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Leveraging the cortical cholinergic system to enhance attention

Elise Demeter^{a,b,*} and Martin Sarter^c

^aPsychiatry Department, 4250 Plymouth Road, University of Michigan, Ann Arbor, MI 48109-5765, USA

^bFunctional MRI Laboratory, 2360 Bonisteel Blvd., University of Michigan, Ann Arbor, MI 48109-2108

^cDepartment of Psychology, 530 Church Street, 4032 East Hall, University of Michigan, Ann Arbor, MI 48109-1109, USA

Abstract

Attentional impairments are found in a range of neurodegenerative and neuropsychiatric disorders. However, the development of procognitive enhancers to alleviate these impairments has been hindered by a lack of comprehensive hypotheses regarding the circuitry mediating the targeted attentional functions. Here we discuss the role of the cortical cholinergic system in mediating cue detection and attentional control and propose two target mechanisms for cognition enhancers: stimulation of prefrontal $\alpha 4\beta 2^*$ nicotinic acetylcholine receptors (nAChR) for the enhancement of cue detection and augmentation of tonic acetylcholine levels for the enhancement of attentional control.

Keywords

acetylcholine; cognition enhancers; attentional control; cue detection

1. Introduction

Attentional functions are often parsed into “bottom-up” processes, including processes associated with the detection and processing of relevant cues, and “top-down” processes associated with selecting relevant inputs, ignoring irrelevant inputs, and maintaining the appropriate task set over time in the face of competing internal or external demands (Kastner & Ungerleider, 2000; Sarter et al., 2001; Sarter et al., 2006; Treisman & Gelade, 1980). Converging evidence from numerous animal model studies, including lesion and pharmacological manipulations, and human psychopharmacological and pharmacofMRI studies demonstrates the importance and necessity of the cortical cholinergic input system for attention (e.g., Robbins et al., 1989; Muir et al., 1994; McGaughy et al., 1996; Sarter et al., 2005; Giocomo & Hasselmo, 2007; Hahn et al., 2007; Deco & Thiele, 2009; Hasselmo & Sarter, 2011). The cortical cholinergic system exerts its effects on attention via sensory, prefrontal, and parietal regions and interactions among those regions (e.g., Sato et al., 1987; Golmayo et al., 2003; Nelson et al., 2005). Prefrontal cortex, particularly right prefrontal

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*Corresponding author: elisemd@med.umich.edu, Phone: (734) 232-0373, Fax: (734) 936-7868.

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cortex, is a key site for cortical cholinergic mediation of both cue detection and top-down attentional control processes, including the enhancement of control in response to challenging or distracting conditions (e.g., Parikh et al., 2007; Gill et al., 2000; Sarter et al., 2006; see also Cabeza & Nyberg, 2000 for a review of neuroimaging studies of attention supporting the involvement of a right-lateralized frontoparietal network, particularly for selective and sustained attention).

Given the cortical cholinergic system's importance in mediating attentional functions, this system is a frequent target of drug development programs aimed at improving cognition. Here, we propose two target mechanisms for cognition enhancers, cue detection and attentional control. To this end, we describe these attentional functions in healthy individuals and impairments in these functions in patient populations, review the literature on the use of acetylcholinesterase inhibitors and agonists at muscarinic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs) to enhance cognition and attention, and detail recent data indicating tonic cholinergic activity mediates top-down attentional control functions while phasic cholinergic activity mediates cue detection. Collectively, the available evidence and literature supports the use of cholinergic drugs, particularly agonists targeting $\alpha 4\beta 2^*$ nAChRs, for enhancing attentional and cognitive functions and capacities.

2. Cue detection and attentional control in healthy and patient populations

A critical aspect of attention is the ability to detect relevant environmental cues and discriminate these cues from noise. Detection is defined as a cognitive process which consists of "...the entry of information concerning the presence of a signal into a system that allows the subject to report the existence of the signal by an arbitrary response indicated by the experimenter" (Posner et al., 1980). Behaviorally relevant stimuli, particularly unexpected or salient stimuli, are detected by the ventral frontoparietal network, including regions in right inferior frontal and temporoparietal cortex (see review by Corbetta & Shulman, 2002). This ventral, stimulus-driven network directs attention to salient environmental events and interacts with the dorsal frontoparietal attention network, which consists of regions in superior frontal cortex and intraparietal cortex.

In addition to being influenced by the detection of cues, the dorsal attention network is involved in the top-down control of attention. Top-down attentional control processes modulate the detection and processing of cues on the basis of goals and prior knowledge of or experience with relevant stimuli, and allowing the enhancement of behaviorally-relevant cues and the suppression of irrelevant stimuli (e.g., Serences et al., 2005; O'Connor et al., 2002; for review, see Corbetta & Shulman, 2002; Pessoa et al., 2003). Attentional control processes are also engaged when attention is challenged, say by the presentation of distractors, fatigue, changing target stimulus characteristics or presentation parameters, or other detrimental events, in order to increase motivated participants' *attentional effort* and stabilize or maintain attentional performance in the face of the challenging conditions (Sarter et al., 2006; Sarter & Paolone, 2011).

Disruption of cholinergic transmission and associated impairments in attention are seen in a variety of neurodegenerative and neuropsychiatric disorders, including age-related cognitive declines, mild cognitive impairment, Alzheimer's, attention deficit hyperactivity disorder (ADHD) and schizophrenia. In schizophrenia, for example, research has consistently demonstrated impairments in attention and attentional control (Heinrichs & Zakzanis, 1998; Nuechterlein et al., 2004) that persist across both periods of psychosis and remission (Asarnow & MacCrimmon, 1978; Nuechterlein et al., 1992; Wohlberg & Kornetsky, 1973). Patients' difficulties with controlled, effortful attentional processing become even more

apparent when the attentional systems are highly taxed, such as in tasks with high loads, tasks with rapid processing of information requirements, and in tasks with distraction (e.g., Braff & Saccuzzo, 1985; Dawson & Nuechterlein, 1984; Dawson, 1990; Kietzman et al., 1985). Attentional deficits have a significant relationship to functional outcome, including the ability to acquire basic life skills, social problem solving and social competence (Green et al., 2000), suggesting that improving attentional capabilities may benefit several aspects of patients' lives.

Yet, while the need for pro-cognitive enhancers is there and there has been renewed interest in addressing the cognitive symptoms in disorders such as schizophrenia (i.e., the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative: Carter & Barch, 2007; Carter et al., 2008; see also review by Sarter et al., 2012), the success of preclinical and clinical psychopharmacological research to develop procognitive treatments has been limited. Our previous reviews on the reasons behind this failure have largely pointed to the use of atheoretical research strategies in preclinical drug development, including the widespread use of high-throughput behavioral screening tests with limited or unknown validity in terms of modeling clinically-relevant cognitive outcomes and a focus on accumulating evidence that drugs in development show beneficial effects on a wide range of behavioral measures instead of focusing on defining specific mechanisms underlying pharmacologically-induced cognitive enhancement (see Sarter et al., 1992a,b; Sarter, 2006). Below, we review the evidence supporting the use of acetylcholinesterase inhibitors, mAChR agonists and nAChR agonists for enhancing attention and propose two target mechanisms in order to support hypothesis-guided development of procognitive compounds.

3. Enhancement of attention via acetylcholinesterase inhibitors

The interest in acetylcholinesterase inhibitors like donepezil or galantamine for the enhancement of attention stems largely from their use clinically to treat the cognitive impairments associated with dementia (e.g., Rogers et al., 1996; 1998; Raskind et al., 2000). In animal model studies, selective lesions to the basal forebrain cortical cholinergic system in attention task-performing animals result in a severe and lasting impairment in signal detection, while the ability to correctly reject nonsignals remains intact (McGaughy et al., 1996; McGaughy & Sarter, 1998). While these studies demonstrate the necessity of the cortical cholinergic system for attentional performance, follow-up experiments attempting to rescue attentional performance with cholinesterase inhibitors following limited basal forebrain lesions have seen mixed results, with some experiments finding attenuation of attentional impairments (Muir et al., 1995) and others finding no benefit of cholinesterase inhibitors for attentional performance in lesioned animals (McGaughy & Sarter, 1998). This suggests the usefulness of cholinesterase inhibitors to rescue attention in cases where the cholinergic neurons have degenerated is limited.

Studies in healthy humans show some support for the ability of cholinesterase inhibitors to enhance attention. Behavioral studies of donepezil in healthy humans demonstrate that donepezil can improve voluntary attention, but does not affect involuntary attention (Rokem et al., 2010). In human pharmacofMRI studies, cholinergic enhancement through administration of acetylcholinesterase inhibitors increases activation in sensory regions in response to attended, task-relevant stimuli, and suppresses activation in response to task-irrelevant stimuli (e.g., Furey et al., 2000; Bentley et al., 2004; Silver et al., 2008). Cholinergic enhancement also modulates frontoparietal regions, with findings indicating reductions in frontoparietal activations when sensory activations are heightened and task-demands are low, presumably reflecting increased efficiency in executive attentional processes (e.g., Furey et al., 2000; Ricciardi et al., 2009).

The evidence on the ability of cholinesterase inhibitors to enhance attention in patient populations suggests that these compounds may be more effective for some patient populations than for others. For example, an fMRI study of patients with Alzheimer's disease and age-matched healthy controls with and without the cholinesterase inhibitor physostigmine found that physostigmine improved stimulus- and attention-dependent responses in patients, normalizing activation in areas known to be affected by Alzheimer's disease like extrastriate and frontoparietal cortex, while perturbing activation in those same regions in the controls (Bentley et al., 2008). In contrast to the beneficial effects seen in dementia patients, the collective evidence for patients with schizophrenia suggests cholinesterase inhibitors are not effective treatments for the attentional deficits seen in this population (e.g., Buchanan et al., 2008; Keefe et al., 2008; Kohler et al., 2007). Some have speculated that cholinergic activity in patients with schizophrenia is elevated compared to healthy controls (Tandon & Greden, 1989). The ability of cholinesterase inhibitors to improve attentional functions may thus depend on the baseline activity of the cholinergic system, and in cases where cholinergic activity is already high, further augmentation of acetylcholine (ACh) levels may fail to provide a benefit. The lack of procognitive results in schizophrenia may also be due to the fact that cholinesterase inhibitors exert broad effects on ACh concentrations in the extracellular space, and do not act to optimize the tonic and phasic components (described below) of cholinergic activity thought to be the most promising targets for procognitive enhancers (for more discussion of these issues see Hasselmo & Sarter 2011).

4. Enhancement of attention via mAChR agonists

4.1 Effects of nonselective mAChR antagonists

In mammals, there are five mAChR subtypes, M1–M5 (Wess, 1996; Caulfield & Birdsall, 1998). Nonselective mAChR antagonists such as scopolamine impair attention and the encoding of new memories in animal models (Aigner et al., 1991; McGaughy et al., 1994) and in healthy humans (e.g., Ghoneim & Mewaldt, 1975, 1977; Wesnes & Warburton, 1984), and exacerbate the cognitive impairments seen in healthy aged individuals and patients with Alzheimer's disease (eg, Molchan et al., 1992; Sunderland et al., 1987, 1988). Acute administration of nonselective mAChR antagonists to healthy humans has been used as a pharmacological model of dementia (e.g., Beatty et al., 1986; Broks et al., 1988). While this may be a useful model in some respects, the interpretation of the results from nonselective mAChR antagonists must be informed and modified by the fact that these drugs not only block postsynaptic mAChRs, but also antagonize presynaptic M2 receptors (e.g., Herzog et al, 2003). Antagonism of these presynaptic receptors leads to an increase in ACh release, resulting in extremely high extracellular levels of ACh. This in turn stimulates nAChRs, leading to an interaction between the blockade of mAChRs and the stimulation of nAChRs and a complex pattern of behavioral and cognitive effects. Supporting the idea of this interaction between nAChRs and mAChRs, several studies demonstrated that blocking nAChRs alone does not affect cognition, but co-administration of nAChR antagonists and mAChR antagonists significantly impairs cognition (e.g., Little et al, 1998; Ellis et al, 2006; Erskine et al, 2004; see Hasselmo & Sarter, 2011 for further discussion of these issues).

4.2 Development of mAChR subtype-specific agonists

Relatively little is known about the contribution of specific mAChR subtypes to cognitive functions or the usefulness of mAChR agonists for enhancing attention and other cognitive functions. This is largely due to the fact that development of subtype-selective antagonists and agonists has been hindered due to the high sequence homology among the orthosteric binding sites of the five mAChR subtypes. Alternative strategies, such as the use of immunoprecipitation assays with subtype-specific antibodies (e.g., Levey et al., 1991) and

the development of muscarinic receptor knockout mice (e.g., Yamada et al., 2001; Jeon et al., 2010) has helped shed light onto the roles of specific mAChR subtypes. For example, M4 mAChRs are expressed widely throughout the forebrain, but are also expressed in D1 dopamine receptor-expressing cells in striatal projecting neurons (Jeon et al., 2010). Deletion of this specific subpopulation of M4 receptors alters several dopamine-dependent behaviors, including increasing behavioral sensitization following psychostimulant treatment, and leads to an increase in dopamine efflux in the nucleus accumbens. This evidence points to a mechanisms for how mAChRs could play a role in the increased central dopaminergic neurotransmission seen in disorders such as schizophrenia (Jeon et al., 2010). The M5 subtype also influences dopamine neurotransmission, as it has been implicated in aiding muscarinic agonist-induced striatal dopamine release. It is also necessary for the dilation of cerebral blood vessels by acetylcholine (Yamada et al., 2001). This latter fact is of special interest from the perspective of developing targets for cognition enhancers, as impairments in cholinergic dilation of cerebral blood vessels may be important for the pathophysiology of Alzheimer's disease.

While developing subtype-selective mAChR agonists has been challenging, recent advances on this issue have been made by developing compounds that target allosteric binding sites distinct from the ACh binding site (for review, see Conn et al., 2009). These compounds have helped clarify the roles of mAChR subtypes in mediating cognitive functions. For example, the M1 receptor subtype is thought to be important for memory and attention (Levey et al., 1991; Felder et al., 2000), and selective M1 agonists have been proposed as a treatment for Alzheimer's disease (e.g., Bodick et al., 1997; Caccamo et al., 2006, 2009). Genetic deletion of these receptors failed to produce impairments in hippocampal-dependent learning and failed to influence impairments following mAChR antagonist administration (Rouse et al., 2000; Miyakawa et al., 2001; Anagnostaras et al., 2003), but did reveal specific deficits in learning and memory tasks requiring engagement of the prefrontal cortex (Anagnostaras et al., 2003). This suggests the M1 receptor may help regulate prefrontal function. Recently, compounds that are positive allosteric modulators (PAMs) at the M1 receptor have been discovered and synthesized (Marlo et al., 2009; Shirey et al., 2009). These compounds substantially increase the affinity of the M1 receptor for ACh and potentiate the response to orthosteric agonist. Investigations with these compounds demonstrate that they can increase medial prefrontal neuronal firing *in vivo* and reverse impairments in prefrontal cortex-dependent learning in mouse models of Alzheimer's disease, suggesting the M1 receptor is important for regulating excitation of the prefrontal cortex and that selective activation of M1 receptors could help alleviate impairments in prefrontal cortex-dependent cognition (Shirey et al., 2009).

5. Enhancement of attention via nAChR agonists

5.1 Effects of nicotine and nonspecific nAChR agonists

Overall, much more is known about the effects of nAChR agonists than mAChR agonists. While only a few animal model studies have assessed the effects of nicotine on attentional performance, nicotine's effects on attention have been extensively studied in smoker and nonsmoker healthy and patient populations (see Levin, 2002; Kassel, 1997; and Bentley et al., 2011 for reviews). In general, the available evidence indicates nicotine improves basic attentional functions, but these beneficial effects are sometimes difficult to replicate and are usually less robust than the effects seen with specific nAChR agonists. In animal model studies, while some reports have failed to find significant effects of nicotine (e.g., Turchi et al., 1995; Bushnell et al., 1997; Kozak et al., 2007), others have demonstrated that nicotine improves accuracy in attention tasks. Nicotine improves choice-accuracy in a five-choice serial reaction-time task in rats with lesions of the nucleus basalis magnocellularis (Muir et al., 1995). Similarly, Mirza and Stolerman (1998) demonstrated increased accuracy on an

attention task with nicotine when the task condition included low rates of stimulus presentation. Blondel et al. (2000) investigated the effects of acute and repeated administration of nicotine on rat performance of the five-choice serial reaction-time task and found nicotine did not improve animals' accuracy, but did improve response readiness and target scanning as response latencies decreased and performance in the less-well attended stimulus locations improved. Antagonism of specific nicotinic receptor subtypes revealed these beneficial effects were most likely mediated through $\alpha 4\beta 2^*$, $\alpha 4\beta 4^*$, or $\alpha 3\beta 2^*$ but not through $\alpha 7$ nAChRs (Blondel et al., 2000).

Nicotine has been used extensively in human behavioral and pharmacofMRI studies to enhance attention. Behavioral studies in non-smokers or deprived smokers consistently find nicotine improves attentional functions (e.g., Le Houezec et al., 1994; Mancuso et al., 1999; Warburton & Mancuso, 1998; Vangkilde et al., 2011), and can also improve memory through the attentional enhancement of items during encoding (Marchant et al., 2008; Rusted et al., 2009). Neuroimaging studies of nicotine generally see changes in activation with nicotine that mirror the patterns seen with cholinesterase inhibitors. Activation in sensory regions increases during attentionally-demanding task conditions compared to less-demanding control conditions, such as when target-detection tasks use low-contrast targets (Hahn et al., 2007) or invalidly cued targets (Thiel et al., 2005), or in visual maze tasks (Ghatan et al., 1998). In response to increased activation in sensory regions and resulting gains in perceptual or encoding efficiency, decreases are often seen in frontal and parietal regions. These effects are interpreted as reflective of reduced demands on top-down attentional control processes (Ghatan et al., 1998; Ettinger et al., 2009). In contrast, when the demands on executive attention functions are high, nicotine increases activation in frontal and parietal regions in order to recruit additional top-down control processes to maintain or improve performance under the attentionally-challenging conditions (Ernst et al., 2001; Lawrence et al., 2002; Thiel et al., 2005; Giessing et al., 2006; Vossel et al., 2008). The modest improvements in attentional functions following nicotine administration seems to generalize from healthy individuals to patient populations, with nicotine or nonspecific nAChR agonists enhancing attentional function in adults with ADHD (Conners et al., 1996; Levin et al., 1996; Wilens et al., 2007), Alzheimer's disease (Jones et al., 1992; Sahakian et al., 1989; Newhouse et al., 2001) and schizophrenia (Freedman et al., 2008).

5.2 Effects of agonists at $\alpha 4\beta 2^*$ nAChRs

$\alpha 4\beta 2$ and $\alpha 7$ receptors represent the two most predominate nicotinic receptors in the brain. Unlike the current state of the literature with respect to muscarinic receptor subtypes, much more is known about the potential of selective agonists of nicotinic receptor subtypes as cognition enhancers, particularly for $\alpha 4\beta 2^*$ agonists. In contrast to the modest and often unreliable effects of nicotine on attention, the available evidence on agonists that specifically target $\alpha 4\beta 2^*$ nAChR subtypes show much more robust effects. Animal model studies show administration of $\alpha 4\beta 2^*$ agonists can significantly improve the relative number of hits in a sustained attention task (McGaughy et al. 1999) and improve accuracy on the five-choice serial reaction time task under conditions of enhanced difficulty or in poor-performers (Mohler et al., 2010). Corresponding to the robust attentional enhancement effects seen with $\alpha 4\beta 2^*$ agonists, nAChR $\beta 2$ subunit deletions impair attentional

¹Asterisks indicate possible presence of other subunits in the nAChR subtypes. For example in the layer VI pyramidal neurons of prefrontal cortex, the less common $\alpha 5$ subunit is also incorporated into the $\alpha 4\beta 2$ subtype. This additional subunit enhances the conductance and currents of these neurons (Ramirez-Latorre et al., 1996; Bailey et al., 2010). nAChR activation of layer VI pyramidal neurons results in a net increase in neuronal activity (see Poorthuis et al., 2012 for a description of the layer-specific effects of nAChR stimulation). These neurons are important for attention through their feedback projections onto the thalamus (Crick, 1984; Zikopoulos & Barbas, 2006; Briggs & Usrey, 2011), and deletion of the $\alpha 5$ subunit in mice results in deficits on attentional tasks when demands on attention are high (Bailey et al., 2010). Hence, this additional $\alpha 5$ subunit may contribute to the mechanisms supporting top-down control described in this review.

performance in mice, an effect that can be reversed by re-expressing functional $\beta 2$ subunit-containing nAChRs in prefrontal neurons in the prelimbic area (Guillem et al., 2011). While the literature on specific $\alpha 4\beta 2^*$ agonists in humans is sparse, these agonists appear to have more robust attentional enhancement effects than those seen with nicotine in patient populations such as age associated memory impairment (Dunbar et al., 2007) and schizophrenia (Taylor et al. 2011). Interestingly, clinical trials on the $\alpha 4\beta 2^*$ agonist ABT-089 demonstrate this agonist can robustly improve attention in adult ADHD patients (Wilens et al., 2006; Apostol et al., 2012), but not in pediatric ADHD patients (Wilens et al., 2011). While still speculative, this evidence seems to support the ideas presented here that nAChR agonists and specifically $\alpha 4\beta 2^*$ agonists work to enhance attention primarily by enhancing attentional control. As attentional control is still developing well into young adulthood (e.g., Andrews-Hanna et al., 2011) the cognitive mechanisms underlying the attentional deficits seen in pediatric versus adult ADHD may be distinct in certain respects. If deficits in adult, but not pediatric, ADHD are primarily related to deficits in the top-down control of attention, this would account for the findings that $\alpha 4\beta 2^*$ agonists benefit adult ADHD patients, but do not show the same effects in pediatric ADHD (see Sarter & Paolone, 2011 for further discussion).

5.3 Effects of agonists at the $\alpha 7$ nAChR

In contrast to the evidence that nicotine and especially $\alpha 4\beta 2^*$ agonists enhance attention, the evidence concerning the effects of selective $\alpha 7$ agonists is limited and conflicted. Several animal model studies of $\alpha 7$ agonists have failed to show effects on attention (Grottick et al., 2000; 2003; Hahn et al. 2003). However, $\alpha 7$ nAChR knockout mice show impairments in acquiring and performing an attention task, and improvements following nicotine administration, suggesting that this receptor plays a role in the effects of nicotine (Young et al., 2004). While $\alpha 7$ agonists may have a place among other procognitive enhancers for treating the cognitive deficits in certain disorders (Olinicy et al., 2007), evidence from animal models on the mechanisms underlying the cortical cholinergic system's role in cue detection and top-down attentional control suggests that selective stimulation of $\alpha 4\beta 2^*$ receptors represents a critical target mechanism for the enhancement of attention and stimulation of $\alpha 7$ receptors may weaken or blunt these beneficial effects (Howe et al., 2010).

6. Tonic and phasic cholinergic activity mediates attention

As described above, selective lesions of cholinergic neurons in the basal forebrain demonstrate the necessity of the cortical cholinergic system for attentional performance (McGaughy et al., 1996; Turchi & Sarter, 1997). Much of our own work on the cortical cholinergic system's role in mediating attention utilizes the sustained attention task (SAT), a task developed for use in, and validated for, mice, rats, and humans (St. Peters et al., 2011a; McGaughy & Sarter, 1995; Demeter et al., 2008). In the SAT, a brief, variable duration signal/cue is either presented (signal trial) or not presented (nonsignal trial). Participants must then report the presence or the absence of the cue and are rewarded for correct performance. The attentional control demands of this task can be manipulated through the introduction of a visual distractor (distractor condition sustained attention task, dSAT), allowing for the assessment of multiple aspects of attentional performance. *In vivo* microdialysis studies of the cholinergic system find that ACh release in right prefrontal cortex increases during performance of the SAT, beyond the levels of release seen in control tasks with matched motor and reward components (Himmelheber et al., 2000; Arnold et al., 2002; Dalley et al., 2001; Kozak et al., 2006, 2007; St. Peters et al., 2011b). While the low temporal resolution of microdialysis (on the scale of minutes) places limitations on the ability to map changes in ACh release onto specific task events, more recent evidence suggested that it samples a separate and indeed more tonically active component of

cholinergic neurotransmission that is separate from phasic increases in cholinergic activity (“transients”; Parikh & Sarter, 2008; Paolone et al., 2010; see below).

These limitations have been overcome by recent technological advances that led to the ability to measure the synaptic release of ACh in task-performing animals at a sub-second resolution using choline-sensitive microelectrodes (Parikh et al., 2004). Studies using this microelectrode technology demonstrate the necessity of transient increases in ACh in right prefrontal cortex for cue detection and begin to unravel the neurochemical circuitry responsible for mediating cue detection (e.g., Parikh et al., 2007). Further, we now understand that ACh acts through two separable components: a sub-second phasic component responsible for mediating cue detection, and a tonic, minutes-based component responsible for mediating the top-down attentional control. The circuitry supporting cue detection and attentional control are described in detail below. Collectively, this evidence suggests the cortical cholinergic system can play a dynamic role in optimizing both sensory and frontoparietal control regions in response to behaviorally-relevant stimuli and task demands and provides the rationale for target mechanisms for procognitive enhancers.

7. Target mechanism for enhancing cue detection and attentional switching

The evidence concerning the phasic component of the cortical cholinergic system and its role in cue detection has evolved rapidly in the past few years. Below we describe how transient increases in prefrontal ACh release mediates the detection of cues and how these transient ACh increases are dependent, but not sufficiently, upon prefrontal glutamatergic activity. We also explain a complex pattern of data on when increases in transient ACh are seen and reconcile these findings by describing a model for the role of phasic cholinergic activity in facilitating attentional switches between internal and external processing modes.

7.1 Phasic increases in cholinergic activity mediates cue detection

Initial investigations using choline-sensitive microelectrodes in rats to study the phasic release of ACh made use of a simple cued-appetitive task in order to minimize the electrical interference arising from computerized operant tasks (Parikh et al., 2007). Recordings from the medial prefrontal cortex revealed that cues that evoked transient increases in cholinergic activity were correctly detected, while cues that did not evoke transient increases in cholinergic activity were missed. Transient increases in cholinergic activity were not evoked by the motor and reward components of the task. Further, the increase in cholinergic activity for detected cues was specific to the prefrontal cortex, as recordings from control regions in motor cortex did not show these transients. Deafferentation of the prefrontal cholinergic neurons using the selective immunotoxin 192 IgG-saporin attenuated the cue-evoked cholinergic activity and cue detection, confirming the neuronal origin of the activity observed by the microelectrodes and the necessity of prefrontal cholinergic transients for cue detection (Parikh et al., 2007).

7.2 Glutamatergic-cholinergic interactions

Experiments in anesthetized rats and in rats performing the SAT further elucidate the mechanism underlying the transient increases in cholinergic activity seen when cues were detected (Parikh et al., 2008; Howe et al., 2010). These experiments show the key role that glutamatergic-cholinergic interactions play in mediating cue detection and help explain why selective $\alpha 4\beta 2^*$ nAChR agonists produce more robust pro-attentional effects than nonspecific nAChR agonists. Using microelectrodes sensitive to glutamate and glutamate antagonists, Parikh and colleagues (2008) demonstrate that prefrontal glutamate release and stimulation of presynaptic ionotropic glutamate receptors (presumably on cholinergic terminals) is necessary for the generation of cue-evoked cholinergic transients.

Glutamatergic inputs to prefrontal cortex arise from the medial dorsal nucleus of the thalamus (Sarter & Markowitsch, 1984). Our current model for the circuitry supporting cue detection proposes that input from sensory regions is projected to the thalamic reticular nucleus, which in turn makes contacts with the medial dorsal nucleus. Together, this circuitry is believed to import a pre-attentionally-processed cue into the prefrontal cortex. Thus, via glutamatergic-cholinergic interactions, the neuronal representation of the pre-attentionally processed cue evokes a cholinergic transient responsible for the conscious detection of a cue.

Related studies also help connect the proposed circuitry model to the pattern of results seen when nicotine or $\alpha 4\beta 2^*$ agonists are used to enhance attentional performance. Pressure injection of nicotine into the prefrontal cortex of anesthetized animals elicits cholinergic transients; however, injection of the $\alpha 4\beta 2^*$ specific agonist ABT-089 more potently elicits cholinergic transients, and these transients have higher amplitudes than the transients seen with nicotine (Parikh et al., 2008). Interestingly, the rise and fall of the cholinergic transients elicited with ABT-089 is also substantially sharper than the pattern seen with nicotine (Parikh et al., 2008), and ABT-089 is more potent than nicotine at eliciting the glutamatergic signals necessary for cue-evoked cholinergic transients (Parikh et al., 2008). In awake animals performing the SAT, systemic injection of a $\alpha 4\beta 2^*$ agonist also results in cholinergic transients with higher amplitudes and sharper, faster decay profiles than injections of nicotine, confirming the patterns seen in anesthetized animals (Howe et al., 2010). The necessity of $\alpha 4\beta 2^*$ nAChR stimulation to evoke the glutamatergic release necessary for the generation of cue-evoked cholinergic transients has been confirmed in studies with mice lacking $\beta 2$ subunits (Parikh et al., 2010). ABT-089-evoked cholinergic transients are completely abolished in mice missing the $\beta 2$ subunits, and lesions of the thalamic glutamatergic inputs to prefrontal cortex also abolish the cholinergic transients. Together, these results support the model that cholinergic inputs from the basal forebrain to prefrontal cortex stimulate $\alpha 4\beta 2^*$ nAChRs on prefrontal glutamatergic projections arising from the thalamus. $\alpha 4\beta 2^*$ nAChR stimulation evokes transient glutamatergic signals that are necessary for the generation of the prefrontal cholinergic transients mediating cue detection. Positive modulation of glutamate release by nAChR agonists augments the amplitudes of the cholinergic transients necessary for cue detection, supporting enhanced detection capabilities (Howe & Sarter, 2010).

We hypothesize that because specific $\alpha 4\beta 2^*$ agonists evoke cholinergic transients with larger amplitudes and sharper decay rates than the transients evoked by nicotine, this leads to greater stimulation of the glutamatergic projections. This in turn increases the likelihood of cue-evoked cholinergic transients, as the glutamatergic transients are necessary for the generation of the cue-evoked cholinergic transients, and hence leads to more robust attentional enhancements. The amplitudes and decay rate profiles of the prefrontal cholinergic transients evoked by selective nicotinic agonists are expected to be informative for deciding whether experimental compounds are likely to show procognitive effects. These data also help explain the limited procognitive effects seen with cholinesterase inhibitors, as these compounds would not be capable of enhancing or restoring the phasic glutamatergic-cholinergic interactions described here.

7.3 Phasic increases in cholinergic activity facilitates attentional switching

Adding to the complexity of the data described above on the role of cholinergic transients in mediating cue detection, while cholinergic transients are never seen when an animal fails to detect a cue, these transients are only seen on roughly 60% of the trials where cues are accurately detected ("hit" trials; Howe et al., 2007). Interestingly, further analysis reveals that transient increases in cholinergic activity are only seen on hit trials when the preceding trial is a correctly rejected uncued (nonsignal) trial, or when the preceding trial is a miss

(undetected cue; Howe et al., 2007; see also Sarter et al., 2009 and Hasselmo & Sarter, 2011 for discussion of these data). When the preceding trial is also a hit trial, no increases in cholinergic activity are seen on the subsequent hit trial.

Based on this data, we propose that the phasic component of the cortical cholinergic system facilitates a switch from an internal mode of processing to an external mode of processing, and suggest that this switch readies the prefrontal cortex for cue detection. Trials where no cue/signal is presented or when the cue is missed encourage an internally-directed processing mode. In contrast, on cued trials the brain needs to switch to an external processing mode in order to correctly detect the cue. Sequences of successive hits therefore do not generate additional cholinergic transients because in those cases shifts from ongoing behavior are not required as the cue-directed behavior and associated response rules have already been activated by the first hit trial. Similarly, trials where the cue is missed also fail to generate cholinergic transients because though the cue may have been perceived on some level, it has failed to initiate the shift from ongoing behavior to the appropriate response. Thus, cholinergic transients are hypothesized to facilitate shifts from ongoing cue-independent attentional processing to cue-dependent processing, specifically the activation of cue-associated response rules and reward expectation.

A role for the cortical cholinergic system in switching between internal and external processing modes also helps explain results from pharmacofMRI experiments concerning the effects of cholinergics, particularly nicotine, on brain regions that are typically considered part of the “default” or “resting state” network (Raichle & Snyder, 2007). fMRI studies using nicotine frequently observe that nicotine causes further deactivations in medially-located regions such as cingulate, precuneus, and parahippocampal gyri, and in regions in the superior-middle temporal and angular gyri during attentionally-demanding tasks, while not affecting activation in those regions during rest (e.g., Ghatan et al., 1998; Bentley et al., 2004; Hahn et al., 2007, 2009; Ettinger et al., 2009). In addition to these exaggerated deactivations during attentionally-demanding tasks, these studies also observe a concurrent increase in task-related activation in dorsolateral frontoparietal and posterior regions. These data support a role for nAChR agonists in facilitating the switch from the internally-directed processing modes (reflected in the activation of the default network during rest) to externally-directed processing modes capable of reacting to externally-driven tasks and external, task-relevant cues (for further discussion, see also Hahn et al., 2007).

8. Target mechanism for enhancing top-down control

In addition to the second-based phasic component of the cortical cholinergic system that is theorized to mediate attentional switching and hence the detection of external, task-relevant cues, the cortical cholinergic system also operates via another, minutes-based component (“tonic” ACh release). Importantly, the tonic component of the cholinergic system cannot be fully explained by simply summing the cholinergic transients described above over time (Parikh et al., 2007). Tonic cholinergic activity is theorized to mediate top-down attentional control, with increases in tonic cholinergic activity reflecting the engagement of attentional effort processes designed to help stabilize or maintain attentional performance in the face of attentionally-challenging conditions.

As described above, *in-vivo* microdialysis studies in SAT-performing rats demonstrate that ACh release increases in right prefrontal cortex during attentional performance, above and beyond the release levels seen in tasks with matched motor or reward components, but low demands on attention (Arnold et al., 2002; Dalley et al., 2001; Himmelheber et al., 2000; Passetti et al., 2000). While initial theories proposed that the levels of ACh release would simply mirror the success of attentional performance (low levels of release when

performance was poor and high levels of release when performance was strong), the evidence has instead demonstrated that tonic ACh levels vary as a function of the demands on attentional control. For example, pharmaceutical challenges that impair attentional performance *increase* levels of prefrontal ACh release above and beyond the levels seen during normal attention-task performance (Kozak et al., 2006). This data lead to the development of the theory that tonic ACh levels reflect the amount of *attentional effort* an individual is exerting (Sarter et al., 2006).

According to the theory of attentional effort, following a challenge to attention, motivated individuals will engage top-down attentional control processes in order to stabilize or recover their performance. This idea was recently tested in an *in-vivo* microdialysis study using a visual distractor to impair performance of a sustained attention task (the dSAT; St. Peters et al., 2011b; Figure 1). In this study, the distractor robustly impaired attentional performance, but increased the levels of prefrontal ACh release significantly over the levels seen from pre-distractor task performance. Furthermore, the levels of ACh during distraction correlated with how well animals were able to maintain their performance during distraction, with higher levels of ACh seen for animals with less severe distractor effects.

Mirroring the increases seen in ACh release in rats during distraction, an arterial spin labeling (ASL) fMRI study using the human version of the dSAT found that activation in right frontal regions increases during distraction (Demeter et al., 2011). Interestingly, however, this study found that higher levels of activation during distractor were correlated with *worse* attentional performance – the opposite relationship to what was seen in ACh release in rats. We hypothesize that increases in right prefrontal ACh in response to attentionally challenging conditions acts to optimize the prefrontal circuitry necessary for the top-down control of attention, leading to reduced metabolic demands and hence less blood flow to this region.

The neuronal circuitry supporting top-down attention control is believed to include cholinergic projections from the basal forebrain to the prefrontal cortex and glutamatergic projections from prefrontal cortex back to the basal forebrain, both directly and indirectly via projections to mesolimbic regions including the nucleus accumbens, the ventral tegmentum, and the amygdala (Mogenson et al., 1980; Gruber et al., 2009; Zaborszky et al., 1986; Ingham et al., 1988; Zaborszky & Cullinan, 1992, 1996; Zaborszky, 2002; Zaborszky et al., 2005; Zaborszky et al., 1993; Zaborszky et al., 1997; Zaborszky et al., 1984; Zaborszky et al., 1999). In response to increases in attentional control demands, tonic release of ACh in right prefrontal cortex is believed to be upregulated, helping to enhance the preattentional representation of cues. Augmenting the tonic levels of ACh is therefore hypothesized to represent a central mechanism for enhancing attentional control and optimizing cue detection processes. In addition to this somewhat simplified story, the top-down effects of cholinergic activity may also act through cortex-wide mechanisms, including cortico-cortico mechanisms (Nelson, Sarter & Bruno, 2005), and feedback projections from prefrontal cortex to thalamus (e.g., see Crick, 1984; McAlonan et al., 2006).

9. Conclusions

Here, we propose two target mechanisms for the development of procognitive enhancers: stimulation of $\alpha 4\beta 2^*$ nAChRs on prefrontal glutamatergic neurons in order to facilitate attentional switching and cue detection, and augmentation of the tonic levels of ACh in order to improve attentional control functions. While cholinesterase inhibitors and nAChR agonists have been intensely studied in regards to their putative pro-attentional effects, the recent mechanistic evidence on the circuitry supporting cue detection and attentional control

suggest that specific $\alpha 4\beta 2^*$ nAChR agonists are likely to be the most successful cognition enhancers. Thus, the two target mechanisms proposed here allow for the hypothesis-driven development and characterization of new cognitive enhancers.

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Highlights

- Cue detection and top-down attentional control represent key attentional functions.
- Agonism of specific nicotinic receptor subtypes aids cue detection.
- Augmentation of tonic acetylcholine levels aids attentional control.
- Development of cognition enhancers should focus on these aspects of attention.

Figure 1.

Distractor-induced impairment in attentional performance and prefrontal acetylcholine (ACh) release in the presence and absence of a distractor. (a) The sustained attention task (SAT) consists of randomly ordered signal (light signals 500, 50, or 25 ms long) and non-signal events, spaced by 9 ± 3 s. Two seconds after an event, levers are made available and animals need to respond within 4 s. Following a lever press or after 4 s, levers are withdrawn. (b) Hits and correct rejections, but not misses and false alarms, are rewarded (note that arrows indicating the 4 response types in a are color-coded and match arrows in b). Sessions lasted 40 min and were blocked post hoc into five 8-min blocks of trials (t1–t5). (c) For testing on the distractor condition sustained attention task (dSAT), the distractor (chamber lights flashing on/off at 0.5 Hz) occurred during blocks 2 and 3. The vertical red and black bars illustrate a random sequence of signal and non-signal trials (signal duration indicated by the length of the red bars). (d) In the absence of a distractor (SAT; $n=6$), performance varied with signal duration and remained stable over the 5 task blocks (t1–t5). This plot and the plot in e show SAT and dSAT scores, respectively, which are an overall measure of performance calculated as follows: $\text{SAT/dSAT} = (\text{hit} - \text{false alarm}) / [2(\text{hit} + \text{false alarm})^2]$. (e) Presentation of the distractor (dSAT; $n=9$) during task blocks 2 and 3 transiently impaired performance. During the post-distractor blocks, animals' performance recovered. (f) SAT performance evoked a steep initial increase in ACh release in the medial prefrontal cortex as measured via *in-vivo* microdialysis. Release levels remained stable throughout the remainder of the performance session. Presentation of the distractor further increased ACh release (b1–b3 depict baseline collections prior to task onset, t1–t5 depict the 5 task blocks and at1–at4 indicate data from four collections following completion of the task (8 min/collection)). (g) The severity of the distractor-induced impairment of performance was significantly correlated with distractor-induced increases in cholinergic activity. The abscissa of this graph depicts the differences between t1 and t2/t3 dSAT scores, with larger numbers indicating more severe impairments. Thus, higher increases in ACh release were correlated with less severe distractor effects on performance. (Post hoc multiple comparisons, using t-test or the Least Significance Difference (LSD), are indicated by symbols: * $p < 0.05$). Adapted and modified from Figure 1 in St. Peters, M., Demeter, E., Lustig, C., Bruno, J.P., Sarter, M., 2011. Enhanced control of

attention by stimulating mesolimbic-cortical cholinergic circuitry. *J. Neurosci.* 31, 9760–9771, with permission from the Society for Neuroscience.