gyrus correlates with disorientation for time and place in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 64(4): 552–554.
Holland P and Gallagher M (1993) Amygdala central nucleus lesions disrupt increments, but not decrements, in conditioned stimulus processing. *Behav. Neurosci.* 107(2): 246–253.
Holscher C, Anwyl R, and Rowan MJ (1997) Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. *J. Neurosci.* 17(16): 6470–6477.
Huang C, Wahlund LO, Svensson L, Winblad B, and Julin P (2002) Cingulate cortex hypoperfusion predicts Alzheimer's disease in mild cognitive impairment. *BMC Neurol.* 2: 9.
Jackson J and Bland BH (2006) Medial septal modulation of the ascending brainstem hippocampal synchronizing pathways in the anesthetized rat. *Hippocampus* 16(1): 1–10.
Janisiewicz AM and Baxter MG (2003) Transfer effects and conditional learning in rats with selective lesions of medial septal/diagonal band cholinergic neurons. *Behav. Neurosci.* 117(6): 1342–1352.
Janisiewicz AM, Jackson O 3rd, Firoz EF, and Baxter MG (2004) Environment-spatial conditional learning in rats with selective lesions of medial septal cholinergic neurons. *Hippocampus* 14(2): 265–273.
Jonasson Z, Cahill JF, Tobey RE, and Baxter MG (2004) Sexually dimorphic effects of hippocampal cholinergic deafferentation in rats. *Eur. J. Neurosci.* 20(11): 3041–3053.

Jones BE and Mühlethaler M (1999) Cholinergic and GABAergic neurons of the basal forebrain: role in cortical activation. In: Lydic R and Baghdoyan H (eds.) *Handbook of Behavioral State Control: Cellular and Molecular Mechanisms*, pp. 213–233. Boca Raton, FL: CRC Press.

Kanai T and Szerb JC (1965) Mesencephalic reticular activating system and cortical acetylcholine output. *Nature* 205: 80–82.

Kelsey JE and Landry BA (1988) Medial septal lesions disrupt spatial mapping ability in rats. *Behav. Neurosci.* 102(2): 289–293.

Kesner RP, Adelstein T, and Crutcher KA (1987) Rats with nucleus basalis magnocellularis lesions mimic mnemonic symptomatology observed in patients with dementia of the Alzheimer's type. *Behav. Neurosci.* 101(4): 451–456.

Kesner RP, Crutcher K, and Beers DR (1988) Serial position curves for item (spatial location) information: Role of the dorsal hippocampal formation and medial septum. *Brain Res.* 454(1–2): 219–226.

Kilgard M (2003) Cholinergic modulation of skill learning and plasticity. *Neuron* 38(5): 678–680.

Kilgard M and Merzenich M (1998) Cortical map reorganization enabled by nucleus basalis activity. *Science* 279(5357): 1714–1718.

Kim JJ and Baxter MG (2001) Multiple brain-memory systems: The whole does not equal the sum of its parts. *Trends Neurosci.* 24(6): 324–330.

King C, Recce M, and O'Keefe J (1998) The rhythmicity of cells of the medial septum/diagonal band of Broca in the awake freely moving rat: Relationships with behaviour and hippocampal theta. *Eur. J. Neurosci.* 10(2): 464–477.

Knowlton BJ, Wenk GL, Olton DS, and Coyle JT (1985) Basal forebrain lesions produce a dissociation of trial-dependent and trial-independent memory performance. *Brain Res.* 345(2): 315–321.

Kozak R, Bruno JP, and Sarter M (2006) Augmented prefrontal acetylcholine release during challenged attentional performance. *Cereb. Cortex* 16(1): 9–17.

Krebs DL and Parent MB (2005) Hippocampal infusions of pyruvate reverse the memory-impairing effects of septal muscimol infusions. *Eur. J. Pharmacol.* 520(1–3): 91–99.

Lee MG, Chrobak JJ, Sik A, Wiley RG, and Buzsaki G (1994) Hippocampal theta activity following selective lesion of the septal cholinergic system. *Neuroscience* 62(4): 1033–1047.

Lee MG, Manns ID, Alonso A, and Jones BE (2004) Sleep-wake related discharge properties of basal forebrain neurons recorded with micropipettes in head-fixed rats. *J. Neurophysiol.* 92(2): 1182–1198.

Linster C and Hasselmo ME (2001) Neuromodulation and the functional dynamics of piriform cortex. *Chem. Senses* 26(5): 585–594.

Linster C, Garcia PA, Hasselmo ME, and Baxter MG (2001) Selective loss of cholinergic neurons projecting to the olfactory system increases perceptual generalization between similar, but not dissimilar, odorants. *Behav. Neurosci.* 115(4): 826–833.

Longo VG (1966) Behavioral and electroencephalographic effects of atropine and related compounds. *Pharmacol. Rev.* 18(2): 965–996.

Manns ID, Alonso A, and Jones BE (2000a) Discharge properties of juxtacellularly labeled and immunohistochemically identified cholinergic basal forebrain neurons recorded in association with the electroencephalogram in anesthetized rats. *J. Neurosci.* 20(4): 1505–1518.

Manns ID, Alonso A, and Jones BE (2000b) Discharge profiles of juxtacellularly labeled and immunohistochemically identified GABAergic basal forebrain neurons recorded in association with the electroencephalogram in anesthetized rats. *J. Neurosci.* 20(24): 9252–9263.

Manns ID, Mainville L, and Jones BE (2001) Evidence for glutamate, in addition to acetylcholine and GABA, neurotransmitter synthesis in basal forebrain neurons projecting to the entorhinal cortex. *Neuroscience* 107(2): 249–263.

Manns ID, Alonso A, and Jones BE (2003) Rhythmically discharging basal forebrain units comprise cholinergic GABAergic, and putative glutamatergic cells. *J. Neurophysiol.* 89(2): 1057–1066.

Markowska AL, Wenk GL, and Olton DS (1990) Nucleus basalis magnocellularis and memory: Differential effects of two neurotoxins. *Behav. Neural Biol.* 54(1): 13–26.

Matsuoka N, Maeda N, Ohkubo Y, and Yamaguchi I (1991) Differential effects of physostigmine and pilocarpine on the spatial memory deficits produced by two septo-hippocampal deafferentations in rats. *Brain Res.* 559(2): 233–240.

McCormick DA and Bal T (1997) Sleep and arousal: Thalamocortical mechanisms. *Annu. Rev. Neurosci.* 20: 185–215.

McGaughy J and Sarter M (1988) Sustained attention performance in rats with intracortical infusions of 192 IgG-saporin-induced cortical cholinergic deafferentation: Effects of physostigmine and FG (7142). *Behav. Neurosci.* 112(6): 1519–1525.

McGaughy J, Everitt BJ, Robbins TW, and Sarter M (2000) The role of cortical cholinergic afferent projections in cognition: Impact of new selective immunotoxins. *Behav. Brain Res.* 115(2): 251–263.

McGaughy J, Dalley JW, Morrison CH, Everitt BJ, and Robbins TW (2002) Selective behavioral and neurochemical effects of cholinergic lesions produced by intrabasalis infusions of 192 IgG-saporin on attentional performance in a five-choice serial reaction time task. *J. Neurosci.* 22(5): 1905–1913.

McGaughy J, Koene RA, Eichenbaum H, and Hasselmo ME (2005) Cholinergic deafferentation of the entorhinal cortex in rats impairs encoding of novel but not familiar stimuli in a delayed nonmatch-to-sample task. *J. Neurosci.* 25(44): 10273–10281.

McKinney M and Jacksonville MC (2005) Brain cholinergic vulnerability: Relevance to behavior and disease. *Biochem. Pharmacol.* 70(8): 1115–1124.

McMahan RW, Sobel TJ, and Baxter MG (1997) Selective immunolesions of hippocampal cholinergic input fail to impair spatial working memory. *Hippocampus* 7(2): 130–136.

Meck WH, Church RM, Wenk GL, and Olton DS (1987) Nucleus basalis magnocellularis and medial septal area lesions differentially impair temporal memory. *J. Neurosci.* 7(11): 3505–3511.

Mercado E, Bao S, Orduna I, Gluck MA, and Merzenich MM (2001) Basal forebrain stimulation changes cortical sensitivities to complex sound. *Neuroreport* 20;12(10): 2283–2287.

Mesulam MM (2004) The cholinergic innervation of the human cerebral cortex. *Prog. Brain Res.* 145: 67–78.

Metherate R and Ashe JH (1991) Basal forebrain stimulation modifies auditory cortex responsiveness by an action at muscarinic receptors. *Brain Res.* 559(1): 163–167.

Metherate R and Ashe JH (1993) Nucleus basalis stimulation facilitates thalamocortical synaptic transmission in the rat auditory cortex. *Synapse* 14(2): 132–143.

Metherate R, Tremblay N, and Dykes RW (1987) Acetylcholine permits long-term enhancement of neuronal responsiveness in cat primary somatosensory cortex. *Neuroscience* 22(1): 75–81.

Metherate R, Tremblay N, and Dykes RW (1988) Transient and prolonged effects of acetylcholine on responsiveness of cat somatosensory cortical neurons. *J. Neurophysiol.* 59(4): 1253–1276 [Erratum in *J. Neurophysiol*. 63(1): 223].

Miasnikov AA, McLin D 3rd, and Weinberger NM (2001) Muscarinic dependence of nucleus basalis-induced conditioned receptive field plasticity. *Neuroreport* 12(7): 1537–1542.

Milner B (2005) The medial temporal-lobe amnesic syndrome. *Psychiatr. Clin. North Am.* 28(3): 599–611.

Mitchel SJ, Rawlins JN, Steward O, and Olton DS (1982) Medial septal area lesions disrupt theta rhythm and cholinergic staining in medial entorhinal cortex and produce impaired radial arm maze behavior in rats. *J. Neurosci.* 2(3): 292–302.

Mizumori SJ, Perez GM, Alvarado MC, Barnes CA, and McNaughton BL (1990) Reversible inactivation of the medial septum differentially affects two forms of learning in rats. *Brain Res.* 528(1): 12–20.

Moser E, Moser MB, and Andersen P (1993) Synaptic potentiation in the rat dentate gyrus during exploratory learning. *Neuroreport* 5(3): 317–320.

Mufson EJ, Ma SY, Dills J, et al. (2002) Loss of basal forebrain P75(NTR) immunoreactivity in subjects with mild cognitive impairment and Alzheimer's disease. *J. Comp. Neurol.* 443(2): 136–153.

Muir JL, Page KJ, Sirinathsinghji DJ, Robbins TW, and Everitt BJ (1993) Excitotoxic lesions of basal forebrain cholinergic neurons: effects on learning, memory and attention. *Behav. Brain Res.* 57(2): 123–131.

Myers CE, Bryant D, DeLuca J, and Gluck MA (2002) Dissociating basal forebrain and medial temporal amnesic syndromes: insights from classical conditioning. *Integr. Physiol. Behav. Sci.* 37(2): 85–102.

Myers CE, DeLuca J, Hopkins RO, and Gluck MA (2005) Conditional discrimination and reversal in amnesia subsequent to hypoxic brain injury or anterior communicating artery aneurysm rupture. *Neuropsychologia* 44(1): 130–139.

Nelson CL, Sarter M, and Bruno JP (2005) Prefrontal cortical modulation of acetylcholine release in posterior parietal cortex. *Neuroscience* 132(2): 347–359.

Nestor PJ, Fryer TD, Ikeda M, and Hodges JR (2003) Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). *Eur. J. Neurosci.* 18(9): 2663–2667.

O'Keefe J and Burgess N (1999) Theta activity, virtual navigation and the human hippocampus. *Trends Cogn. Sci.* 3(11): 403–406.

O'Keefe J and Recce ML (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3(3): 317–330.

Oldford E and Castro-Alamancos MA (2003) Input-specific effects of acetylcholine on sensory and intracortical evoked responses in the ''barrel cortex'' in vivo. *Neuroscience* 117(3): 769–778.

Olton DS, Wenk GL, Church RM, and Meck WH (1988) Attention and the frontal cortex as examined by simultaneous temporal processing. *Neuropsychologia* 26(2): 307–318.

Osimani A, Vakil E, Blinder G, Sobel R, and Abarbanel JM (2006) Basal forebrain amnesia: A case study. *Cogn. Behav. Neurol.* 19(2): 65–70.

Pang KC and Nocera R (1999) Interactions between 192-IgG saporin and intraseptal cholinergic and GABAergic drugs: Role of cholinergic medial septal neurons in spatial working memory. *Behav. Neurosci.* 113(2): 265–275.

Pang K, Williams MJ, Egeth H, and Olton DS (1993) Nucleus basalis magnocellularis and attention: Effects of muscimol infusions. *Behav. Neurosci.* 107(6): 1031–1038.

Pang KC, Nocera R, Secor AJ, and Yoder RM (2001) GABAergic septohippocampal neurons are not necessary for spatial memory. *Hippocampus* 11(6): 814–827.

Parent MB and Baxter MG (2004) Septohippocampal acetylcholine: involved in but not necessary for learning and memory? *Learn. Mem.* 11(1): 9–20.

Parent MB and Gold PE (1997) Intra-septal infusions of glucose potentiate inhibitory avoidance deficits when co-infused with the GABA agonist muscimol. *Brain Res.* 745(1–2): 317–320.

Parent MB, Laurey PT, Wilkniss S, and Gold PE (1997) Intraseptal infusions of muscimol impair spontaneous alternation performance: Infusions of glucose into the hippocampus, but not the medial septum, reverse the deficit. *Neurobiol. Learn. Mem.* 68(1): 75–85.

Pavlides C, Greenstein YJ, Grudman M, and Winson J (1988) Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. *Brain Res.* 439(1–2): 383–387.

Pearce JM and Hall G (1980) A model for Pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychol. Rev.* 87(6): 532–552.

Pennanen C, Kivipelto M, Tuomainen S, et al. (2004) Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiol. Aging* 25(3): 303–310.

Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH, and Perry RH (1978) Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *BMJ* 2(6150): 1457–1459.

Petsche H and Stumpf C (1962) The origin of theta-rhythm in the rabbit hippocampus. *Wien Klin. Wochenschr.* 74: 696–700.

Power AE, Thal LJ, and McGaugh JL (2002) Lesions of the nucleus basalis magnocellularis induced by 192 IgG-saporin block memory enhancement with posttraining norepinephrine in the basolateral amygdala. *Proc. Natl. Acad. Sci. USA* 99(4): 2315–2319.

Quinn LK, Pechenik GM, Chiba AA, and Nitz DA (2002) Local field potential recordings in the rat basal forebrain reveal prominent bursts of theta- and beta/gamma frequency activity. *Soc. Neurosci. Abst.* 28: 584.

Rashidy-Pour A, Motamedi F, Semnanian S, Zarrindast MR, Fatollahi Y, and Behzadi G (1996) Effects of reversible inactivation of the medial septal area on long-term potentiation and recurrent inhibition of hippocampal population spikes in rats. *Brain Res.* 734(1–2): 43–48.

Rasmusson DD (2000) The role of acetylcholine in cortical synaptic plasticity. *Behav. Brain Res.* 115(2): 205–218.

Ridley RM, Baker HF, Leow-Dyke A, and Cummings RM (2005) Further analysis of the effects of immunotoxic lesions of the basal nucleus of Meynert reveals substantial impairment on visual discrimination learning in monkeys. *Brain Res. Bull.* 65(5): 433–442.

Ridley RM, Barefoot HC, Maclean CJ, Pugh P, and Baker HF (1999a) Different effects on learning ability after injection of the cholinergic immunotoxin ME20.4IgG-saporin into the diagonal band of Broca, basal nucleus of Meynert, or both in monkeys. *Behav. Neurosci.* 113(2): 303–315.

Ridley RM, Pugh P, Maclean CJ, and Baker HF (1999b) Severe learning impairment caused by combined immunotoxic lesion of the cholinergic projections to the cortex and hippocampus in monkeys. *Brain Res.* 836(1–2): 120–132.

Roberts AC, Robbins TW, Everitt BJ, et al. (1990) The effects of excitotoxic lesions of the basal forebrain on the acquisition, retention and serial reversal of visual discriminations in marmosets. *Neuroscience* 34(2): 311–329.

Roberts AC, Robbins TW, Everitt BJ, and Muir JL (1992) A specific form of cognitive rigidity following excitotoxic lesions of the basal forebrain in marmosets. *Neuroscience* 47(2): 251–264.

Rogan MT, Staubli UV, and LeDoux JE (1997) Fear conditioning induces associative long-term potentiation in the amygdala. *Nature* 390(6660): 604–607.

Ross RS, McGaughy J, and Eichenbaum H (2005) Acetylcholine in the orbitofrontal cortex is necessary for the acquisition of a socially transmitted food preference. *Learn. Mem.* 12(3): 302–306.

Sarter M and Bruno JP (2002) The neglected constituent of the basal forebrain corticopetal projection system: GABAergic projections. *Eur. J. Neurosci.* 15(12): 1867–1873.

Sarter M, Bruno JP, and Turchi J (1999) Basal forebrain afferent projections modulating cortical acetylcholine, attention, and implications for neuropsychiatric disorders. *Ann. N. Y. Acad. Sci.* 877: 368–382.

Sarter M, Bruno JP, Miner LA, and McGaughy J (2000) Development of a method for intraparenchymal infusions of 192 IgG-saporin: a comment on Pizzo et al. (1999). *J. Neurosci. Methods* 96(2): 169–170.

Sarter M, Hasselmo ME, Bruno JP, and Givens B (2005) Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. *Brain Res. Brain Res. Rev.* 48(1): 98–111.

Sarter M and Parikh V (2005) Choline transporters, cholinergic transmission and cognition. *Nat. Rev. Neurosci.* 6(1): 48–56.

Sato H, Hata Y, Hagihara K, and Tsumoto T (1987) Effects of cholinergic depletion on neuron activities in the cat visual cortex. *J. Neurophysiol.* 58(4): 781–794.

Satoh K and Fibiger HC (1986) Cholinergic neurons of the laterodorsal tegmental nucleus: efferent and afferent connections. *J. Comp. Neurol.* 253(3): 277–302.

Seager MA, Johnson LD, Chabot ES, Asaka Y, and Berry SD (2002) Oscillatory brain states and learning: Impact of hippocampal theta-contingent training. *Proc. Natl. Acad. Sci. USA* 99(3): 1616–1620.

Semba K, Reiner PB, McGeer EG, and Fibiger HC (1988) Brainstem afferents to the magnocellular basal forebrain studied by axonal transport, immunohistochemistry, and electrophysiology in the rat. *J. Comp. Neurol.* 267(3): 433–453.

Serafin M, Williams S, Khateb A, Fort P, and Muhlethaler M (1996) Rhythmic firing of medial septum non-cholinergic neurons. *Neuroscience* 75(3): 671–675.

Shah AA and Parent MB (2003) Septal infusions of glucose or pyruvate, but not fructose, produce avoidance deficits when co-infused with the GABA agonist muscimol. *Neurobiol. Learn. Mem.* 79(3): 243–251.

Shah AA and Parent MB (2004) Septal infusions of glucose or pyruvate with muscimol impair spontaneous alternation. *Brain Res.* 996(2): 246–250.

Shute CC and Lewis PR (1967) The ascending cholinergic reticular system: Neocortical, olfactory and subcortical projections. *Brain* 90(3): 497–520.

Sillito AM and Kemp JA (1983) Cholinergic modulation of the functional organization of the cat visual cortex. *Brain Res.* 289(1–2): 143–155.

Skaggs WE, McNaughton BL, Wilson MA, and Barnes CA (1996) Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 6(2): 149–172.

Smith HR and Pang KC (2005) Orexin-saporin lesions of the medial septum impair spatial memory. *Neuroscience* 132(2): 261–271.

Stewart M and Fox SE (1990a) Do septal neurons pace the hippocampal theta rhythm? *Trends Neurosci.* 13(5): 163–168.

Stewart M and Fox SE (1990b) Firing relations of lateral septal neurons to the hippocampal theta rhythm in urethane anesthetized rats. *Exp. Brain Res.* 79(1): 92–96.

Szymusiak R, Alam N, and McGinty D (2000) Discharge patterns of neurons in cholinergic regions of the basal forebrain during waking and sleep. *Behav. Brain Res.* 115(2): 171–182.

Tranel D (2002) Functional neuroanatomy: Neuropsychological correlates of cortical and subcortical damage. In: Yudofsky SC and Hales RE (eds.) *Textbook of Neuropsychiatry and Clinical Neurosciences,* 4th edn., pp. 71–113. Arlington, VA: American Psychiatric Press.

Tranel D and Jones RD (2006) Knowing ''what'' and knowing ''when.'' *J. Clin. Exp. Neuropsychol.* 28(1): 43–66.

Tuszynski MH, Thal L, Pay M, et al. (2005) A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. *Nat. Med.* 11(5): 551–555.

Vale-Martinez A, Baxter MG, and Eichenbaum H (2002) Selective lesions of basal forebrain cholinergic neurons produce anterograde and retrograde deficits in a social transmission of food preference task in rats. *Eur. J. Neurosci.* 16(6): 983–998.

Valenstein E, Bowers D, Verfaellie M, Heilman KM, Day A, and Watson RT (1987) Retrosplenial amnesia. *Brain* 110: 1631–1646.

Vinogradova OS (1995) Expression, control, and probable functional significance of the neuronal theta-rhythm. *Prog. Neurobiol.* 45(6): 523–583.

Voytko ML, Olton DS, Richardson RT, Gorman LK, Tobin JR, and Price DL (1994) Basal forebrain lesions in monkeys disrupt attention but not learning and memory. *J. Neurosci.* 14(1): 167–186.

Vuckovich JA, Semel ME, and Baxter MG (2004) Extensive lesions of cholinergic basal forebrain neurons do not impair spatial working memory. *Learn. Mem.* 11(1): 87–94.

Wais PE, Wixted JT, Hopkins RO, and Squire LR (2006) The hippocampus supports both the recollection and the familiarity components of recognition memory. *Neuron* 49: 459–468.

Walker LC, Price DL, and Young WS 3rd (1989) GABAergic neurons in the primate basal forebrain magnocellular complex. *Brain Res.* 499(1): 188–192.

Weinberger NM (2003) The nucleus basalis and memory codes: auditory cortical plasticity and the induction of specific, associative behavioral memory. *Neurobiol. Learn. Mem.* 80(3): 268–284.

Weinberger NM and Bakin JS (1998) Research on auditory cortex plasticity. *Science* 280(5367): 1174.

Wellman CL and Pelleymounter MA (1999) Differential effects of nucleus basalis lesions in young adult and aging rats. *Neurobiol. Aging* 20(4): 381–393.

Wenk GL (1997) The nucleus basalis magnocellularis cholinergic system: One hundred years of progress. *Neurobiol. Learn. Mem.* 67(2): 85–95.

Wenk GL (2006) Neuropathologic changes in Alzheimer's disease: potential targets for treatment. *J. Clin. Psychiatry* 67(supplement 3): 3–7.

Wenk GL, Markowska AL, and Olton DS (1989) Basal forebrain lesions and memory: Alterations in neurotensin, not acetylcholine, may cause amnesia. *Behav. Neurosci.* 103(4): 765–769.

Wenk GL, Stoehr JD, Quintana G, Mobley S, and Wiley RG (1994) Behavioral, biochemical, histological, and electrophysiological effects of 192 IgG-saporin injections into the basal forebrain of rats. *J. Neurosci.* 14(10): 5986–5995.

Westerberg CE, Paller KA, Weintraub S, et al. (2006) When memory does not fail: Familiarity-based recognition in mild cognitive impairment and Alzheimer's disease. *Neuropsychology* 20(2): 193–205.

Whalen PJ, Kapp BS, and Pascoe JP (1994) Neuronal activity within the nucleus basalis and conditioned neocortical electroencephalographic activation. *J. Neurosci.* 14(3): 1623–1633.

Wiley RG, Oeltmann TN, and Lappi DA (1991) Immunolesioning: Selective destruction of neurons using immunotoxin to rat NGF receptor. *Brain Res.* 562: 149–153.

Wilson FA and Ma YY (2004) Reinforcement-related neurons in the primate basal forebrain respond to the learned

significance of task events rather than to the hedonic attributes of reward. *Brain Res. Cogn. Brain Res.* 19(1): 74–81.

Wilson FA and Rolls ET (1990a) Learning and memory is reflected in the responses of reinforcement-related neurons in the primate basal forebrain. *J. Neurosci.* 10(4): 1254–1267.

Wilson FA and Rolls ET (1990b) Neuronal responses related to the novelty and familiarity of visual stimuli in the substantia innominata, diagonal band of Broca and periventricular region of the primate basal forebrain. *Exp. Brain Res.* 80(1): 104–120.

Wilson MA and Tonegawa S (1997) Synaptic plasticity, place cells and spatial memory: Study with second generation knockouts. *Trends Neurosci.* 20(3): 102–106.

Winson J (1972) Interspecies differences in the occurrence of theta. *Behav. Biol.* 7(4): 479–487.

Winson J (1978) Loss of hippocampal theta rhythm results in spatial memory deficit in the rat. *Science* 201(4351): 160–163.

Winters BD and Bussey TJ (2005) Removal of cholinergic input to perirhinal cortex disrupts object recognition but not spatial working memory in the rat. *Eur. J. Neurosci.* 21(8): 2263–2270.

Woolf NJ (1991) Cholinergic systems in mammalian brain and spinal cord. *Prog. Neurobiol.* 37(6): 475–524.

Woolf NJ and Butcher LL (1986) Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain. *Brain Res. Bull.* 16(5): 603–637.

Wu CK, Thal L, Pizzo D, Hansen L, Masliah E, and Geula C (2005) Apoptotic signals within the basal forebrain cholinergic neurons in Alzheimer's disease. *Exp. Neurol.* 195(2): 484–496.

Yoder RM and Pang KC (2005) Involvement of GABAergic and cholinergic medial septal neurons in hippocampal theta rhythm. *Hippocampus* 15(3): 381–392.

Yu AJ and Dayan P (2005) Uncertainty, neuromodulation, and attention. *Neuron* 46(4): 681–692.

Zaborszky L (2002) The modular organization of brain systems. Basal forebrain: the last frontier. *Prog. Brain Res.* 136: 359–372.

Zaborszky L, Pang K, Somogyi J, Nadasdy Z, and Kallo I (1999) The basal forebrain corticopetal system revisited. *Ann. NY Acad. Sci.* 877: 339–367.

Zaborszky L, Buhl DL, Pobalashingham S, Bjaalie JG, and Nadasdy Z (2005) Three-dimensional chemoarchitecture of the basal forebrain: spatially specific association of cholinergic and calcium binding protein-containing neurons. *Neuroscience* 136(3): 697–713. Erratum in: *Neuroscience* 139(3): 1161.

Zahm DS (2006) The evolving theory of basal forebrain functional-anatomical ''macrosystems.'' *Neurosci. Biobehav. Rev.* 30(2): 148–172.