Modes and Models of Forebrain Cholinergic Neuromodulation of Cognition

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As indicated by the profound cognitive impairments caused by cholinergic receptor antagonists, cholinergic neurotransmission has a vital role in cognitive function, specifically attention and memory encoding. Abnormally regulated cholinergic neurotransmission has been hypothesized to contribute to the cognitive symptoms of neuropsychiatric disorders. Loss of cholinergic neurons enhances the severity of the symptoms of dementia. Cholinergic receptor agonists and acetylcholinesterase inhibitors have been investigated for the treatment of cognitive dysfunction. Evidence from experiments using new techniques for measuring rapid changes in cholinergic neurotransmission provides a novel perspective on the cholinergic regulation of cognitive processes. This evidence indicates that changes in cholinergic modulation on a timescale of seconds is triggered by sensory input cues and serves to facilitate cue detection and attentional performance. Furthermore, the evidence indicates cholinergic induction of evoked intrinsic, persistent spiking mechanisms for active maintenance of sensory input, and planned responses. Models have been developed to describe the neuronal mechanisms underlying the transient modulation of cortical target circuits by cholinergic activity. These models postulate specific locations and roles of nicotinic and muscarinic acetylcholine receptors and that cholinergic neurotransmission is controlled in part by (cortical) target circuits. The available evidence and these models point to new principles governing the development of the next generation of cholinergic treatments for cognitive disorders.

INTRODUCTION

The entire cortex and hippocampus are innervated by cholinergic projections that originate from several regions in the basal forebrain (Rye et al, 1984; Lysakowski et al, 1989; Mesulam et al, 1992; Kitt et al, 1994). The anatomical organization of this neuronal system predicts that abnormalities in cholinergic activity profoundly impairs cortical and hippocampal information processing (eg, Bartus, 2000; Mesulam, 2004; Sarter et al, 2005a). Consequently, attempts to treat cognitive symptoms and disorders have extensively focused on cholinomimetic strategies.

The traditional description of the forebrain cholinergic system as a diffusely organized neuromodulator system suggests that a relatively small number of neurons show widespread influence on information processing across large portions of the cortex and hippocampus. However, we will point out that recent evidence supports an alternative hypothesis, proposing that the cognitive functions of cholinergic projections are determined in part by telencephalic circuitry controlling cholinergic synaptic neurotransmission. Such local control of cholinergic activity may imply that the cholinergic system influences target regions in a more specific manner than previously assumed.

Early theories suggested that the cortical cholinergic input system contributes to the induction of 'arousal' and elevates input processing to the level of awareness or consciousness (Wenk, 1989; Woolf, 1991; Perry et al, 1999). Although recent research indicated that specific cognitive operations are mediated by precisely orchestrated and spatially restricted changes in cholinergic neurotransmission, our current model integrates multiple roles and neurotransmission modes of forebrain cholinergic systems, including the modulation of more global states of target regions as well as the mediation of highly selective cognitive operations. Collectively, these states and cognitive

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operations support attentional performance and the encoding of new information (as illustrated in Figure 2).

In this article, we will explore specifically the effect of more recent findings on the cholinergic mediation of cognitive operations for the development of novel neuropsychopharmacological treatment strategies. We will describe a circuit-based model that is designed to capture key elements of the current evidence and associated hypotheses. The new evidence and this model, together with a model derived from the neurophysiological evidence on the effects of cholinergic modulation, form the basis for new treatment strategies that venture beyond the traditional cholinomimetic mechanisms targeted by acetylcholinesterase (AChE) inhibitors and nonselective muscarinic and nicotinic acetylcholine receptor (m/nAChR) agonists.

OVERVIEW OF CHOLINERGIC NEUROPSYCHOPHARMACOLOGY

Early psychopharmacological studies of the role of cholinergic systems in cognition were conducted, to name a few, by Giancarlo Pepeu, David M Warburton, J Anthony Deutsch, and David A Drachman (eg, Pazzagli and Pepeu, 1965; Deutsch and Rocklin, 1967; Deutsch, 1971; Warburton and Brown, 1971; Drachman, 1977; Drachman and Sahakian, 1980). Then and now, this research has depended mainly on the availability of three groups of cholinergic drugs for studies in humans and animals: AChE inhibitors, nonspecific mAChR antagonists (scopolamine and atropine), and the non-selective nAChR agonist nicotine. The interpretation of the cognitive effects of these drugs has rarely taken into account the enormous complexity of their effects on cholinergic neurotransmission.

AChE inhibitors have been shown to enhance cognitive performance (Aigner and Mishkin, 1986; Aigner et al, 1987) and to reduce the impairments caused by mAChR antagonists (Ghoneim and Mewaldt, 1977). However, the consequences of sustained, high levels of extracellular ACh levels include the excessive stimulation of presynaptic M2 receptors. Stimulation of these receptors inhibits the release of ACh and thereby attenuates presynaptic signaling. Furthermore, the presence of extremely high concentrations of ACh in the extrasynaptic space (volume transmission) results in the stimulation of extrasynaptic mAChRs (Yamasaki et al, 2010) and nAChRs, to a degree and at locations that may not be achieved in the absence of an AChE inhibitor (Sarter et al, 2009a). Even within the constraints of classic synapses, high levels of ACh are expected to excessively stimulate nAChRs that in turn stimulate the release of several neuromodulators, including ACh itself, thereby robustly modulating the state of local circuitry (eg, Sarter et al, 2009b). Thus, AChE inhibitors do not merely increase cholinergic neurotransmission but they also uncouple presynaptic from postsynaptic information transmission and produce complex changes in local and efferent circuitry.

With respect to the nonselective mAChR antagonists, atropine and scopolamine, these drugs have been shown to impair encoding of new memories (Ghoneim and Mewaldt, 1975, 1977; Aigner et al, 1991) and to impair attention (Wesnes and Warburton, 1984; Broks et al, 1988). However, the attribution of the cognitive effects to blockade of postsynaptic mAChRs must be modified by awareness that these drugs also increase the release of ACh because of presynaptic M2 receptor antagonism (eg, Herzog et al, 2003). As a result, extremely high extracellular ACh levels stimulate nAChRs, and such effects may interact with the blockade of postsynaptic mAChRs to cause rather complex behavioral and cognitive effects. Consistent with such a potential interaction, several studies showed that blockade of nAChRs alone did not affect cognitive performance; however, when administered together with a mAChR antagonist, substantial or significantly greater cognitive impairments were observed (eg, Little et al, 1998; Ellis et al, 2006; Erskine et al, 2004).

The investigation of the cognitive effects of nicotine has given rise to an enormously productive field of research on the cognitive functions of nAChRs (eg, Warburton and Mancuso, 1998; Stolerman et al, 2000; Levin et al, 1998; Levin et al, 2006). As will be pointed out below, recent evidence identified the nAChR subtypes that may be of central interest for pharmacological strategies aimed at enhancing attentional performance effects. Furthermore, research on the role of these subtypes has begun to identify the neuronal circuitry underlying the procognitive effects of selective nAChR agonists.

The empirical and conceptual complexities associated with the use of traditional cholinergic drugs as research tools generalize to efforts aimed at modeling and treating the cognitive symptoms of neuropsychiatric and neurodegenerative disorders. In particular, the role of abnormalities in cholinergic neurotransmission and eventually of cholinergic cell loss in the cognitive decline of Alzheimer's disease has been intensely debated, in part because the administration of mAChR antagonists to healthy subjects does not fully reproduce the symptoms of dementia (Flicker et al, 1992; Huff et al, 1988; Beatty et al, 1986; Kopelman and Corn, 1988; Fibiger, 1991). However, given the complex neuronal effects of mAChR antagonists described above, and specifically the increases in ACh release and subsequent nAChR stimulation, it should be expected that such drugs do not produce the range of cognitive impairments that results from the disintegration of cortical afferent, local, and efferent circuitry. Moreover, psychopharmacological studies aimed at modeling dementia have focused on the effects of acute administration of scopolamine or atropine (Beatty et al, 1986; Broks et al, 1988), or of a combination of mAChR and nAChR antagonists (Little et al, 1998). Therefore, debates about the limitations of such pharmacological models need to consider that effects of a single administration of a mAChR antagonist are contrasted against the chronic, escalating cognitive consequences of dysregulated and disintegrating cholinergic systems. In addition, the

dementia of Alzheimer's disease is associated with neuronal death that destroys the input to and output from the hippocampal formation (Hyman *et al*, 1984), removing the glutamatergic circuits modulated by acetylcholine. In light of these considerations, the degree to which acute mAChR blockade models such dementias seems rather impressive (see also Christensen *et al*, 1992; Aarsland *et al*, 1994; Broks *et al*, 1988). The augmented cognitive impairment caused by scopolamine in healthy aged subjects (eg, Molchan *et al*, 1992; Sunderland *et al*, 1987, 1988), and the finding that scopolamine administration exacerbates the cognitive impairments of patients with Alzheimer's disease, further support the validity of this pharmacological model.

The limited therapeutic, procognitive efficacy of AChE inhibitors (eg, Pepeu and Giovannini, 2009) seems to be an expected finding when considering that inhibition of AChE is not capable of restoring or augmenting the phasic glutamatergic–cholinergic interactions that, as will be described below, mediate defined cognitive operations (see also Sarter and Bruno, 2002; Sarter *et al*, 2007). As noted above, the limited cognitive effects of acute mAChR antagonist administration does not reject the significance of this model for understanding the role of cholinergic cell loss in dementia (see also Bartus, 2000). Similarly, the finding that AChE inhibitors do not consistently produce robust beneficial cognitive enhancement does not serve as a conclusive basis for rejecting the hypothesis that a declining and dysregulated cholinergic system contributes to the severity of the symptoms of dementia (Mesulam, 2004). Moreover, a relatively small number of studies reported that AChE inhibitors produce small yet significant enhancement of cognitive, specifically attentional functions in patients with Alzheimer's disease (eg, Sahakian *et al*, 1993; Foldi *et al*, 2005). These complexities and resulting debates reflect the limited degree to which these drugs serve as sufficiently selective neuropsychopharmacological research tools, including for assessing the therapeutic potential of cholinergic treatment approaches.

ACETYLCHOLINE AND THE REGULATION OF ATTENTION

Lesions and Early Microdialysis Studies

A considerable amount of evidence from experiments on the effects of, initially, nonselective lesions of the basal forebrain (Robbins *et al*, 1989; Dunnett *et al*, 1991; Muir *et al*, 1992; Roberts *et al*, 1992; Voytko *et al*, 1994) and, subsequently, selective lesions of the basal forebrain cholinergic projections to the cortex (eg, McGaughy *et al*, 1996, 2000; Turchi and Sarter, 1997; McGaughy and Sarter, 1998; Chiba *et al*, 1995; Baxter *et al*, 1999; Dalley *et al*, 2004; Newman and McGaughy, 2008) indicated that these projections are necessary for performing tasks assessing a range of attentional functions.

The robustness and the selectivity of the attentional impairments produced by selective removal of cortical cholinergic inputs are noteworthy, particularly in light of a considerable literature reporting the absence of effects of such lesions on behaviors that require little or no attentional processing. For example, the effects of cholinergic lesions were assessed in animals performing a sustained attention task (SAT). The SAT consists of a random order of cued and blank trials. Responses are either hit or miss, or correct rejection and false alarm, respectively. Reward is delivered for both types of correct responses (hit or correct rejection; recorded through different levers). Incorrect responses (miss or false alarm) trigger the intertrial interval but do not have other scheduled consequences. Although intact animals detected over 70–80% of the longest (500 ms) cues, cortical cholinergic deafferentation reduced the detection rate for all cues to approximately 30%, with no recovery despite several months of daily postsurgery practice (McGaughy *et al*, 1996). At the same time, this deafferentation did not affect the animals' response accuracy in blank trials (ie, the correct reporting of the absence of a cue).

Another example illustrating the crucial significance of the cholinergic system for attention concerns the ability to divide attention between the processing of visual and auditory conditioned stimulus (Turchi and Sarter, 1997). Cortical cholinergic deafferentation did not affect the animals' performance in blocks of unimodal trials in which all cues were either visual or auditory. In contrast, under the condition of modality uncertainty, the lesion caused a profound speed–accuracy tradeoff, with correct responses requiring 700 ms longer in bimodal than in unimodal blocks of trials (for additional evidence illustrating disruption of basic attentional abilities by selective cholinergic lesions see, eg, Newman and McGaughy, 2008; Botly and De Rosa, 2009). The robustness and the selectivity of the cognitive impairments produced by such lesions is further supported, although indirectly, by a substantial number of experiments that concluded that removal of forebrain cholinergic neurons does not have strong effects on the performance of animals in tasks that do not explicitly tax attentional processes (Vuckovich *et al*, 2004; Frick *et al*, 2004). For example, cholinergic lesions of the medial septum cause only a mild impairment at all delays in a matching-to-place task in the Morris water maze (Baxter *et al*, 1995), and cholinergic lesions of the entire basal forebrain cause only a mild impairment in learning this task (Frick *et al*, 2004). Cholinergic lesions cause transient effects or no impairments in the radial arm maze (Chappell *et al*, 1998; Galani *et al*, 2002; Vuckovich *et al*, 2004) and T-maze alternation (Pang and Nocera, 1999; Galani *et al*, 2002). Cholinergic lesions of inferotemporal cortex in monkeys do not impair visual scene learning unless combined with fornix lesions (Browning *et al*, 2010).

Measures of ACh release in task-performing animals, using microdialysis, consistently showed attentional performance-associated increases in cortical ACh release. These increases in ACh release were not observed in animals performing behavioral procedures that controlled

for noncognitive performance variables, such as lever pressing and reward rates, or the presentation of stimuli and distractors in contexts that do not require attention (eg, Himmelheber *et al*, 1997; Arnold *et al*, 2002). The results from more recent microdialysis studies indicated that levels of ACh release in attentional task-performing animals vary as a function of the demands on attention (or 'attentional effort') but do not correlate with levels of attentional performance (Passetti *et al*, 2000; Dalley *et al*, 2001; Kozak *et al*, 2006, 2007; Sarter *et al*, 2006).

Cholinergic Mediation of Cue Detection

As described above, the evidence from the experiments on the effects of cortical cholinergic deafferentation on SAT performance indicated a remarkably specific and robust impairment in performance (McGaughy *et al*, 1996; McGaughy and Sarter, 1998). Removal of cortical cholinergic inputs selectively and persistently impaired the animals'

detection rate (or number of hits). In contrast, response accuracy in blank trials remained completely spared. This evidence indicates that the cholinergic system is required specifically for the detection of cues. In this context, detection is defined as a cognitive process that involves the insertion of a cue into ongoing behavioral and cognitive activity and subsequent control of such behavior by the cue (Posner *et al*, 1980).

The hypothesis deduced from these lesion experiments predicts that the cholinergic system is active specifically during trials involving cue detection. The use of enzyme-coated microelectrodes for the amperometric measurement allows monitoring ACh release at a sub-second resolution and thus permits the demonstration of changes in ACh release in association with specific task events or behavioral responses (for evidence indicating the validity of this method see Burmeister *et al*, 2000; Parikh *et al*, 2004; Giuliano *et al*, 2008). The first experiments using this technique in task-performing animals used a
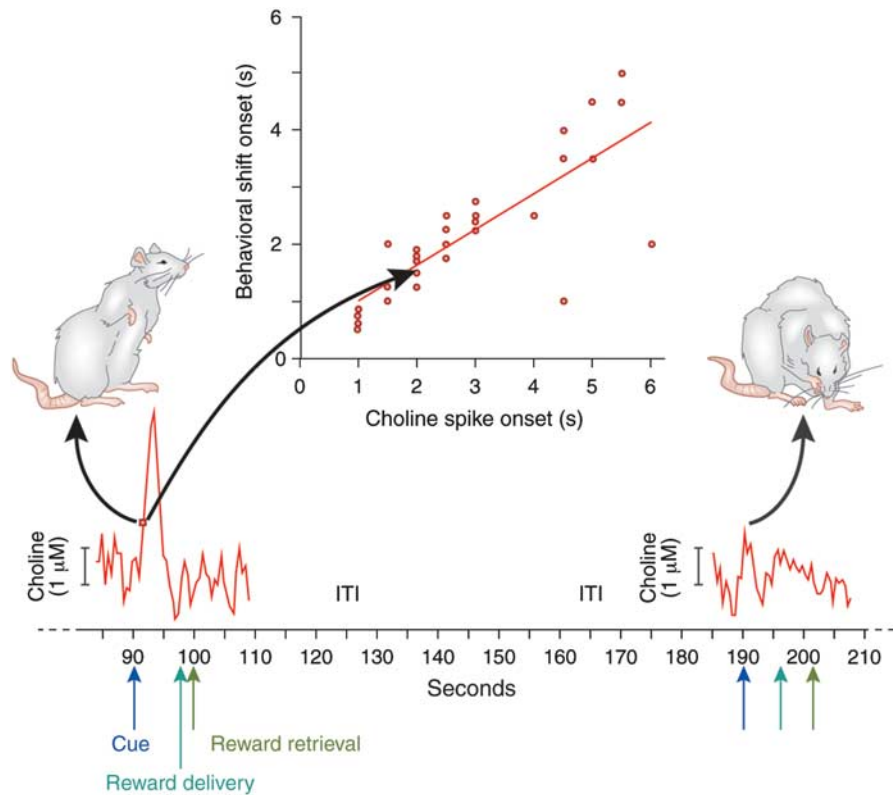

Figure 1. Prefrontal cholinergic transients mediating the detection of cues (data and components of this figure were adopted from Parikh *et al*, 2007). The abscissa depicts the time (seconds) over two trials, one in which the cue was detected (left) and one in which the cue was missed (right). Animals performed a cued appetitive response task. A light cue (presented for 1 s; blue arrows) predicted reward delivery 6 ± 2 s later at one out of two reward ports (dark green arrows). Detection was defined behaviorally by cue-evoked orientation toward and monitoring of the reward ports (as illustrated on the left). Animals detected most of the cues but occasionally missed cues (for detailed results see Parikh *et al*, 2007). Importantly, reward was also delivered if cues were missed, and animals retrieved the reward in such trials, although with longer response latencies. The intertrial interval (ITI) was 90 ± 30 s. The red traces depict electrochemical recordings of choline that were self-referenced against recordings from adjacent platinum recording site that lacked immobilized choline oxidase. As illustrated on the left, cues that were detected were associated with a cholinergic transient. The onset of the increase in cholinergic activity and the onset of detection-indicating behavior (defined in Parikh *et al*, 2007) were highly correlated (inserted plot; red dots and arrows indicating the timepoints for both measures). The initial, steep increase in cholinergic activity (between approximately 92 and 93 s on the abscissa) is thought to stimulate mAChRs, thereby initiating a period of persistent spiking (see Figure 3). During trials in which the cue was missed, no such transients were observed, and reward delivery and retrieval did not evoke increases in cholinergic activity (for details see Parikh *et al*, 2007).

cued appetitive response task to determine cholinergic activity in the medial prefrontal cortex (mPFC) and a control region (forelimb region in the motor cortex). In this task (for details see Parikh et al, 2007), animals were presented with a rarely occurring cue that predicted subsequent reward delivery at one out of two reward ports. Animals detected the majority of these cues, as indicated by cue-evoked disengagement from ongoing behavior (usually grooming), and orientation toward, and monitoring of, the reward ports (see Figure 1). Occasionally, cues did not evoke such behavior. Video tape-based inspection of the animals' behavior during trials involving such misses indicated a brief, cue-evoked orientation-like response that, however, was followed by an immediate return to grooming behavior.

In the mPFC, cues that were detected evoked transient increases in cholinergic activity (Figure 1). Such transients were not observed in trials in which cues were missed, and they were not observed in motor cortex. Even if a cue was missed, reward was eventually delivered and retrieved. Recordings from such trials as well as from several control procedures indicated that the presence or absence of reward and reward-related behavior did not contribute to the generation of cholinergic transients. Furthermore, the timing of the peak amplitude varied with the duration of the interval between cue and reward, with peak times at approximately 1.5 s after cue presentation recorded in animals trained on shortest cue–reward intervals (2 ± 1 s; see Parikh et al, 2007).

Collectively, the results from these experiments support the hypothesis that prefrontal cholinergic transients mediate cue detection (as defined above). Such transients were not observed in motor cortex. Removal of cholinergic input to the PFC impaired the animals' detection rate. Furthermore, because the attentional impairments caused by cholinergic lesions are not restored by pharmacologically mimicking the contributions of the tonic component of cholinergic neurotransmission (see below; McGaughy et al, 1999), the consequences of the lesions can be primarily attributed to the absence of cholinergic transients.

Cholinergic Mode Switch, Orienting, and Detection

On the basis of the findings described above, we predicted that in rats performing the SAT, cue-evoked cholinergic transients would occur in all trials in which cues are detected, but not in trials in which such cues are missed or during blank trials. Evidence from ongoing experiments (preliminary data were described in Howe et al, 2007) has challenged this hypothesis. As expected, cue-evoked cholinergic transients were observed in trials yielding hits. However, this was not consistently the case. Cholinergic transients were not observed in trials resulting in a hit if these trials were preceded by identical trials, that is, by cued trials ending with a hit. In contrast, transients were observed in cued trials resulting in a hit if preceded by a

miss, or if preceded by 'blank' trials resulting in correct rejections.

Nonsignal trials do not involve the detection of cues and, thus, the performance in such trials is governed primarily by an extensively practiced response (a correct rejection); a response that is generated in the absence of a cue may constitute the default response (eg, Maclean et al, 2009). Cued trials resulting in misses can be categorized as perceived blanks and thus also be interpreted as reflecting the execution of a default response. In contrast, a hit requires that an external sensory cue is selected and incorporated into ongoing cognitive processing. Thus, it may be speculated that a cue may evoke a switch away from the default response mode, to a mode that increases the likelihood that it will be selected for behavioral and cognitive control (ie, detection; see above).

The nature of this mode switch may conceptually correspond with Posner's concept of attentional 'orienting', defined as a mental process designed to align attention with a source of sensory input. Importantly, Posner clearly differentiates between orienting and the cognitive act of cue detection, emphasizing that '…some responses (eg, saccadic eye movements) may be available to a stimulus before it has been detected…' (Posner, 1980; p 4). Attentional orienting, overtly or covertly, fosters cue detection; however, orienting is neither sufficient nor necessary for detection. The conceptualization of cholinergic transients in terms of mediating attentional orienting is consistent with the finding that cholinergic lesions or systemic or local cortical blockade of mAChRs impair attentional orienting (Davidson and Marrocco, 2000; Davidson et al, 1999; Chiba et al, 1999; Phillips et al, 2000). As orienting is not necessary for detection, the residual hit rate after cortical cholinergic deafferentation (McGaughy et al, 1996) may have been because of detections that occurred without the facilitating benefits of attentional orienting.

In keeping with this conceptualization, misses are attributed to orienting failures, therefore decreasing the likelihood for subsequent detection and increasing the likelihood that the default response (a correct rejection) will be executed (and counted as a miss in a cued trial). The model described below, specifically the key interactions between thalamic glutamatergic and cholinergic afferents of the PFC, is capable of explaining why less salient cues are more likely to fail in generating cholinergically mediated attentional orienting and thus are more likely to be missed.

This conceptualization further requires the assumption that after a hit, attention was successfully aligned with the source of input and that this alignment remains stable for a brief period of time (perhaps 10–20 s during SAT performance; ITI: average of 9 s). If the subsequent trial is cued, detection of this cue therefore would not require attentional (re-) orienting, and therefore, transients are not observed in successive trials ending with hits. Further below we will speculate about neuronal mechanisms mediating the transfer of cue-evoked attentional orienting to the next

trial. If the next trial is a noncued trial, the circuit returns to the default state and a subsequent cue is again more likely to be detected if it evokes attentional orienting. Whether SAT performance permits identifying a behavioral correlate of orienting that can be dissociated from the obvious behavior that indicates detection (a hit) is currently being explored.

Orienting differs from 'alerting', which is defined as 'achieving and maintaining a state of high sensitivity to incoming stimuli' (Posner and Rothbart, 2007; p 7), and presumably varies on a longer timescale (minutes and tens of minutes) than orienting (milliseconds and seconds). Although other neuromodulator systems, specifically the noradrenergic system (eg, Witte and Marrocco, 1997; Posner, 2008), have been proposed to contribute to alerting, in the context of a circuitry model (below), we will suggest that a tonic component of cholinergic neurotransmission may also contribute to alerting and thereby to successful orienting, perhaps in part through local cortical and distributed interactions between the two neuromodulator systems (Briand et al, 2007; Dalley et al, 2001).

Neurophysiological Correlates of Mode Shifts

Previous neurophysiological research, recording from brain slices, concluded that ACh acts to enhance the (glutamatergic) representation of thalamic input through stimulation of nAChRs, while suppressing cortico-cortical or associational input through stimulation of mAChRs (Hasselmo and Bower, 1992; Hasselmo et al, 1992; Hasselmo and Schnell, 1994; Gil et al, 1997; Kimura and Baughman, 1997; Roberts et al, 2005; see below). The cholinergically mediated shift from a default mode to the detection mode, or orienting (above), corresponds conceptually with the conclusions from this neurophysiological work. Orienting is generated in part by enhancing the cortical representation of thalamic input. At the same time, the cortico-cortical (associational or default mode-based) processing would need to be suppressed to minimize interference with effective orienting and the subsequent detection process. Through stimulation of mAChR, we may also begin to speculate about mechanisms that sustain orienting over longer periods of time, allowing successive detections to occur without generating additional cholinergic transients (see below).

PREFRONTAL CIRCUITRY MEDIATING ORIENTING AND DETECTION: TOWARD A MECHANISTIC MODEL OF CHOLINERGIC FUNCTION

Evidence from neuropharmacological studies, including from animals lacking various nAChRs after lesions of the thalamic mediodorsal (MD) nucleus projections to PFC or after removal of mesolimbic dopaminergic projections to the PFC, has begun to define key components of a circuit that mediates orienting and thereby fosters cue detection (Parikh et al, 2008; Parikh et al, 2010; Sarter et al, 2009b).

Importantly, some essential features of this circuitry have been validated in terms of predicting the effects of cholinergic drugs on attentional performance (Howe et al, 2010). This section will focus on this model and therefore will combine evidence from electrochemical and behavioral studies with hypotheses and, to a minor degree, some speculations.

Before addressing details in support of this circuitry model, and as illustrated in Figure 2, it is useful to introduce an important yet potentially complicating aspect of this model. The model postulates that cholinergic projections to the PFC have two separate roles. First, evidence indicates that, by stimulating a specific nAChR subtype expressed by inputs from the MD, cholinergic activity modulates glutamatergic neurotransmission. Second, as was also shown, such glutamate release dictates, through stimulation of ionotropic glutamate receptors, the amplitudes of the cholinergic transients that mediate, as is hypothesized above, attentional orienting and foster cue detection. The model speculates that separate populations of cholinergic neurons influence the release of glutamate from MD inputs and are targeted by such inputs, respectively (Figure 2). Although evidence supporting such a segregation of cholinergic projections has remained limited, our current model is consistent with contemporary anatomical theories suggesting a highly differentiated, topographic organization of the cholinergic system (Zaborszky, 2002; Zaborszky et al, 2005, 2008).

Prefrontal Glutamatergic–Cholinergic Interactions

Evidence from neuropharmacological studies using selective nAChR ligands and antagonists at ionotropic glutamate receptors, and assessing the effects of infusions of these compounds into the PFC of animals lacking $\alpha4\beta2^\star$ or $\alpha7$ nAChRs, or animals with lesions of the MD, collectively indicated that the amplitude of cholinergic transients is determined by glutamatergic stimulation of ionotropic glutamate receptors. Furthermore, cholinergic stimulation of $\alpha4\beta2^\star$ nAChRs evoked cholinergic transients through stimulating glutamate release, and the MD input is required to generate such transients. In contrast to the amplitude of cholinergic transients, the decay rate of such transients, that is, the duration and rate of decrease of ACh release, is not controlled by these glutamatergic–cholinergic interactions (Parikh et al, 2008, 2010; Howe et al, 2010).

We can only speculate about the nature of the information about the cue that is 'imported' by MD projections. The MD may be considered as the thalamic 'exit' station for a circuit that involves projections from sensory cortical regions to the thalamic reticular nucleus that, in turn, projects to the MD. This circuit has been proposed to generate preattentionally processed representations of cues (Guillery et al, 1998; Zikopoulos and Barbas, 2006, 2007a, b; Pinault, 2004; Weese et al, 1999; McAlonan et al, 2006). The term 'pre-attention' has often been explained using the
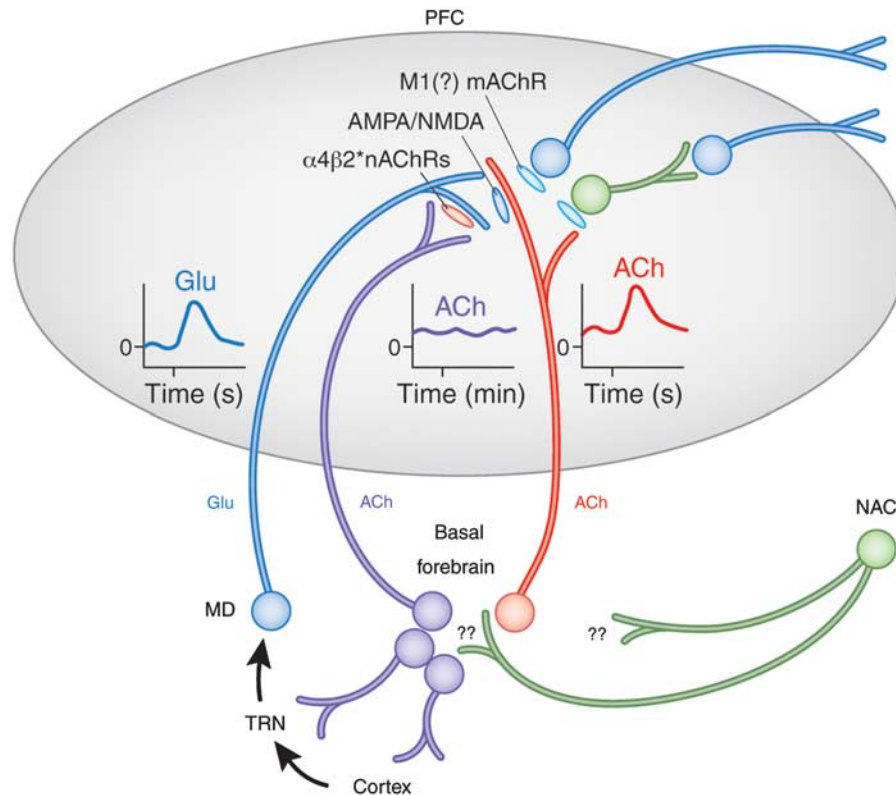
Figure 2. Circuitry model describing the main components of the prefrontal cortex (PFC) circuitry mediating signal detection and processing mode shifts. The model combines evidence with parsimonious assumptions required to explain electrochemical and attentional performance data (see main text for details). The glutamatergic (GLU) inputs to the PFC, originating from the mediodorsal thalamic nucleus (MD) 'import' a preattentionally processed representation of the signal into the PFC (see text for definition). MD neurons are part of a network that includes the thalamic reticular nucleus (TRN) and its topographic afferents from sensory cortical regions. The cue-evoked glutamatergic transient (see insert) generates a cholinergic transient (see insert) through stimulation of ionotropic presynaptic glutamate receptors (Parikh *et al*, 2008, 2010). This cholinergic transient mediates the actual detection process or, depending on the task, a processing mode shift that fosters detection (see main text). Prefrontal output neuron activity is stimulated by ACh primarily through muscarinic (m)AChRs, thereby organizing the behavioral responses that indicate successful detection. The terminals of the MD inputs to the PFC are equipped with $\alpha 4 \beta 2^*$ nAChRs. Cholinergic stimulation of these receptors is thought to vary over minutes, reflecting a tonic component of cholinergic neurotransmission (see elevated release illustrated by the insert). nAChR agonists enhance detection performance primarily by positively modulating GLU release from these terminals, thereby augmenting the amplitudes of the cholinergic transients (Parikh *et al*, 2010; Howe *et al*, 2010). As is further explained in the text, this model therefore proposes two separate roles for cholinergic inputs, mediated through separate populations of cholinergic neurons. A rather tonically active input modulates glutamate release from MD neurons that, in turn, target the terminals of a separate group of cholinergic neurons, generating the transients that enhance attentional orienting and cue detection (adapted and modified from Sarter *et al*, 2009b).

'attentional searchlight' analogy, '…like a searchlight at dusk, it intensifies part of a scene that is already visible to some extent' (Crick, 1984; p 4586). Such a preattentional narrowing may be considered a necessary precursor of attentional orienting (as defined above), as the former concerns attention to part of a scene (eg, attention toward an intelligence panel of an operant chamber) whereas the latter concerns the orientation of attention to a specific source for a target (eg, attention to the location of a bulb). Attentional orienting may also involve prospective timing processes and estimating target onset.

Exactly how MD projections to the PFC encode the searchlight effect and bias the processing of information by PFC circuitry toward a particular part of a scene is not understood. Similarly, exactly how PFC cholinergic transients further narrow and presumably specify such biasing or, to keep with the searchlight analogy, increase the

brightness and the focus of the searchlight to illuminate a specific aspect of the scene remain speculative. Certainly, these processes involve top-down control, as the scene and the target that are subject to preattentional processes and attentional orienting are guided by their established significance. It is noteworthy, however, that preattention-processing thalamic nuclei, including the MD, also receive cholinergic input from the basal forebrain (eg, Hallanger *et al*, 1987; see Figure 2), suggesting an orchestrated cholinergic recruitment of thalamic and cortical circuitries to foster cue detection.

These glutamatergic–cholinergic interactions do not readily account for occasional misses of salient stimuli. We hypothesize that as a result of, for example, task-unrelated increases in activity in this network before the presentation of signals, as shown in Parikh *et al* (2007), attentional interference results from GABAergic inhibition

of the cholinergic terminals that generate transients (Rasmusson *et al*, 2007). The cholinergic receptors situated on GABAergic interneurons are not clear but likely involve *β2* subunit containing nAChRs and also mAChRs (Bandyopadhyay *et al*, 2006; Azam *et al*, 2003; Disney and Aoki, 2008).

Prefrontal nAChR-Mediated Upregulation of Glutamatergic–Cholinergic Interactions

The glutamatergic terminals of MD projections express α4β2* nAChRs (Lambe *et al*, 2003: Figure 2). We showed that removal of these thalamic inputs blocks the ability of α4β2* nAChR agonists to evoke glutamatergic and cholinergic transients (Parikh *et al*, 2010). Furthermore, stimulation of α4β2* nAChRs, by administering systemically a full α4β2* nAChR agonist, increased the number of cue detections in SAT-performing animals; this effect was observed specifically during performance recovery subsequently to the presentation of a distractor ('dSAT' performance; Howe *et al*, 2010). Moreover, this increase in hits occurred specifically in trials that were preceded by misses or blanks, consistent with the hypothesis that α4β2* nAChR agonists facilitate the generation of cholinergic transients that foster attentional orienting and/or the shift into the detection mode. As already mentioned, removal of cholinergic neurons abolishes this effect of stimulation of α4β2* nAChRs.

The effects of α4β2* nAChR agonists are thought to mimic the effects of a more tonic component of cholinergic neurotransmission at these receptors. In addition to the second-based cholinergic transients, several sets of data suggest that more slowly changing (tonic; scale of minutes and tens of minutes) levels of cholinergic neurotransmission are also present in this system. First, in our previous microdialysis studies we observed increases in cholinergic neurotransmission before the onset of the attention task (Kozak *et al*, 2006, 2007). These increases were interpreted as evoked by the testing context and anticipation of performance and associated reward. Ongoing studies suggest that these tonic changes in cholinergic activity are not confounded by phasic cholinergic activity. Rather, the direction of changes in tonic cholinergic activity (as indicated by microdialysis) and the amplitudes of cholinergic transients (measured electrochemically) are not necessarily correlated and, as evidenced by effects of different nAChR agonists on both measures, may in fact be dissociated (G Paolone, unpublished findings; see also Parikh and Sarter, 2008).

The model illustrated in Figure 2 implies that a separate group of cholinergic neurons contacts MD glutamatergic terminals in the PFC, allowing for relatively slowly changing levels of ACh released by these neurons to modulate the gain of glutamatergic–cholinergic interactions through stimulation of α4β2* nAChRs. Evidence indicating that α4β2* nAChRs do not downregulate in response to lasting cholinergic stimulation (Walsh *et al*, 2008; Yates *et al*, 1995)

is consistent with this assumption. As a result, the likelihood and the amplitude of cholinergic transients are increased over longer periods of time (minutes to hours).

The effects of such tonic cholinergic modulation of the efficacy of cortical information processing conceptually may correspond with the more traditional view of the role of cholinergic inputs in elevating levels of 'arousal', 'the readiness for input processing', or to enhance preattentional processes (for corresponding conclusions about the role of nAChRs in the thalamic input layer of V1, see Disney *et al*, 2007). Furthermore, the effects of motivational variations of cognitive performance, specifically the mesolimbic–basal forebrain interactions that control levels of attentional effort (Zmarowski *et al*, 2005, 2007; Sarter *et al*, 2006), are readily integrated into this model. Mesolimbic systems selectively and tonically influence cholinergic neurotransmission of prefrontal inputs and thereby gate prefrontal glutamatergic–cholinergic interactions as a function of the motivation to perform, particularly in interaction with performance challenges (Kozak *et al*, 2006).

ROLE OF CHOLINERGIC RECEPTORS IN ATTENTION

Nicotinic AChRs

α4β2 nAChRs.* A substantial number of studies showed that administration of nicotine enhances attentional performance and aspects of memory encoding (eg, Wesnes and Warburton, 1984; Rusted and Warburton, 1992; Levin *et al*, 1998). However, the demonstration of large and clinically useful effects of nicotine has been difficult (for review, see Rusted *et al*, 2000; Newhouse *et al*, 2001, 2004; Sarter *et al*, 2009b; Sarter, 2010). Recent studies have indicated that agonists selective for α4β2* nAChRs produce perhaps more robust and clinically more promising enhancement of attention and related cognitive abilities (Potter *et al*, 1999; Wilens *et al*, 1999; Wilens *et al*, 2006; Dunbar *et al*, 2007; Wilens and Decker, 2007).

Evidence from animal studies on the effects of a full agonist at α4β2* nAChRs, S 38232, confirmed that such compounds are more efficacious in enhancing attentional performance than nicotine (Howe *et al*, 2010). We explored the hypothesis, deduced from studies on prefrontal circuitry involved in the effects of stimulation of nAChRs (Parikh *et al*, 2008; Parikh *et al*, 2010), that stimulation of the α7 nAChR limits the proattentional efficacy of nicotine. Indeed, although the administration of nicotine alone did not statistically improve performance, coadministration of nicotine and the α7 nAChR antagonist methyllycaconitine (MLA) resulted in a significant enhancement of attention. Corresponding with the behavioral evidence, this combination treatment also 'sharpened' the cholinergic transients evoked by nicotine (Howe *et al*, 2010), suggesting that the more lasting increases in cholinergic activity that result from stimulation of the α7 nAChR limits the efficacy of nicotine. With respect to the model illustrated in Figure 2,

the beneficial cognitive effects of α4β2* nAChR agonists are hypothesized to manifest as an upregulation of transient, glutamatergic–cholinergic interactions.

α7 nAChRs. There is currently a substantial enthusiasm for the potential procognitive therapeutic efficacy of α7 nAChR agonists (Leiser *et al*, 2009; Freedman *et al*, 2008). The α7 nAChR has a relatively high permeability for Ca^{++} and thereby induces vesicular fusion and neurotransmitter release from presynaptic terminals and activates calcium-sensitive protein kinases postsynaptically (Gray *et al*, 1996; Berg and Conroy, 2002; Bitner *et al*, 2007). Such mechanisms could account for lasting and diverse effects at target neurons and presynaptic terminals, including cholinergic terminals (Duffy *et al*, 2009).

The evidence indicating beneficial attentional effects of α7 nAChR agonists remains conflicting. Pharmacological studies failed to implicate this receptor in attention (Grottick and Higgins, 2000; Hahn *et al*, 2003). Similarly, we were not able to observe beneficial attention effects of the administration of the α7 nAChR agonist ABT 107 on either basic SAT performance or on the recovery from the distractor challenge (Paolone *et al,* 2009). In contrast, attentional impairments were observed in mice lacking the α7 nAChR (Hoyle *et al*, 2006; Young *et al*, 2007).

As mentioned above, evidence indicates that, in the presence of an antagonist at the α7 nAChR, nicotine enhanced attentional performance. The electrochemical effects of this combination indicated that stimulation of the α7 nAChR was responsible for the relatively slow rise time and decay rate of nicotine-evoked cholinergic transients. Compared with the 'sharper' transients evoked by α4β2* nAChR agonists and observed in task-performing animals, the more enduring ACh release evoked by nicotine, primarily through stimulation of the α7 nAChR, is hypothesized to interfere, or at least limit, the more precise amplification of glutamatergic–cholinergic interactions that enhance cue detection performance.

Given the diverse neuronal effects triggered by α7 nAChR-mediated calcium influx, it is conceivable that agonists at this receptor alter and may even benefit a range of physiological, behavioral, and cognitive functions (eg, Bitner *et al*, 2007). However, the available evidence, although remaining limited, does not indicate that stimulation of this subtype benefits detection and associated attentional performance.

Muscarinic AChRs

Upon release, ACh also stimulates muscarinic receptors. A number of studies have shown the involvement of muscarinic receptors in the modulation of attention. As already discussed, the lack of selective antagonists and agonists at muscarinic receptor subtypes has remained a major obstacle for research on the functions of mAChRs. New M1-selective ligands have become recently available,

including, importantly, a positive allosteric modulator (Sheffler *et al*, 2009; Shirey *et al*, 2009).

However, despite such limitations, a considerable literature describes robust scopolamine-induced attentional impairments in healthy subjects (see Introduction for a more general discussion of the effects of mAChR antagonists as a model for dementia). These studies uniformly indicate that blocking mAChRs disrupts continuous or sustained attention, the detection of cues in attentional contexts, and the resulting encoding of new information (eg, Dunne and Hartley, 1986; Parrott, 1986; Wesnes *et al*, 1988).

The effects of mAChR blockade in sensory and associational cortical regions parallel the consequences of systemic blockade in humans. Herrero *et al* (2008) showed that in the primary visual cortex, blockade of muscarinic but not nicotinic AChRs impaired the attentional modulation of V1 neurons (see also Deco and Thiele, 2009). Using a cued target detection task, Davidson and Marrocco (2000) found that blockade of mAChR in the intraparietal cortex impaired performance. Stimulation of mAChRs in parietal regions is speculated to contribute to the recruitment of local and efferent circuitry that enhance cue processing and distractor filtering (see effects of cholinergic deafferentation of the parietal cortex in Broussard *et al*, 2009).

Stimulation of mAChRs in one region may modulate attentional mechanisms in other regions by influencing ACh release through larger, multisynaptic mechanisms. For example, stimulation of PFC muscarinic receptors influences ACh release in parietal cortex, presumably through prefrontal projections to the basal forebrain and/or cortico-cortical networks (Nelson *et al*, 2005). Such prefrontal, muscarinic recruitment of efferent circuitry may mediate top-down effects to, for example, combat performance decay as a result of time-on-task and other performance challenges, such as distractors (Gill *et al*, 2000; Kozak *et al*, 2006; Sarter *et al*, 2006). Evidence indicating scopolamine-induced impairments in attentional set shifting performance (Chen *et al*, 2004) is consistent with a role of mAChR for the mediation of cognitive functions that involve top-down control.

The hypothesis that nAChRs mediate attentional orienting and cue detection whereas mAChRs recruit circuitry that is required for attentional performance in situations demanding top-down control suggests that both cholinergic receptor populations act synergistically to support performance (see also Greenwood *et al*, 2009). This basic hypothesis indicates the need for studies assessing the consequences of combined antagonisms of nicotinic and muscarinic AChRs. It will also be important to determine whether the location of mAChRs predominantly on GABAergic interneurons, showed in V1 (Disney and Aoki, 2008), generalizes to other cortical regions. Such a preferential distribution of nAChRs in thalamic input layers and mAChRs on cortical inhibitory interneurons would be consistent with hypotheses describing the complementary roles of ACh on cue detection on one hand, and interference filtering and cue competition resolution on the other

(Mitchell *et al*, 2007). Furthermore, as will be addressed below, stimulation of mAChRs evoke persistent firing patterns that may serve to stabilize the state of attention circuits and maintain cue representation over longer periods of time.

Evidence from Human fMRI Studies Assessing AChE Inhibitors

As discussed in the Introduction, the interpretation of the effects of AChE inhibitors requires caution in view of the complex pre- and postsynaptic consequences of large increases in extracellular ACh levels. Despite these complexities, results from fMRI studies using physostigmine and, less frequently, donepezil indicate that these drugs have continued to serve as productive tools. These studies collectively indicated that AChE inhibition facilitated stimulus-induced increases in activity in several brain regions, depending in part on the type of task and the nature of the stimuli. As a result, memory-based performance was facilitated, and often associated, with reduced activity in prefrontal and even sensory regions. The latter finding has been interpreted as indicating the beneficial consequences of enhanced encoding for the performance during the memory test (eg, Furey *et al*, 2000; Robbins *et al*, 2000; Bentley *et al*, 2004, 2009; Kukolja *et al*, 2009). Furthermore, several studies identified enhanced attention to stimuli as a key mechanism that contributes to the effects of physostigmine on encoding, and determined that frontoparietal as well as sensory and sensory-associational areas mediate these effects (eg, Bentley *et al*, 2003, 2008; Furey *et al*, 2008; Silver *et al*, 2008). In broadest terms, these conclusions correspond with the role of increases in cortical cholinergic activity for attentional orienting and cue detection that has been derived from animal studies (above).

Although the behavioral or cognitive effects of AChE inhibitors in these fMRI studies were not consistently present or were of limited magnitude, the collective evidence from these studies has raised important questions as to the effects of AChE inhibitors on extracellular levels of ACh in task-performing subjects. Specifically, it would be of interest to determine the orchestration of cholinergic transients against a background of increased levels of synaptic and perhaps extrasynaptic ACh (Sarter *et al*, 2009a). Unfortunately, the electrochemical techniques for the rapid measurement of ACh release prohibit the presence of an AChE inhibitor as this would block the generation of the reporter molecule (choline). Thus, studies of AChE effects at a high temporal resolution will require future, alternative measurement techniques.

fMRI Studies Assessing Nicotine or Scopolamine

Similar to the purely behavioral studies discussed above, administration of nicotine to subjects undergoing fMRI scanning did not consistently produce significant effects on cognitive performance (Giessing *et al*, 2006; Thiel and Fink, 2008; Vossel *et al*, 2008). However, consistent with the conclusions derived from experiments in rodents, nicotine enhanced neuronal activity in prefrontal cingulate and parietal regions specifically in trials requiring cue detection and attentional re-orienting in subjects performing a cued target detection task (Giessing *et al*, 2006; Vossel *et al*, 2008). Additional analyses indicated that individual differences in performance-associated activity in prefrontal and parietal regions predict performance effects of nicotine (Giessing *et al*, 2007). Although we do not know the relationships between (transient) cholinergic activity and blood oxygenation level-dependent contrast or other hemodynamic responses, it is intriguing to speculate that a significant proportion of the nicotine-induced activation of specifically prefrontal regions is causally related to the drug-induced augmentation of cholinergic transients that mediate cue detection and attention mode shifts.

fMRI studies that investigated the effects of scopolamine have focused on memory performance and, to our knowledge, did not study attention. These studies must be interpreted with awareness of the effects of blocking pre- and postsynaptic muscarinic receptors (see Introduction) and potential effects of the blockade of ACh-induced vasodilation through M5 mAChR (Yamada *et al*, 2003). Studies on scopolamine have produced a range of performance effects on memory tasks and associated changes in blood flow occurring in a diverse set of brain regions (Grasby *et al*, 1995; Bozzali *et al*, 2006). Consistent with the general view that attention-dependent encoding depends on stimulation of mAChR in hippocampal, parahippocampal, and entorhinal regions, several studies showed disruption of encoding-evoked neuronal activity in these regions and resulting impairments in recognition memory (Rosier *et al*, 1999; Schon *et al*, 2005).

CHOLINERGIC MODULATION OF CELLULAR PHYSIOLOGY

Intracellular recordings of the cellular modulatory effects of ACh provide additional information about the functional role of ACh. Cellular data on the effects of ACh in cortical structures guide the development of circuit-level models of the behavioral role of ACh (Hasselmo, 2006; Hasselmo and Stern, 2006). The effects of ACh within cortical structures are consistent with a role of ACh in attentional orienting and cue detection (above). Previous studies have shown that stimulation of nAChRs enhances the glutamatergic transmission at thalamocortical synapses (Gil *et al*, 1997; Gioanni *et al*, 1999; Hsieh *et al*, 2000), thereby enhancing the thalamic activation of subsets of cortical neurons. The spiking response of cortical neurons to sensory input is further enhanced by muscarinic receptors causing a decrease in potassium conductances, including resting conductances (Krnjevic *et al*, 1971; Cole and Nicoll, 1984; Barkai and Hasselmo, 1994; Gulledge *et al*, 2009), the

M current (Madison et al, 1987), and the calcium-dependent potassium current (Madison and Nicoll, 1984; Schwindt et al, 1988; Barkai and Hasselmo, 1994; Gulledge et al, 2009).

Muscarinic receptor activation also causes heterosynaptic and presynaptic inhibition of glutamatergic synaptic transmission at excitatory recurrent synapses between neurons within the cortex (Hasselmo and Bower, 1992; Hasselmo and Schnell, 1994; Hasselmo and Cekic, 1996; Kimura, 2000; Kimura and Baughman, 1997), thereby reducing the spread of neural activity and enhancing the relative influence of external input on cortical activity. These cellular effects are consistent with unit recording and fMRI data showing that cholinergic modulation reduces the spatial spread of activity in visual cortex (Roberts et al, 2005; Roberts and Thiele, 2008; Silver et al, 2008) and showing that cholinergic mechanisms underlie the enhancement of unit responses with attention (Herrero et al, 2008; Roberts and Thiele, 2008).

The relative influence of external input can also be enhanced by cholinergic depolarization of selective sets of inhibitory interneurons (Xiang et al, 1998; McQuiston and Madison, 1999a, b, c; Christophe et al, 2002), coupled with the cholinergic suppression of evoked GABAergic synaptic transmission (Pitler and Alger, 1992; Behrends and ten Bruggencate, 1993; Patil and Hasselmo, 1999). Computational modeling of cortical circuitry indicates that these effects of cholinergic modulation on inhibitory neurons can enhance the response to sensory input while reducing background activity in cortical circuits (Patil and Hasselmo, 1999). Cholinergic modulation also causes transient inhibition of layer V neocortical neurons, thereby reducing cortical output (Gulledge and Stuart, 2005).

In addition to the enhancement of attention to sensory input, other cellular effects of ACh could contribute to active maintenance of stimuli. ACh enhances persistent spiking or plateau potentials within cortical structures, as shown in brain slice preparations of the entorhinal cortex (Klink and Alonso, 1997; Egorov et al, 2002; Fransen et al, 2006; Tahvildari et al, 2007), PFC (Haj-Dahmane and Andrade, 1996, 1997, 1998), postsubiculum (Yoshida and Hasselmo, 2009), and perirhinal cortex (Leung et al, 2006). In the absence of cholinergic modulation, cortical neurons in slices will usually only spike during direct depolarizing current injection, terminating their spiking after the current injection ends. In contrast, in the presence of drugs that activate muscarinic acetylcholine receptors, a neuron responds to the same current injection with spiking that continues after the termination of the current injection (see Figure 3). The cholinergic enhancement of persistent spiking is reduced by muscarinic antagonists such as scopolamine, indicating a dependence on mechanisms activated by mAChRs (Klink and Alonso 1997; Egorov et al, 2002; Yoshida and Hasselmo, 2009). This persistent spiking occurs even when glutamatergic and GABAergic synaptic connections have been blocked pharmacologically, indicating that it arises from intrinsic mechanisms for
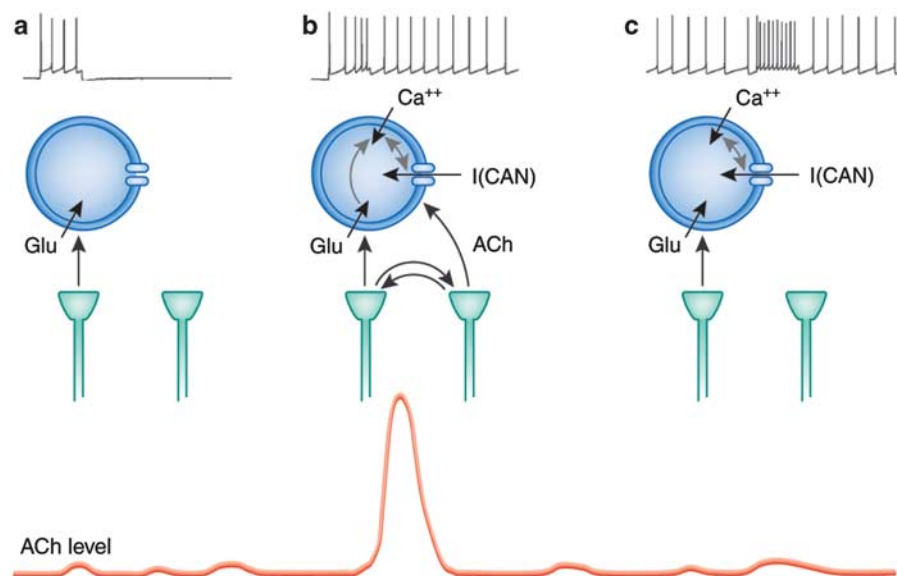
Figure 3. Theoretical perspective on the interaction of glutamatergic and cholinergic input for inducing persistent spiking in cortical structures. (a) Depolarization of cortical neurons because of glutamatergic input alone causes a transient period of spiking that ends after depolarization. (b) In an attentional task, a cue triggers glutamatergic input that causes a local positive feedback interaction with cholinergic terminals. This can cause a transient increase in acetylcholine (ACh) levels associated with cue detection (bottom) as also shown in Figure 1. Slice physiology studies (Egorov et al, 2002; Shalinsky et al, 2002; Yoshida and Hasselmo, 2009) have shown that an ACh increase combined with calcium influx (because of glutamatergic input) activates the calcium-sensitive nonspecific cation current I(CAN) current in the membrane that causes depolarization that causes further calcium influx that keeps the current activated. This results in self-sustained persistent spiking (Fransen et al, 2002; Fransen et al, 2006; Hasselmo and Stern, 2006) that provides active maintenance of network activity such as the plan for a future lever press response. (c) If persistent spiking has been induced by a previous cue, then the persistent spiking continues through the next trial and does not require cueing. The persistent activity might suppress the mechanism for transient increase in ACh levels, resulting in the lack of an cholinergic transient for a cue trial after a successful cue trial.

self-sustained persistent spiking activity. Persistent spiking seems to result from muscarinic receptor activation of a calcium-sensitive nonspecific cation current I(CAN) (Egorov et al, 2002; Shalinsky et al, 2002; Fransen et al, 2006). As shown in Figure 3, during muscarinic receptor activation the spiking caused by glutamatergic synaptic input causes calcium influx through voltage-dependent calcium channels that increase the I(CAN) current, causing further depolarization and regenerative persistent spiking (Fransen et al, 2006; Hasselmo and Stern, 2006).

Cholinergic induction of persistent spiking activity may contribute to active maintenance function in a range of different tasks (see Hasselmo and Stern, 2006 for review). For example, persistent spiking could contribute to delay activity observed in traditional delayed match-to-sample tasks. Neural response properties such as delay activity (Young et al, 1997; Schon et al, 2005), match enhancement, or match suppression (Young et al, 1997; Suzuki et al, 1997) can be simulated using persistent spiking in a circuit model of entorhinal cortex (Fransen et al, 2002). Cholinergic regulation of the onset of persistent spiking could provide a mechanism for gating information into active maintenance. The selective gating of information into active maintenance is necessary to perform delayed matching tasks in which a sample stimulus that must be maintained is followed by distractor stimuli that must be ignored until the test stimulus appears (Suzuki et al, 1997). Selective cholinergic activation of persistent spiking could gate just the sample stimulus into active maintenance. This is consistent with some data showing that pharmacological blockade of muscarinic cholinergic receptors impairs performance in delayed match-to-sample tasks in non-human primates (Penetar and McDonough, 1983; Miller and Desimone, 1993) and humans (Robbins et al, 1997). In working memory tasks, scopolamine does not impair tasks using the articulatory loop such as digit span (Kopelman and Corn, 1988), but does cause impairments in tasks that include interfering stimuli such as the n-back task (Green et al, 2005). Further data are needed on this topic. In unit recording studies, muscarinic blockade did not reduce match suppression in a delayed matching task, but its effect on spiking during the delay or match enhancement was not tested (Miller and Desimone, 1993). Selective lesions of the cholinergic innervation of rhinal cortex impaired delayed recognition in rats (McGaughy et al, 2005) and monkeys (Turchi et al, 2005), but cholinergic lesions of inferotemporal cortex in monkeys did not (Browning et al, 2010).

Cholinergic induction of cortical persistent spiking could underlie active maintenance of the conditioned stimulus in trace conditioning. Descriptions of this potential role for cellular mechanisms of persistent spiking (Hasselmo and Stern, 2006) motivated studies that examined the effect of cholinergic blockade on trace conditioning in rats (Bang and Brown, 2009; Esclassan et al, 2009). Consistent with the evidence for persistent spiking in entorhinal cortex, lesions of the entorhinal cortex were shown to impair trace conditioning, and local infusions of the M1 antagonist

pirenzepine during conditioning impaired learning of a fear response when a stimulus was separated from a shock by a trace interval, but did not impair expression of a previously learned trace fear response (Esclassan et al, 2009). Persistent spiking has also been shown in the perirhinal cortex (Leung et al, 2006) and infusion of scopolamine into the perirhinal cortex was shown to impair trace conditioning without impairing delay conditioning (Bang and Brown, 2009). These data indicate the important role of cholinergic modulation in providing active maintenance of a conditioned stimulus during the trace interval, possibly through induction of the cellular mechanism of persistent spiking for bridging across the continuous dimension of time (Hasselmo and Stern, 2006).

Persistent spiking may contribute to the generation of responses in the sustained attention task (Sarter et al, 2005; McGaughy and Sarter, 1998). In this task, signal trials involve presentation of a panel light illuminated for 25–500 ms, but the response to the signal cannot be generated until levers are inserted into the operant chamber, when the rat can respond to one lever indicating a signal, or a different lever indicating a nonsignal trial. The generation of a correct 'hit' response therefore requires a combination of cue detection of the signal, and maintenance of this signal for a period of time until the response can be generated. The amperometric measurement of ACh levels in this task indicates that cue detection causes a transient increase in cortical ACh levels on a time scale on the order of seconds. This transient ACh increase may specifically mediate the loading of a response into working memory through cholinergic modulation of persistent spiking, as shown in Figure 3, for maintenance until the levers enter the chamber allowing a response. If a cue-based response is already maintained by persistent spiking, then a new transient acetylcholine increase is not necessary to trigger the correct response on a subsequent hit trial, as shown in Figure 3. The regulation of persistent spiking by transient ACh allows selective gating of the cue but not other stimuli into working memory. In contrast, distractor stimuli in the sustained attention task should not evoke cholinergic transients (Himmelheber et al, 2000; Gill et al, 2000; WM Howe et al, unpublished results). Similarly, in delayed match-to-sample tasks with distractor stimuli (Miller and Desimone, 1993; Suzuki et al, 1997), the initial stimulus should be associated with a transient increase of ACh, but the distractor stimuli should not. Alternatively, as discussed above, such challenges may increase the tonic component of cholinergic neurotransmission, thereby enhancing the gain of prefrontal glutamatergic–cholinergic interactions and thus the amplitude of cholinergic transients.

The loading of a signal or a sample stimulus into active maintenance requires temporal specificity of the cholinergic transient (Fransen et al, 2002). As pointed out above, this specificity can be obtained by local interactions between thalamic glutamatergic and cholinergic input. Sensory information during the nonsignal period or during distractor stimuli will activate glutamatergic thalamic input to

cortical structures such as the PFC. However, in most cases this glutamatergic input will not be associated with a transient increase of acetylcholine levels. In these cases, glutamatergic synaptic input can drive cortical neurons to spike, but after the synaptic input terminates, these cells will stop spiking, and hence sensory input will not be loaded into active maintenance (see Figure 3a). In contrast, a signal event will cause sufficient glutamatergic release to cause an excitatory feedback interaction with cholinergic modulation. The thalamic fiber glutamate release evokes acetylcholine release through AMPA and NMDA receptors on ACh terminals (Parikh et al, 2008), and the increased acetylcholine release can enhance glutamate release from thalamic fibers by activation of $\alpha 4\beta 2^*$ nAChRs on the thalamic terminals (Lambe et al, 2003; Parikh et al, 2008; Parikh et al, 2010). This results in an excitatory feedback process that drives the large transient increase in acetylcholine observed with cue detection (Parikh et al, 2007), as shown in Figure 3b. This transient increase activates postsynaptic muscarinic receptors that activate calcium-sensitive non-specific cation currents in cortical pyramidal cells (Fransen et al, 2002), allowing them to show sustained depolarization and persistent spiking activity even after the stimulus input has terminated. This persistent spiking activity can then be maintained until the levers enter the chamber and the response is generated.

The persistent spiking mechanisms described above are consistent with fMRI studies using a delayed match-to-sample task (Schon et al, 2004). fMRI activity in the entorhinal and perirhinal cortex during the delay period correlates with subsequent memory for the sample stimulus in a post-scan recognition memory task (Schon et al, 2004). Injections of scopolamine in human subjects decrease the fMRI activity in entorhinal cortex and perirhinal cortex associated with subsequent memory for the sample stimuli (Schon et al, 2005). This supports the hypothesis that muscarinic activation of persistent spiking could underlie the maintenance of activity for encoding into long-term memory (Schon et al, 2005; Hasselmo and Stern, 2006).

The transient increase in cholinergic activity during a signal could also regulate mechanisms for detecting familiarity of a stimulus. Muscarinic receptor activation causes long-term depression of synaptic efficacy (Kirkwood et al, 1999; Warburton et al, 2003). This depression of synaptic efficacy could contribute to the repetition suppression of neural responses in areas such as the perirhinal cortex (Bogacz and Brown, 2003; Warburton et al, 2003).

ACETYLCHOLINE AND HIPPOCAMPAL ENCODING

The framework described above indicates how cholinergic modulation of persistent spiking could allow encoding of information into working memory for performance of tasks ranging from delayed match to sample to trace conditioning to cue detection. This hypothesis for cholinergic regulation

of active maintenance is consistent with earlier data indicating a role of cholinergic modulation in encoding into long-term episodic memory. Evidence in humans shows that infusion of muscarinic blockers impairs encoding of stimuli for subsequent free recall (Ghoneim and Mewaldt, 1975, 1977; Petersen, 1977), and cued recall (Atri et al, 2004), while sparing procedural memory (Nissen et al, 1987). In non-human primates, systemic scopolamine impairs encoding for subsequent recognition (Aigner and Mishkin, 1986), an effect that can be replicated by selective muscarinic blockade in the perirhinal cortex (Tang et al, 1997) or by cholinergic lesions of the perirhinal cortex (Turchi et al, 2005), although Browning et al (2010) did not see impaired recognition memory after cholinergic lesions of inferotemporal cortex that include perirhinal cortex.

The cholinergic innervation of the hippocampal formation has been implicated in the encoding of episodic memories. Lesions of the fornix or medial septum, which are the source of most of the cholinergic fibers innervating the hippocampus, cause profound impairments in memory-guided tasks such as spatial alternation and reversal in rats (M'Harzi et al, 1987; Givens and Olton, 1990; Ennaceur et al, 1996; Aggleton and Brown, 1999; Bussey et al, 2000), and lesions including fornix and basal forebrain impair scene learning in monkeys (Gaffan and Harrison, 1989; Easton et al, 2002). Local infusions of scopolamine into the hippocampus impair encoding of spatial information (Blokland et al, 1992; Rogers and Kesner, 2003). However, as discussed above, selective lesions of the cholinergic innervation arising from the medial septum in the rat do not show such robust effects on encoding. These lesions do not impair the traditional spatial discrimination in the water maze (Baxter et al, 1996) that is impaired by fornix lesions (Nilsson et al, 1987), and show small or transient effects in other tasks (see above). The lack of impairment with selective ACh lesions could be due to GABAergic modulation having a redundant role with cholinergic modulation, because combined lesions of both cholinergic and GABAergic input from the medial septum impair spatial memory (Pang and Nocera, 1999; Pang et al, 2001).

The cellular mechanisms of cholinergic modulation in cortical structures may be described as attentional processes in neocortical structures because they regulate entry of new sensory information into active maintenance to guide behavioral responses. Similar cellular mechanisms in circuits mediating long-term memory may be described as encoding of memory in the hippocampal formation (Hasselmo and McGaughy, 2004). With the exception of persistent spiking, cellular effects within the hippocampal formation resemble those observed in neocortical structures, and could change the dynamics of hippocampal function to enhance the encoding of new information.

On a cellular level, cholinergic modulation in the hippocampus causes effects similar to those in other cortical regions. Similar to thalamic input to neocortex, nicotinic receptor activation enhances the influence of afferent synaptic input in the hippocampus (Radcliffe and Dani, 1998;

Giocomo and Hasselmo, 2005) including glutamatergic input to interneurons (Alkondon and Albuquerque, 2002). Muscarinic receptor activation causes suppression of recurrent excitatory connections in hippocampal region CA3 (Hasselmo et al, 1995; Vogt and Regehr, 2001; Kremin and Hasselmo, 2007) and suppresses connections from CA3 to CA1 (Hounsgaard, 1978; Valentino and Dingledine, 1981; Hasselmo and Schnell, 1994), similar to effects shown in piriform cortex (Hasselmo and Bower, 1993) and neocortex (Hsieh et al, 2000; Kimura, 2000). Muscarinic receptor activation also enhances the hippocampal pyramidal cell spiking response to afferent input (Cole and Nicoll, 1984; Madison and Nicoll, 1984). Muscarinic modulation depolarizes inhibitory interneurons while suppressing inhibitory transmission (Pitler and Alger, 1992; Patil and Hasselmo, 1999) in a manner that could enhance the response to afferent input while decreasing tonic endogenous activity.

Afterdepolarization and plateau potentials have been observed in slices of the hippocampus (Fraser and MacVicar, 1996) similar to those observed in other cortical structures (Haj-Dahmane and Andrade, 1998). However, stable intrinsic mechanisms for persistent spiking do not appear in hippocampal slice recordings, consistent with the lower spontaneous background firing rate of hippocampal neurons, suggesting that the hippocampus is less engaged with active maintenance for working memory and more engaged with encoding into long-term episodic memory. In this framework, cholinergic modulation may enhance persistent spiking in the entorhinal cortex and perirhinal cortex as a short-term buffer for new information (Hasselmo and Stern, 2006), while also enhancing the responsiveness of hippocampus to afferent input for encoding through enhanced induction of long-term potentiation. The enhancement of long-term encoding could be at least partially mediated by the cholinergic enhancement of long-term potentiation in the hippocampus (Blitzer et al, 1990; Burgard and Sarvey, 1990; Auerbach and Segal, 1994; Isaac et al, 2009).

The effects of ACh cannot be considered in terms of static patterns of activity, as the hippocampus shows complex dynamical properties including prominent field potential oscillations in the theta frequency range (Buzsaki, 2002). Cholinergic modulation may have an important role in the induction of theta rhythm oscillations (Bland and Colom, 1993). On a cellular level, acetylcholine induces theta rhythmic activity in hippocampal interneurons of stratum lacunosum-moleculare (Chapman and Lacaille, 1999). Muscarinic activation also selectively enhances the response to theta rhythmic input in interneurons projecting from stratum oriens to lacunosum-moleculare (Lawrence et al, 2006a, b). In entorhinal cortex, cholinergic modulation of oscillations has been proposed to underlie the expansion of grid cell spacing in novel environments (Burgess et al, 2007), and this proposal is supported by data showing that cholinergic modulation lowers the intrinsic resonance frequency of entorhinal stellate cells (Heys et al, 2010). On a network level, cholinergic modulation of the medial

septum induces theta rhythm oscillations (Lawson and Bland, 1993) and theta rhythm is correlated with higher levels of acetylcholine in the hippocampus (Marrosu et al, 1995; Monmaur et al, 1997), whereas lesions of the cholinergic innervation reduce the magnitude of theta rhythm (Lee et al, 1994). Theta rhythm oscillations might induce dynamical changes similar to the change in circuit dynamics induced by acetylcholine in the neocortex.

The cholinergic modulation of hippocampal encoding dynamics might also include selective activation of a loop through the dentate gyrus and region CA3 for encoding. The direct entorhinal projections to region CA1 have been shown to be sufficient for driving hippocampal neural activity of place cells (Mizumori et al, 1989; Brun et al, 2002). Lesions of CA3 impair both encoding and retrieval of the context of fear conditioning, whereas lesions of CA1 impair only the retrieval (Ji and Maren, 2008). Cholinergic modulation of region CA3 seems to be important for the encoding of new information. Infusion of scopolamine into CA3 impairs the encoding of information in spatial memory tasks (Rogers and Kesner, 2003) as well as fear conditioning tasks (Rogers and Kesner, 2004), possibly by reducing the depolarization of CA3 neurons and the induction of long-term potentiation. Cholinergic modulation also affects the functional activation of the dentate gyrus, as infusion of acetylcholine into the dentate gyrus enhances the population spike response to perforant pathway stimulation (Foster and Deadwyler, 1992). The cholinergic enhancement of encoding of sensory stimuli might be coupled with a reduction in the retrieval mediated by internal feedback influences, as suggested by the reduction of evoked synaptic potentials in CA1 during acetylcholine infusion (Herreras et al, 1988) and during behavioral states associated with higher levels of acetylcholine such as REM sleep (Winson and Abzug, 1977, 1978; Hasselmo, 1999). Consistent with this, the AChE inhibitor physostigmine reduces behavioral retrieval of previous learning (Rogers and Kesner, 2003, 2004), suggesting that cholinergic modulation reduces the influence of retrieval. Physostigmine also impairs consolidation (Gais and Born, 2004) and scopolamine enhances consolidation (Rasch et al, 2006), consistent with the theory that lower levels of ACh during slow-wave sleep might allow enhanced feedback appropriate for consolidation (Hasselmo, 1999).

Recent computational modeling shows how a circuit including grid cells, place cells, and head direction cells could mediate the encoding and retrieval of spatiotemporal trajectories for episodic memory (Hasselmo, 2008b, 2009). These models require a shift in the dynamics of the network between encoding and retrieval, in which the encoding of new information involves enhancement of long-term potentiation at intrinsic connections of the hippocampus and at connections from the hippocampus to the post-subiculum. During encoding the synapses being modified must not influence their postsynaptic target, to avoid distorting the stored representation (Hasselmo and Bower, 1992, 1993; Hasselmo and Schnell, 1994). In contrast, during

retrieval, the previously modified synapses must have a stronger influence to drive retrieval of a trajectory within the network. This transition from encoding to retrieval could be mediated by changes in cholinergic neurotransmission on a time scale of the sort shown with amperometry in the neocortex (Parikh *et al*, 2007).

In summary, the cellular effects of acetylcholine are similar within the hippocampal formation and the neocortex. The behavioral effect of this cholinergic modulation might depend on the nature of the processing in local circuits. Cholinergic modulation of cellular properties in the neocortex might switch dynamics from a default state to a state of fostering cue detection. Enhancement of persistent spiking might gate sensory information into working memory for the active maintenance of future responses. The enhancement of afferent input to the hippocampus might enhance encoding into long-term episodic memory, whereas the enhancement of the response to thalamic input to the neocortex might enhance attention to sensory stimuli.

FUTURE RESEARCH DIRECTIONS: TOWARD A NEW CHOLINERGIC NEUROPSYCHOPHARMACOLOGY

We began this article by pointing to the limitations of conventional neuropsychopharmacological tools to probe the cognitive functions of the cholinergic system and to assess the usefulness of cholinergic treatments for the cognitive impairments on a wide range of disorders. Although our understanding of the regulation and function of cholinergic systems remains rudimentary, research has indicated that cholinergic systems act in strikingly more complex ways than was assumed just a decade ago. It is likely that different yet complementary functions are mediated by cholinergic signaling mechanisms that occur on different time scales (seconds *vs* minutes). Furthermore, it seems that within a major branch of the brain's cholinergic systems there is substantially greater topographic differentiation than originally assumed, and that the potentially highly specific functions of ACh within a particular target region are based in part on highly topographic projection systems. Moreover, the cognitive selectivity of the effects of cholinergic modulation may be largely determined by the target circuit, based on local microcircuitry controlling cholinergic presynaptic activity, through heteroreceptors expressed on cholinergic terminals.

Such a description of the cholinergic system may suggest daunting challenges for efforts to develop new cholinergic therapies. Certainly, these complexities may explain in part the limitations of conventional approaches, such as elevating ACh levels through AChE inhibition or direct stimulation of mAChRs (see Introduction). However, the new evidence and related circuitry models also provide the basis for new and innovative approaches to enhance cholinergic function. Most obviously, we can stimulate $\alpha 4\beta 2^*$ nAChRs

to amplify cholinergic transients and enhance attentional performance (eg, Howe *et al*, 2010). Although the clinical evidence remains limited, some evidence supports the view that such compounds may be useful for treating the cognitive symptoms of ADHD, schizophrenia, and aging (Dunbar *et al*, 2007; Wilens *et al*, 1999, 2006; Wilens and Decker, 2007; Potter *et al*, 1999). Other nAChR subunits are likely to modulate the gain in other aspects of cortical circuitry (eg, Dickinson *et al*, 2008) and thus may similarly be found to modulate relatively specific aspects of information processing.

The potential clinical significance of $\alpha 7$ nAChR agonists is more difficult to predict. As pointed out above, our own evidence does not allow deduction of a specific hypothesis about the cognitive functions that may benefit from stimulation of these receptors. To the contrary, we find that removing the contribution of these receptors to the effects of nicotine transforms nicotine into a more efficacious enhancer of attentional performance (Howe *et al*, 2010). The treatment of the cognitive symptoms of schizophrenia has been a focus of $\alpha 7$ nAChR agonists; however, their potential utility remains to be determined (eg, Martin *et al*, 2004; Freedman *et al*, 2008).

As discussed above, our understanding of the potential therapeutic significance of mAChR agonists has remained poor, perhaps largely because of the paucity of ligands available for probing mAChR subtypes (eg, Wienrich *et al*, 2002; Bodick *et al,* 1997; Raffaele *et al*, 1996). New, selective ligands are becoming available now, allowing the test of the hypothesis that mAChRs control mechanisms that concern the maintenance of the state of prefrontal circuits and the recruitment of efferent projections in situations requiring top-down control of cognitive performance.

Emerging positive allosteric modulators (PAMs) for both nAChRs and mAChRs (Shirey *et al*, 2009; Hurst *et al*, 2005; Taly *et al*, 2009) allow addressing particularly important questions. The promise for such ligands is based on the general assumption that modification of an endogenous signal represents a superior approach to cognitive enhancement when contrasted against introducing a pharmacological signal to influence circuit functions (Sarter and Bruno 1997). Although the potential efficacy of such a strategy may be limited by structural alterations in brain circuitry, PAMs acting at AChRs are expected to afford a level of modulatory selectivity and temporal precision that will not only assist in revealing the precise role of cholinergic systems in a particular behavioral or cognitive context, but also may allow the manifestation of effect sizes that are of clinical relevance. For example, PAMs targeted at M4 receptors may allow selective suppression of glutamatergic excitatory transmission (Shirey *et al*, 2008) to enhance the specificity of neural firing and synaptic modification without causing excess activation of excitatory postsynaptic M1 receptors.

The administration of cholinergic drugs as a co-treatment will be a clinical necessity for many indications, including for treating the cognitive symptoms of schizophrenia. With the exception of studies on donepezil as a co-treatment in

schizophrenia (eg, Keefe *et al*, 2008; Kohler *et al*, 2007), neuropsychopharmacological, and specifically preclinical, research on such co-treatment strategies has received little attention, perhaps due to a considerable part to the regulatory and commercial challenges associated with the development of combination treatments. However, it seems paramount that such approaches be investigated to determine the true clinical potential of new cholinergic drugs.

Finally, the importance of interactions between new cholinergic treatments and cognitive practice for revealing the full efficacy of treatments deserves reiteration. As previously discussed (Sarter and Bruno 1997), treating, for example, heart disease is commonly expected to consist of combinations of pharmacological and behavioral therapies (see also Keefe *et al*, 2010). In contrast, treatments of cognitive disorders often are expected to consist solely of the administration of a pharmacological 'magic bullet'. Selective n/mAChR agonists and PAMs at these receptors may come as close to magic bullets as can be currently envisioned. However, obtaining their full benefit requires that they interact with cognitive demand-induced recruitment of forebrain circuitry. Conducting clinical trials that seek to show interactions between the effects of a pharmacological treatment and cognitive practice may not constitute an exotic, luxurious effort but perhaps a psychopharmacological necessity for discovering truly effective treatments for cognitive impairments.

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