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Attentional functions of cortical cholinergic inputs: What does it mean for learning and memory?☆

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Abstract

The hypothesis that cortical cholinergic inputs mediate attentional functions and capacities has been extensively substantiated by experiments assessing the attentional effects of specific cholinotoxic lesions of cortical cholinergic inputs, attentional performance-associated cortical acetylcholine release, and the effects of pharmacological manipulations of the excitability of basal forebrain corticopetal cholinergic projections on attentional performance. At the same time, numerous animal experiments have suggested that the integrity of cortical cholinergic inputs is not necessary for learning and memory, and a dissociation between the role of the cortical cholinergic input system in attentional functions and in learning and memory has been proposed. We speculate that this dissociation is due, at least in part, to the use of standard animal behavioral tests for the assessment of learning and memory which do not sufficiently tax defined attentional functions. Attentional processes and the allocation of attentional capacities would be expected to influence the efficacy of the acquisition and recall of declarative information and therefore, persistent abnormalities in the regulation of the cortical cholinergic input system may yield escalating impairments in learning and memory. Furthermore, the cognitive effects of loss of cortical cholinergic inputs are augmented by the disruption of the top–down regulation of attentional functions that normally acts to optimize information processing in posterior cortical areas. Because cortical cholinergic inputs play an integral role in the mediation of attentional processing, the activity of cortical cholinergic inputs is hypothesized to also determine the efficacy of learning and memory.

1. Introduction

The general hypothesis that cortical acetylcholine (ACh) release mediates arousal, alertness, wakefulness, and electroencephalographic desynchronization was substantiated by early studies assessing ACh efflux using the cup technique and muscle assays to determine the concentration of ACh (Celesia & Jasper, 1966; Phillis, 1968; Phillis & Chong, 1965).[1] Because these studies were largely limited to experimentation in anesthetized animals and thus, by default, to activating mechanisms mediated via the ascending reticular system (Pepeu & Mantegazzini, 1964; Szerb, 1967), cortical cholinergic inputs were considered to be an elementary component of the ascending reticular system and to mediate arousal (Buzsaki et al., 1988). In recent decades, the scientific viability of the construct of 'arousal' has been questioned and conceptually dissociated from defined attentional processes and capacities (Robbins & Everitt, 1995). Furthermore, the ascending reticular system has been refined anatomically and functionally (Sarter & Bruno, 2002b; Sarter, Bruno, & Berntson, 2002a), with the basal forebrain (BF) corticopetal cholinergic system positioned as a rostral target of its ascending projections. The ascending recruitment of the BF[2] cholinergic system is in the focus of models describing the 'bottom–up' activation of the

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[1] The sensitivity of the methods used in these early studies is remarkable; for example, Celesia and Jaspers were able to detect approximately 100 pmol of ACh.

[2] The term BF refers to the corticopetal neurons arising from the nucleus basalis of Meynert and the substantia innominata.

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cortical cholinergic input system by novel, stressful, or fear- and anxiety-related stimuli, and during REM sleep (Berntson, Sarter, & Cacioppo, 1998; Berntson, Shafi, & Sarter, 2002; Sarter, Givens, & Bruno, 2001).

The contemporary focus on the attentional functions of cortical cholinergic inputs has several conceptual and empirical origins, including psychopharmacological evidence indicating the effects of cholinergic drugs on attention (Warburton & Wesnes, 1984), neurophysiological evidence demonstrating the ACh-mediated amplification and filtering of sensory inputs (Metherate & Weinberger, 1989, 1990; Murphy & Sillito, 1991), and the original experiments by Robbins, Everitt and co-workers on the effects of excitotoxic BF lesions on the performance of rats in procedures assessing attentional functions (Everitt & Robbins, 1997). Since the development and characterization of the selective cholinotoxin 192 IgG-saporin (Holley, Wiley, Lappi, & Sarter, 1994; Wiley, Oeltmann, & Lappi, 1991), and the development of animal tests for the measurement of sustained (McGaughy & Sarter, 1995) and divided attention (McGaughy, Turchi, & Sarter, 1994), numerous experiments demonstrated that the integrity of the cortical cholinergic input system is necessary for attentional performance (Bucci, Holland, & Gallagher, 1998; Chiba, Bushnell, Oshiro, & Gallagher, 1999; McGaughy, Dalley, Morrison, Everitt, & Robbins, 2002; McGaughy, Everitt, Robbins, & Sarter, 2000; McGaughy, Kaiser, & Sarter, 1996; McGaughy & Sarter, 1998; Turchi & Sarter, 1997; Turchi & Sarter, 2000). Furthermore, neuropharmacological manipulations that increase or decrease the excitability of BF corticopetal cholinergic projections systematically affect attentional performance and cortical ACh efflux (Fadel, Sarter, & Bruno, 2001; Holley, Turchi, Apple, & Sarter, 1995; Moore, Sarter, & Bruno, 1993; Moore, Sarter, & Bruno, 1995; Turchi & Sarter, 2001a, 2001b). Using in vivo microdialysis, several studies demonstrated that the performance of rats in attention-demanding procedures, but not in behavioral procedures controlling for the effects of motor activity, reward rate, and the effects of stimuli in contexts that do not tax attentional abilities, is associated with robust increases in cortical ACh efflux (Arnold, Burk, Hodgson, Sarter, & Bruno, 2002; Dalley et al., 2001; Himmelheber, Sarter, & Bruno, 1997, 2000). Neurophysiological studies demonstrated that increases in the attentional demands produced by a distractor produces changes in prefrontal neuronal activity that are cholinergically mediated (Gill, Sarter, & Givens, 2000). Collectively, these data strongly support the hypothesis that the cortical cholinergic input system is necessary for intact attentional functions.

The afferent activation of the cortical cholinergic input system, and thus the recruitment of the attentional performance-mediating neuronal network, can be described as based on two fundamentally different contexts. First, corticopetal cholinergic neurons can be activated by new, salient, stressful, or affectively significant stimuli via ascending, primarily noradrenergic projections (''bottom–up'') (Berntson, Cacioppo, & Sarter, 2003a, 1998; Berntson, Shafi, Knox, & Sarter, 2003b). The pathways that mediate the ascending component of the processing of stress, fear- and anxiety-related stimulation include the monitoring of autonomic reactivity changes by noradrenergic brain stem neurons (Aston-Jones, Rajkowski, Kubiak, Valentino, & Shipley, 1996; Aston-Jones et al., 1991; Van Bockstaele & Aston-Jones, 1992), and the ascending modulations of the excitability of cortical cholinergic inputs (Berntson et al., 2003a, 1998). For example, using the effects of peripherally administered epinephrine on auditory evoked potentials as a marker of the ascending processing of a stressful stimulus, lesions of the corticopetal cholinergic projections attenuate the effects of epinephrine (Berntson et al., 2003b). As epinephrine does not enter the brain, and as the effects of epinephrine are known to be blocked by, for example, inactivation of the nucleus of the solitary tract (NTS), which is one of the stations within the ascending system (Clayton & Williams, 2000; Williams & McGaugh, 1993), the attenuation of the epinephrine effect as a result of cortical cholinergic deafferentation likely reflects the failure of ascending, primarily noradrenergic, projections to recruit, ''bottom–up'', the cholinergic system for the enhanced processing of the epinephrine-primed stimulus. One may extend this conceptualization by interpreting the basal forebrain cholinergic lesion-induced attenuation of the enhancement of the retention for a inhibitory avoidance experience, produced by infusions of epinephrine into the amygdala, likewise as a disruption of the ascending processing of contextual information (Power, Thal, & McGaugh, 2002).

Second, in subjects performing well-practiced tasks that tax attentional capacities the cortical cholinergic input system is hypothesized to be recruited primarily by prefrontal efferent projections (''top–down''; see below; Berntson et al., 2003a, 1998; Sarter et al., 2001). As would be expected, in this latter case, the contributions of the ascending noradrenergic system to attentional performance appear to be limited (Carli, Robbins, Evenden, & Everitt, 1983; Dalley et al., 2001; McGaughy, Sandstrom, Ruland, Bruno, & Sarter, 1997). These dissociations suggest that the neuronal mediation of attentional functions depends strongly on the degree to which attentional performance involves 'bottom–up' and/or 'top–down' regulation of attention-mediating systems (this issue will be further discussed below).

2. Attention versus learning and memory?

The hypothesis that the integrity of corticopetal cholinergic projections is necessary for attentional functions, but not for mnemonic processes, gained

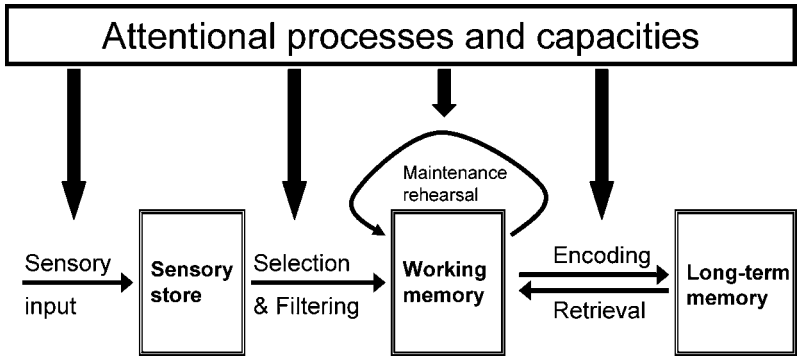

Fig. 1. Role of attentional functions and capacities in learning and memory. As discussed in the text, the efficacy of learning, from the detection, selection, and discrimination of a sensory input to the rehearsal of new information in working memory depends on attentional processes and capacities. Likewise, building and maintaining a chain of associations in order to recall information from memory requires that the subject continues to allocate attentional resources to this task. This conceptualization represents more than a semantic exercise, as it formalizes research on the role of a specific set of attentional variables in learning and memory. Finally, this model also predicts that impairments in attentional functions result in profound and escalating impairments in learning and memory that depends on attentional variables.

prominence by the finding that excitotoxic lesions of the basal forebrain of monkeys did not affect performance of a delayed non-matching-to-sample task, delayed response task, simple or concurrent discriminations, spatial discriminations, and discrimination reversals, but of a version of Posner's orientation task (Voytko, 1996; Voytko et al., 1994). Although excitotoxic lesions of the basal forebrain produce learning and memory deficits in a large variety of tasks, the degree to which loss of corticopetal cholinergic neurons was responsible for these effects was questioned early on (Dekker, Connor, & Thal, 1991; Dunnett, Everitt, & Robbins, 1991; Everitt & Robbins, 1997). Furthermore, a substantial number of experiments failed to find effects of intraparenchymal infusions of 192 IgG-saporin into the basal forebrain on spatial learning and performance, place discrimination learning, delayed alternation learning and performance, passive avoidance performance, taste aversion learning, or olfactory discrimination learning (Baxter, Bucci, Gorman, Wiley, & Gallagher, 1995; Baxter et al., 1996; De Rosa, Hasselmo, & Baxter, 2001; Dornan et al., 1996; Gutierrez et al., 1999; Power et al., 2002; Torres et al., 1994; Wenk, Stoehr, Quintana, Mobley, & Wiley, 1994).[3] The dissociation between the role of the basal forebrain cholinergic system in attention versus learning and memory has emerged as salient topic in the literature, and it has triggered far reaching conclusions, such as the dismissal of basal forebrain cholinergic lesions as a model of the cortical cholinergic denervation in Alzheimer's disease or to study the foundations of age-related decline in cognitive functions, based on the general argument that the model does not reproduce the learning and memory impairments seen in aging and dementia (Bartus, 2000; Baxter et al., 1995; Baxter & Murg, 2002).

From a conceptual perspective, a fundamental dissociation between attention and learning and memory appears unlikely. The efficacy of practically every step in the learning process, from the detection, selection, and filtering of sensory inputs to the manipulation of information in the working memory store, and the construction of associational chains to recall and rehearse information and to re-network it into a new context, has been conceptualized to depend on attentional functions and capacities (Ahissar & Hochstein, 1993; Carrillo, Gabrieli, & Disterhoft, 2000; Craik, Govoni, Naveh-Benjamin, & Anderson, 1996; Fernandes & Moscovitch, 2000; Marsh & Hicks, 1998; Naveh-Benjamin, Craik, Guez, & Dori, 1998; Nissen & Bullemer, 1987; see Fig. 1).

Impairments in filtering sensory stimuli, or impairments in processing resources or time-sharing capabilities, would be expected to result in impairments in the acquisition of new information and the rehearsal and retrieval of stored information. If persistent, attentional impairments would be predicted to produce robust and escalating impairments in learning and memory, in part because weaker memories increasingly fail to guide top–down regulated attentional functions (Chun & Jiang, 1998; Logan & Gordon, 2001), thus giving rise to a vicious cycle of bidirectional, escalating interactions between impairments in attentional and mnemonic functions.

2.1. A semantic exercise?

The evaluation of the role of attentional variables in learning and memory raises the concern that this attempt represents largely a semantic exercise and introduces a set of terms that is completely interchangeable with the more traditional concepts well-established in the learning and

[3] As the loss of cholinergic neurons following intraventricular infusions of 192 IgG-saporin includes neurons other than cortical cholinergic inputs, these studies are excluded from the present discussion.

memory literature. Traditionally, research on learning and memory has focused on variables which determine associational strength, acquisition rate and forgetting, the role of different qualities and rates of motivational events, determinants of stimulus generalization, extinction, transfer effects, and so on (Dragoi & Staddon, 1999; Mackintosh, 1974; Pearce & Bouton, 2001; Pearce & Hall, 1980; Spear, Miller, & Jagielo, 1990). The determination of the contribution of attentional factors to learning and memory does not add a fundamentally new dimension to research on learning and memory, but defines a different—although overlapping—set of parametric variables and offers theoretical guidelines for their operationalization. For example, the construct of sustained attention refers to the subjects' ability to detect, over prolonged periods of time, rarely and unpredictably occurring signals, and discriminate them from background or 'noise' (Parasuraman, 1986). Some performance effects of stimuli that are presented unpredictably and with various durations perhaps could be described in accordance with dynamic theories of operant conditioning (Dragoi & Staddon, 1999); however, the systematic variation of the decrement in performance over time ("vigilance decrement"; Koelega, Brinkman, Zwep, & Verbaten, 1990; McGaughy & Sarter, 1995; Parasuraman & Mouloua, 1987; Sarter & McGaughy, 1998) appears to be more difficult to be accounted for by theories of learning and memory. Likewise, in subjects performing a cross-modal divided attention task, the speed-accuracy tradeoff that characterizes the performance in blocks of trials with modality uncertainty (Hohnsbein, Falkenstein, Hoormann, & Blanke, 1991; McGaughy et al., 1994; Turchi & Sarter, 1997) appears to be difficult to conceptualize in accordance with theories of operant conditioning. Thus, attentional processes and capacities represent a central cluster of variables that contributes to the explanation of the rate of acquisition of new information, level of mnemonic performance, and the decline in performance of learning and memory tasks.

Given this context, how is it then possible that lesions of the cortical cholinergic input system, considered to represent a most crucial neuronal system in the mediation of attentional functions, spare learning and memory? For example, consider the performance of a delayed non-matching-to-sample task. The subjects typically are trained to high levels of accuracy (e.g., 160 trials per daily session; Voytko et al., 1994), they are highly familiar with the objects, the location of the objects, and task procedures. It seems that performance in this working memory task does not, at least not to a significant and defined degree, entail a taxation of attentional functions and capacities (see also the limited effects of immunotoxic lesions on the learning and retention of visual discriminations; Ridley, Barefoot, Maclean, Pugh, & Baker, 1999). The possibility that insufficient attentional demands contributed to the lack of effects of basal forebrain cholinergic lesions on learning and memory has been raised in the literature (Voytko et al., 1994; Wrenn, Lappi, & Wiley, 1999).

Because all task-based performance requires that the subject is awake and "aroused", it is important to note that the recruitment of the cortical cholinergic input system is a function of the degree to which attentional functions are taxed. This point needs to be stressed in light of tendency of the recent literature to attribute reflexively and casually attentional factors to changes in performance of various tasks, often without defining and validating the type and degree of the taxation of attentional function and capacities. [In this context, it may also be worthwhile to refute the widespread assumption that signal duration- or signal brightness-dependent response accuracy per se represents a sufficient criterion to indicate validity in terms of sustained attention; rather, as discussed above, a dynamic stimulus range serves to exhaust more effectively attentional capacities and thus triggers robust vigilance decrements (Parasuraman & Mouloua, 1987).]

Two examples illustrate the view that defined attentional capacities have to be taxed in order to recruit the cortical cholinergic input system. First, Himmelheber et al. demonstrated that, using a version of our operant sustained attention task with lowered attentional demands, by fixing signal length (500 ms) and the intertrial interval (9 s), and by inserting only the correct lever in signal and non-signal trials to minimize the decisional component of the task, near total cortical cholinergic deafferentation no longer affected performance (Himmelheber, Sarter, & Bruno, 2001). Second, experiments were designed to assess cortical ACh efflux in animals performing behavioral procedures that controlled for the effects of non-attentional components of operant performance. For example, animals trained in a fixed interval-9 s (FI-9) schedule of water reinforcement produced exceptionally high number of lever presses (600 presses/6 min-block) when compared to animals performing the sustained attention task (~25 presses per block). The FI-9 performing animals were rewarded with the same frequency as the animals performing the sustained attention task. Despite their extremely high lever pressing activity, increases in ACh efflux in FI-9-performing animals were modest and far lower than those seen in animals performing the sustained attention task (Arnold et al., 2002; Himmelheber et al., 1997). In fact, some data have suggested that the level of ACh efflux is associated not so much with the level of attentional performance (Passetti, Dalley, O'Connell, Everitt, & Robbins, 2000), but with the attentional "effort" required to maintain or regain attentional performance (Himmelheber et al., 2000). It is based on these data that it can be hypothesized that the performance in standard learning and memory tasks, such as the learning of a place discrimination (Baxter et al., 1995) does not sufficiently tax attentional processes

and capacities and thus is insensitive to cholinergic lesions. Rats may solve spatial tasks using strategies and cues which do not demand, at least not to a significant degree, attentional processes, and capacities (Brown, 1992; Lindner, Plone, Schallert, & Emerich, 1997; Means, Alexander, & O'Neal, 1992; Whishaw, 1989; Whishaw, Hines, & Wallace, 2001).

2.2. Circular logic?

Obviously, the hypothesis that the learning and memory performance that remained unaffected by manipulations of the cortical cholinergic input system did not entail a sufficient degree of taxation of defined attentional functions potentially suffers from circular logic, as a negative effect on learning and memory could always be attributed to insufficient demands on attentional processing and capacities. How much is enough? The studies discussed above, particularly those that assessed ACh efflux in attention and control task-performing animals, suggest that activation of the cortical cholinergic input system requires explicit demands on stimulus detection, selection, and discrimination, and/or taxation of processing resources by the competing processing of complex propositional rules. Such demands may be integrated in tasks designed primarily to assess learning and memory, and cortical cholinergic deafferentation would be expected to yield robust impairments in such tasks.

It is also important to consider the studies that demonstrated effects on learning and memory following restricted and selective lesions of the corticopetal cholinergic input system (see also Footnote 2). Berger-Sweeney, Stearns, Frick, Beard, and Baxter (2000) demonstrated that such lesions disrupt the learning of a social food preference (see also Vale-Martinez, Baxter, & Eichenbaum, 2002). These data indicate that olfactory memory formation involves basal forebrain cholinergic projections, and it would be interesting to determine exactly which behavioral or cognitive components of the learning or memory about a socially-transmitted food preference depends on the functions of basal forebrain cholinergic neurons. Likewise, 192 IgG-saporin lesions of the basal forebrain produce a transient impairment in the acquisition of an olfactory discrimination learning set (Bailey, Rudisill, Hoof, & Loving, 2003). Again, the interpretation of these data is complex, although impairments in the ability to learn associations based on a total of 50 odor-unique problems, where a particular odor could be correct in one and incorrect in another problem, may be speculated to reflect resource impairments or suboptimal allocation of resources to the processing of multiple and even conflicting associations.

With respect to the present hypothesis, the experiment by Butt and Bowman on the effects of basal forebrain cholinergic lesions on the learning of a transversal patterning problem appears informative (Butt & Bowman, 2002). Using a water maze procedure, animals learned to discriminate between 3 pairs of stimuli (A+/B−; B+/C−; and C+/A−). Lesions selectively disrupted the acquisition of the 3rd problem that was presented in a third phase of learning with trials for problems 1 and 2 interspersed. Obviously, the learning of the 2nd problem still represents a simple discrimination as C represents a new stimulus that is uniquely paired with B. With respect to the third problem, however, learning depends on the particular stimulus configuration. The authors' speculate that attentional resources, required for the simultaneous processing of both stimuli in the 3rd problem were limited in lesioned animals and responsible for the effect of the lesion on learning.

Again, these speculations are complex, but the finding by Butt and Bowman is not readily explained by effects of the lesions on strictly associational mechanisms (as all stimuli get rewarded on half of the trials). A test of the hypothesis that such lesions disrupt learning and memory processes if they depend on attentional functions requires the development of learning tasks that allow the systematic variation of defined attentional demands of the learning process, such as demands on stimulus search and detection, selection and discrimination, and taxation of processing resources by requiring the processing of (operant) response rules associated with particular stimulus configurations. Because an increasing familiarity with stimuli, their source and position, and well-practiced response rules quickly render task performance to be based on procedural memory or habits, no longer requiring effortful processing of stimuli and response rules, traditional animal learning and memory tasks may have a very limited value in exploring the hypothesis that the cholinergic system disrupts memory formation that depends on attentional processes. New animal tasks capable of assessing learning and memory processes that depend on explicitly defined systematically varied attentional functions and capacities appear to be necessary to test the present hypothesis (see below).

3. Cortical cholinergic mediation of top–down regulation of attentional performance

'Top–down' processes describe knowledge-driven mechanisms designed to optimize the neuronal processing of stimuli and associations, to enhance the discrimination between signal and 'noise' or distractors, and to bias the subject toward particular locations in which signals may appear (Kastner & Ungerleider, 2000). For example, in sustained attention performance, the subject knows where to expect what type or modality of signal, how to respond in accordance with previously acquired response rules, and so forth. Furthermore, the subject develops expectations concerning the probability for signals and strategies for reporting signals versus

false alarms. All these variables influence performance, based on mechanisms that range from changes in sensory signal processing to the enhanced filtering of distractors and the modification of decisional criteria.

Such a 'top–down' biasing of attentional performance contrasts with 'bottom–up' perspectives that describe attentional functions as driven mainly by the characteristics of the target stimulus and its sensory context (Treisman & Gelade, 1980). 'Bottom–up' perspectives attempt to explain a subject's ability to detect targets and target-triggered attentional processing largely by the sensory salience of the targets, and their ability to trigger attentional processing by recruiting 'higher' cortical areas in a bottom–up manner (e.g., from the processing of a visual target in the primary visual cortex to temporal regions for object identification and to parietal regions for location). Importantly, 'top–down' and 'bottom–up' processes represent overlapping organizational principles rather than dichotomous constructs, and in most situations, top–down and bottom–up processes interact to optimize attentional performance (Egeth & Yantis, 1997).

Activation of top–down processes are traditionally considered a component of the frontal cortical mediation of executive functions. Such processes were previously conceptualized in the context of attention by Posner and Petersen's anterior and posterior attention systems that function to detect targets and bias the subjects' orientation to target sources, respectively (Posner & Petersen, 1990). Data from human imaging and primate single unit recording studies have confirmed this concept by demonstrating sequential activation of frontal–parietal–sensory regions, including decreases in activity in task-irrelevant sensory regions, and the modulation of neuronal activity in sensory and sensory-associational areas reflecting the top–down functions described above (Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Burton et al., 1999; Desimone & Duncan, 1995; Hopfinger, Buonocore, & Mangun, 2000; Hopfinger, Woldorff, Fletcher, & Mangun, 2001; Rowe, Friston, Frackowiak, & Passingham, 2002; Shulman et al., 1997; Smith, Singh, & Greenlee, 2000).

The corticopetal cholinergic projection system has been hypothesized to be a component of the neuronal systems that mediate top–down regulation of attentional functions (Sarter et al., 2001), or the interactions and conflicts between top–down and bottom–up influences in processing inputs (Yu & Dayan, 2002).

Accordingly, ACh efflux in posterior cortical areas is expected to be influenced by prefrontal activity, thereby supporting the top–down functions described above. Accumulating data indicate that stimulation of medial prefrontal glutamatergic or cholinergic transmission controls ACh efflux in the posterior parietal cortex (PPC), but not vice versa (Nelson, Sarter, & Bruno, 2002). Presumably, these effects are mediated via the prefrontal projections to the basal forebrain, and via multi-synaptic cortico-cortical networks (Fig. 2).

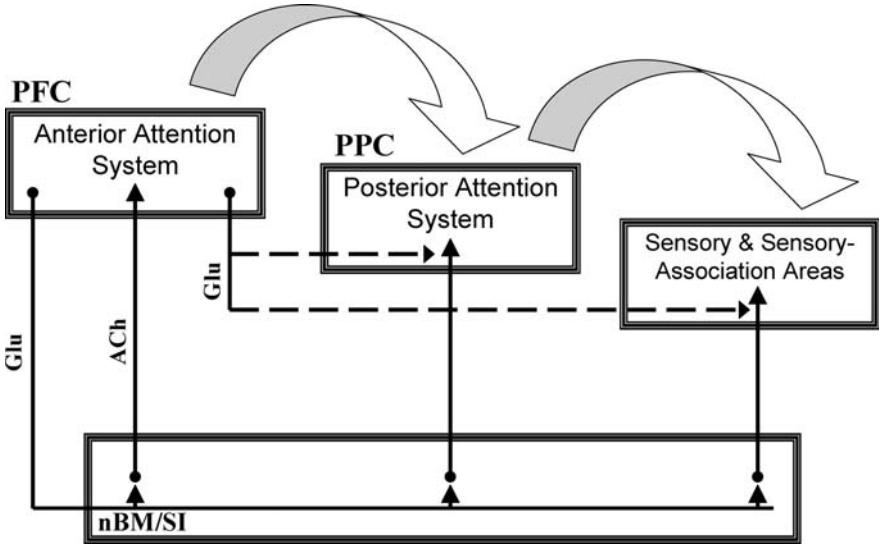

Fig. 2. Schematic illustration of the hypothesis that corticopetal cholinergic (ACh) projections are a major component of the neuronal circuits mediating top–down regulation of attentional functions and capacities. The 'anterior attention system' that reflects mostly the functions of the prefrontal cortex (PFC) acts to optimize input processing in posterior cortical areas, specifically the posterior parietal cortex (PPC) that is the main component of the posterior attention system, but also in sensory and sensory-association areas (references in main text). The PFC modulates cholinergic activity in the cortex via its glutamatergic (Glu) projections to the basal forebrain. However, the cholinergic neurons in the nucleus basalis of Meynert (nBM) and the substantia innominata (SI) are not contacted directly by these neurons (Sarter & Bruno, 2002a; Zaborszky, Gaykema, Swanson, & Cullinan, 1997), and thus the regulation of these neurons by PFC input is not well understood. Likewise, the PFC may regulate ACh output via cortico-cortical networks and modulation of presynaptic steps in ACh efflux. The impairments in attentional functions and in learning and memory that result from a decline in cortical cholinergic transmission are perhaps due mainly to the disruption of top–down mechanisms.

As the prefrontal cortex and the amygdala innervate basal forebrain cholinergic neurons, the effects of disruption of glutamate receptor function in the basal forebrain on attentional performance may primarily reflect the consequences of a disruption of the top–down regulation of these neurons. Blockade of NMDA receptors in the basal forebrain (Turchi & Sarter, 2001b) or 'knocking-down' the NMDA-NR1 subunit in the basal forebrain (Turchi & Sarter, 2001a) did not affect basic operant discrimination but impaired attentional performance. To the degree these effects reflect the disruption of top–down regulation of basal forebrain corticopetal neurons, they suggest that, in subjects performing well-practiced attention tasks, such top–down mechanisms are necessary for normal attentional performance.

In familiar contexts, attentional processes are guided by memory, and the optimization of sensory input processing, including the suppression of activity in irrelevant modalities, and the orientation toward expected sources of information, represent core variables of cognitive activities. Thus, disruption of cortical cholinergic transmission would also be expected to disrupt such memory-guided top–down mechanisms, and it is possible that the impairments seen in attentional performance are, to a considerable degree, due to the disruption of top–down regulation of attentional functions. For example, memory-based attentional switching (e.g., between multiple sets of stimuli, between stimuli or multiple modalities, or between multiple response-guiding rules) may depend on the integrity of top–down mechanisms and thus on the cholinergic system (Butt & Bowman, 2002).

Furthermore, the consolidation of memory may involve the representation of information about the status of top–down processes during the acquisition period, and such information may be instrumental in fostering recall (Miyashita & Hayashi, 2000; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999). One could speculate that this information represents the main modulating contribution of the basal forebrain to memory formation (McGaugh, 2002). Once again, effects of manipulations of cortical cholinergic transmission then would only be expected if the learning process involved taxation of defined attentional functions.

4. Dissociation from septo-hippocampal cholinergic projections

The present discussion focuses on the function of cortical cholinergic inputs. Traditionally, hypotheses covering the functions of the overall cholinergic system in the brain have been favored (Woolf, 1991), and there is little data that would support the idea that the cognitive functions of the two forebrain branches of the brain's cholinergic system, the septo-hippocampal and basal forebrain–cortical cholinergic system, can be readily dissociated. Similar to the effects of selective lesions of basal forebrain corticopetal cholinergic projections, such lesions of hippocampal cholinergic inputs do not produce robust impairments in standard learning and memory tasks (Bannon, Curzon, Gunther, & Decker, 1996; Berger-Sweeney et al., 1994; Cahill & Baxter, 2001; Chappell, McMahan, Chiba, & Gallagher, 1998; Dougherty, Turchin, & Walsh, 1998; Hortnagl & Hellweg, 1997; McMahan, Sobel, & Baxter, 1997; Shen, Barnes, Wenk, & McNaughton, 1996; Vale-Martinez et al., 2002).

Moreover, we did not find, even following several parametric challenges, effects of almost complete cholinergic hippocampal deafferentation on sustained attention performance (Baxter, Holland, & Gallagher, 1997; Sarter, Draut, Herzog, & Bruno, 2002b). However, we found a lesion-induced facilitation of the acquisition of the reversed rules governing the responses to signal and non-signal trials in our sustained attention task (Sarter et al., 2002b). These data suggest that the septo-hippocampal cholinergic system mediates the influences of well-established memories on new learning (Day, Weisand, Sutherland, & Schallert, 1999; Ikonen, McMahan, Gallagher, Eichenbaum, & Tanila, 2002; McIntyre, Pal, Marriott, & Gold, 2002).

In vivo microdialysis experiments do not readily dissociate hippocampal from cortical ACh efflux if the behavioral manipulations included high levels of arousal (Acquas, Wilson, & Fibiger, 1996; Day, Damsma, & Fibiger, 1991; Giovannini et al., 2001; Inglis, Day, & Fibiger, 1994; Inglis & Fibiger, 1995; Mark, Rada, & Shors, 1996; Orsetti, Casamenti, & Pepeu, 1996), possibly reflecting the activation of the ascending noradrenergic inputs to the septo-hippocampal and basal forebrain–cortical cholinergic system (Cape & Jones, 1998; Vizi & Kiss, 1998). The activation of hippocampal ACh obviously is related to memory formation (Chang & Gold, 2003; Hasselmo, 1999a, 1999b; Hasselmo, Bodelon, & Wyble, 2002a, 2002b; Hironaka, Tanaka, Izaki, Hori, & Nomura, 2001; Iso, Ueki, Shinjo, Miwa, & Morita, 1999; McIntyre et al., 2002; Ragozzino, Pal, Unick, Stefani, & Gold, 1998), and hippocampal and cortical cholinergic projection systems are expected to cooperate, at the highest level of analysis, in the formation of new memories. Exploration of this cooperation may further benefit from efforts to define and dissociate the attentional and mnemonic functions of the two cholinergic projection systems (Baxter, Bucci, Holland, & Gallagher, 1999, 1997).

5. Conclusions

Attentional processes and capacities are conceptualized as a set of variables that determine the efficacy of the acquisition of new information in situations

characterized by the presence of multiple and variable stimuli, and complex or even conflicting stimulus–response contingencies. As the cortical cholinergic input system is necessary for the mediation of attentional functions and capacities, the integrity of this system would appear to be necessary for learning in situations that tax attentional resources. The notion that the cortical cholinergic system mediates attentional functions but is not required for learning and memory possibly reflects, at least to some degree, the preferred use of animal tasks for the assessment of learning and memory that tax attention functions only to a limited and largely implicit degree. New tasks that would allow the test of the effects of systematic variation of attentional demands on learning and memory may need to be developed in order to specify the role of cortical cholinergic inputs in learning and memory. Such tests may evolve from current tasks on repeated acquisition (Baxter et al., 1995), or from spatial tasks by increasing and varying the demands on the monitoring of extra-maze cues, for example.

Almost a quarter century ago, Drachman and Sahakian speculated, on the basis of effects of cholinergic drugs on human learning and memory, that the cholinergic system acts to amplify stimulus selection and processing, and to optimize separation of signal and noise, and thereby influence learning and memory (Drachman, 1977; Drachman & Sahakian, 1979). Although this description corresponds with the contemporary understanding of the functions of cortical cholinergic inputs, evidence in support of the influence of cortical cholinergically-mediated functions on learning and memory has remained limited. The demonstration of conditions which produce effects on learning and memory following loss of cortical cholinergic neurons would not only expand theories of cholinergic function but also enrich our understanding of the cognitive variables which determine the efficacy of learning and memory.

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