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Review

Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection

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Abstract

Neurophysiological studies demonstrated that increases in cholinergic transmission in sensory areas enhance the cortical processing of thalamic inputs. Cholinergic activity also suppresses the retrieval of internal associations, thereby further promoting sensory input processing. Behavioral studies documented the role of cortical cholinergic inputs in attentional functions and capacities by demonstrating, for example, that the integrity of the cortical cholinergic input system is necessary for attentional performance, and that the activity of cortical cholinergic inputs is selectively enhanced during attentional performance. This review aims at integrating the neurophysiological and behavioral evidence on the functions of cortical cholinergic inputs and hypothesizes that the cortical cholinergic input system generally acts to optimize the processing of signals in attention-demanding contexts. Such signals 'recruit', via activation of basal forebrain corticopetal cholinergic projections, the cortical attention systems and thereby amplify the processing of attention-demanding signals (termed 'signal-driven cholinergic modulation of detection'). The activity of corticopetal cholinergic projections is also modulated by direct prefrontal projections to the basal forebrain and, indirectly, to cholinergic terminals elsewhere in the cortex; thus, cortical cholinergic inputs are also involved in the mediation of top-down effects, such as the knowledge-based augmentation of detection (see Footnote 1) of signals and the filtering of irrelevant information (termed 'cognitive cholinergic modulation of detection'). Thus, depending on the quality of signals and task characteristics, cortical cholinergic activity reflects the combined effects of signal-driven and cognitive modulation of detection. This hypothesis begins to explain signal intensity or duration-dependent performance in attention tasks, the distinct effects of cortex-wide versus prefrontal cholinergic deafferentation on attention performance, and it generates specific predictions concerning cortical acetylcholine (ACh) release in attention task-performing animals. Finally, the consequences of abnormalities in the regulation of cortical cholinergic inputs for the manifestation of the symptoms of major neuropsychiatric disorders are conceptualized in terms of dysregulation in the signal-driven and cognitive cholinergic modulation of detection processes.

Theme: Neural basis of behavior
Topic: Cognition

Keywords: Cortex; Acetylcholine; Sensory systems; Attention

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Contents

1. Introduction

The basal forebrain corticopetal cholinergic system represents the most rostral of the neuromodulatory cortical input systems, and its anatomical organization reflects its capacity to modulate information processing across the entire cortical mantle [50,68,108,156,162,193]. There is now ample experimental evidence in support of the hypothesis that the integrity of cortical cholinergic inputs is necessary for normal attentional performance, and that such performance robustly activates cortical cholinergic inputs [3,29,32,33,39,50,73,101,99,132,162,183,180,181]. Increases in cholinergic receptor stimulation have also been demonstrated to enhance sensory input processing (below). Thus, questions concerning the contributions of acetylcholine (ACh)-mediated enhancement of sensory input processing to attentional performance have been raised, in part based on the observation that loss of cortical cholinergic inputs primarily affect the animals' ability to respond to cues, signals, or targets in tasks assessing attentional functions [29,34,103,101,100,99,183]. Below, activation of cortical cholinergic inputs is proposed to reflect two interacting mechanisms. In attention-demanding tasks, signals activate the corticopetal cholinergic system and thereby enhance their detection[1] ("signal-driven modulation of detection"). Furthermore, practice- or knowledge-based changes in detection, and requirements for filtering of irrelevant stimuli, are mediated, at least in part, via prefrontal modulation of cortical cholinergic inputs ("cognitive or top-down modulation of detection"). Cortical cholinergic activity reflects the complex interactions between these two recruitment modes and mediates, at the cellular level, enhancement of input processing and, at the behavioral level, attentional performance.

[1] In accordance with Posner's definition, we use the term 'detection' as a description of a cognitive process, consisting 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" (p. 162 in Ref. [141]). Posner also suggested that ". . .detecting means to be aware or conscious of the stimulus" (p. 4 in Ref. [138]).

2. ACh-mediated enhancement of cortical sensory information processing

2.1. Neurophysiological evidence

Over 40 years ago, administration of ACh or muscarinic agonists was reported to increase the activity of cortical neurons [91,92,170,171]. Furthermore, because cortical burst firing produced by thalamic stimulation could be attenuated by cortical administration of atropine, cortical cholinergic inputs were speculated—obviously incorrectly—to originate in the thalamus [171]. However, these and other early studies established a productive research theme on the functions of converging basal forebrain cholinergic and thalamic corticopetal projections, and the ACh-induced enhancement of the processing of thalamic inputs [2,16,90,96,97,166,173]. The main conclusions from this research are briefly summarized as follows (see also [48,189]).

2.1.1. Paired stimulation of thalamic inputs and muscarinic receptors mediates cortical sensory plasticity indicative of enhanced sensory input processing

Experimental evidence in support of this hypothesis is available for all modalities. For example, Tremblay, Dykes and coworkers demonstrated that basal forebrain stimulation paired with cutaneous stimulation resulted in an enhanced response to the latter after pairing, and that atropine administration during basal forebrain stimulation blocked these effects. Moreover, in a majority of neurons recorded, basal forebrain stimulation-induced enhancement of the response to cutaneous stimulation, in terms of firing rate, persisted for minutes and hours [143,175,176]. In the auditory cortex, iontophoretic administration of ACh, or stimulation of the basal forebrain, facilitated tone-evoked responses and, in about half of the neurons recorded from, produced global as well as frequency-specific receptive field changes characterized by an optimized response to the frequency of the paired tone [5,23,59,81,110]. The most frequently observed effect of muscarinic receptor or basal forebrain stimulation was an enhanced 'on' response to the stimulus [104]. Generally, the ACh-mediated enhancement of sensory input processing mirrors the effects of increases in stimulus intensity or the effects of such a stimulus after having gained conditional significance [11,111,188]. In the visual cortex, neurons increase their directional bias following the administration of ACh [117]. The effects of ACh, depending on the baseline properties of visual neurons, are multifaceted; for example, ACh-induced changes in the response properties of complex cells in the visual cortex include suppression of resting firing rate, increase in peak response to one direction of motion, and decrease to the other direction [168].

Generally, loss of cortical cholinergic inputs or administration of muscarinic receptor antagonists prevents the enhanced processing of sensory inputs [42,109,166]. Moreover, the increase in cortical neuronal activity resulting from stimulation of spared whiskers after removal of others—reflecting cortical plasticity—is attenuated by loss of cholinergic inputs to the recording area [12,69,155]. Collectively, these data have formed the basis for the notion that cortical ACh acts to 'increase the signal–noise ratio' of the responses of cortical neurons to sensory inputs, to activate input processing in selective cortical regions and, generally, to facilitate the processing of behaviorally relevant stimuli [5,45,168].

2.1.2. Cholinergic receptor stimulation increases the cortical representation of sensory stimuli

Studies designed to map the representation of stimuli in sensory cortical regions demonstrated that local application of cholinergic agonists enlarge, and antagonists decrease, the size of the area that responds to the stimulus. For example, local application of carbachol drastically increased the somatosensory representation of a whisker, while scopolamine resulted in an almost complete suppression of whisker representation in the somatosensory cortex [133]. Likewise, paired basal forebrain stimulation and presentation of a complex sound robustly increased (by two to five times) the area in the auditory cortex that responded to this sound [86,105]. Again, lesions of the basal forebrain corticopetal cholinergic system attenuated such plastic consequences of whisker denervation by reducing the widening of the representation of spared whiskers in the somatosensory cortex [82,200]. These data indicate that cortical cholinergic inputs mediate adaptive changes in cortical sensory maps, yielding the persistently enhanced processing of behaviorally significant stimuli.

2.1.3. Cortical ACh preferentially amplifies thalamocortical inputs while suppressing associational input

Studies using cortical slices and assessing the effects of electrical stimulation have demonstrated that, in the presence of ACh or muscarinic agonists, inputs from other cortical areas were suppressed while thalamic inputs were either less suppressed, unchanged, or even augmented [55,60,61,62,78,87]. In general, suppression of the activity of excitatory intrinsic connections is mediated primarily via muscarinic receptor mechanisms, while activation of nicotinic receptors has been shown to enhance preferably transmission at thalamocortical synapses [55,58].

Using a voltage-dependent dye for optical recording, Kimura et al. [87] impressively substantiated the ability of ACh to suppress the lateral spread of excitation, thereby allowing afferent (thalamic) input to dominate cortical information processing. Such data have been hypothesized to reflect a cholinergically mediated shift from intracortical processing (e.g., of associations or memories) to an enhanced readiness for the cortical processing of extrinsic stimuli [94,123]. Moreover, Hasselmo and Bower [63] proposed that these effects of ACh foster the acquisition of new information by facilitating plastic changes associated with new inputs and by suppressing the interfering influences of previously acquired information for the encoding of new inputs[2] [65].

2.2. Behavioral significance of ACh-mediated enhancement of sensory input processing

The behavioral significance of the effects of basal forebrain stimulation or local cortical application of cholinergic drugs on receptive field properties and sensory maps has become an intensely studied subject [48,190]. Weinberger [189] proposed that the changes in receptive field properties contribute to the mnemonic coding of a stimulus, reflecting its acquired importance as a result of

[2] There are obvious conceptual overlaps between learning processes and attentional performance, as attentional variables represent one of several sets of determinants of the efficacy of the learning process (see Ref. [164]). The present discussion focuses primarily on the role of ACh in mediating attentional processes.

conditioning. As a result, such stimuli are more extensively and more effectively represented and thus dominate behavioral and associational activities (see also Refs. [47,142]). The expansion of the representation of conditioned tones in the auditory cortex clearly supports this hypothesis [154]. However, the necessity of a cortical cholinergic mediation of such effects is more difficult to ascertain, in part because selective lesions of the basal forebrain corticopetal cholinergic system yield minimal, if any, effect on the performance in tasks or task components that assess basic stimulus-response contingencies or even more complex conditional discriminations (e.g., Refs. [31,152,180]; see also the discussion in Ref. [185]). To reiterate, the available evidence clearly demonstrates that receptive field retuning and the expansion of stimulus representation are cholinergically mediated mechanisms; however, there is less data to indicate that the increasing behavioral significance of a stimulus as a result of, for example, extensive conditioning is necessarily due to cholinergically mediated plasticity in the sensory cortex.

A recent study by Conner et al. [35] demonstrated that basal forebrain cholinergic lesions impeded the learning, but not the performance, of a skilled forelimb reaching task. Moreover, the lesions not only prevented the expansion of the representation of the trained limb in the contralateral sensorimotor cortex, but in fact produced a decrease in the size of forelimb representation. This finding suggests that cholinergic activity is not only required to mediate learning-associated expansion and retuning of cortical receptive fields but contributes continuously to maintaining sensory representation. Such experiments begin to determine the behavioral significance of ACh-mediated sensorimotor cortical plasticity. However, even deafferented animals did eventually learn the skilled reaching task (see the discussion on p. 826 in Ref. [35]), raising the possibility that ACh-mediated motor cortex plasticity contributes to, but may not be necessary for, the learning of skilled reaching. Finally, it is clearly the case that not all stimulus processing requires cholinergic modulation for the stimulus to acquire conditioned or discriminative significance (references above; see also Refs. [15,13,167,185]). Thus, the necessity of cortical cholinergic inputs for the mediation of stimulus-based responding likely is limited to situations characterized by certain stimulus characteristics and behavioral and cognitive contexts that are, collectively, classified as taxing attentional processing and resources[3]. For example, Davidson and Marrocco [40] demonstrated that infusions of scopolamine into attention-related activity sites, but not adjacent regions, in the intraparietal cortex of rhesus monkeys resulted in impairments in attention performance. Such evidence demonstrates, similar to the effects of lesions discussed further below, the necessity of cortical cholinergic transmission for attentional performance.

3. Cholinergic modulation of detection: signal-driven and top-down effects

Signal-driven modulation of detection: The properties of signals per se, such as salience or novelty, are hypothesized to suffice for recruiting the cortical cholinergic input system, thereby promoting the detection and processing of such signals. However, exclusive signal-driven capturing of attentional processes appears to be rare [49], mostly because the attribution of novelty or affective significance to a signal requires top-down information. We will return to this issue below.

The ascending noradrenergic system has been conceptualized as a major mediator of the signal-driven recruitment of attentional systems. Novel, salient, or stress-related stimuli activate ascending noradrenergic inputs via afferents 'importing' information about autonomic reactivity changes [6,7,19–22]. Basal forebrain cholinergic neurons projecting to the cortex are a target of the ascending noradrenergic system, and the integrity of this link appears critical for the cortical processing of stimuli. For example, Berntson et al. [22] assessed the enhanced frontoparietal evoked auditory response in animals treated systemically with epinephrine. As the effects of epinephrine are restricted to visceral activation in the periphery, this experimental model can be employed to determine the ascending neuronal systems which mediate, strictly driven by the stimulus, the enhanced cortical processing of stimuli. Importantly, loss of cortical cholinergic inputs attenuated the effects of epinephrine priming. Furthermore, infusions of an α_1-receptor blocker into the basal forebrain likewise attenuated these effects [88]. These data illustrate the importance of the basal forebrain noradrenergic–cholinergic link in the signal-driven modulation of the processing of stimuli. As will be discussed next, such ascending mediation of signal-driven effects is influenced top-down, based on, for example, prefrontal projections to the locus coeruleus [8,80], and the prefrontal regulation of basal forebrain neurons via direct connections [198] and via multisynaptic connections including limbic and paralimbic regions, particularly the nucleus accumbens and the amygdala [157].

Cognitive modulation of detection: Sensory input processing is modulated top-down based on knowledge, memory, practice, and expectations. Top-down regulation affects all stages of cortical and subcortical sensory input processing [44,83,136], and it consumes processing resources. For example, extensive demands on the suppression of distractors or the filtering of 'noise' may weaken other top-down effects (e.g., Ref. [145]). Attentional modulation of sensory input processing has been particularly well documented in the visual cortex, at the level of single unit

[3] To emphasize this important constraint, the present discussion uses the term 'signal' rather than 'stimulus' to imply the necessity of attention-demanding stimulus presentation characteristics, including relatively low presentation rates, unpredictability, near-threshold psychophysical properties, source uncertainty, and so forth (e.g., Ref. [127]).

activity [44,137,146,147,153,177–179,194], or metabolic activity or blood flow changes in animals [184] and humans [52,84,187]. This evidence also suggests that static models of the representation of sensory information in the cortex (e.g., Ref. [24]), or attempts to isolate the relative contributions of sensory versus attentional operations to the detection of stimuli in attentional tasks, are of restricted heuristic value [138].

The activity of the cortical cholinergic input system is modulated by prefrontal efferent projections, and thus, the ascending cholinergic system can also be conceptualized as a component of the prefrontal output system that acts, top-down, to enhance input processing and to suppress the processing of irrelevant stimuli, distractors, or "noise" (see Fig. 1; [163]).

The ability of the prefrontal cortex to regulate the activity of cholinergic inputs elsewhere in the cortex is a crucial component of this hypothesis (Fig. 1). A recent series of experiments demonstrated that stimulation of prefrontal cholinergic and glutamatergic receptors is sufficient to increase ACh release in the posterior parietal cortex (PPC). In contrast, stimulation of PPC glutamatergic or cholinergic receptors did not alter prefrontal ACh release

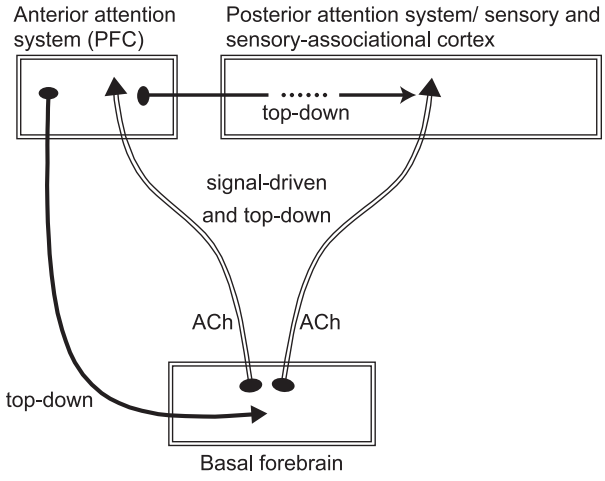

Fig. 1. Schematic illustration of the components of the cholinergic modulation of input processing or signal detection (for the definition of detection see Footnote 1). Attentional performance, particularly the detection of signals is well documented to depend on the integrity of cortical cholinergic inputs. The cortical cholinergic input system can be recruited based on the properties of the signal (signal-driven) and to mediate enhancement of signal detection. The effects of cortical cholinergic deafferentation on well-practiced attention performance, and the persistence of signal duration-dependent hit rates following extensive practice, can be conceptualized as reflecting primarily a disruption of such signal-driven cholinergic modulation of detection. Furthermore, the cortical cholinergic input system can be recruited, largely by prefrontal regions, to mediate cognitive modulation of the detection process in situations characterized by changes in the parameters governing signal presentation or by increased demands on attentional 'effort'. The role of top-down cholinergic modulation can be revealed, for example, by demonstrating the role of this modulator in mediating the performance effects of distractors, and the role of prefrontal regions in modulating cortical cholinergic transmission under such conditions. Collectively, cortical ACh acts to augments signal detection and to suppress or filter irrelevant information.

[121], indicating that the ability to influence ACh release elsewhere in the cortex is a specific property of the prefrontal cortex. These data begin to demonstrate the potential role of cortical cholinergic inputs in mediating top-down mechanisms executed by prefrontal regions. The prefrontal regulation of parietal cholinergic transmission is of particular interest because of the considerable evidence, suggesting that parietal areas, in interactions with prefrontal regions, represent core regions of the brains distributed attention systems [1,36,38,40,140,144,169].

While there is substantial evidence in support of the critical role of cortical cholinergic inputs in the mediation of attentional functions, there is little data from task-performing animals relevant to the specific hypothesis that the activity of cortical cholinergic inputs reflects the cognitive regulation of signal processing, and that such activity is controlled by prefrontal systems. Neurophysiological recordings from the basal forebrain of behaving animals typically were conducted in the context of well-trained discrimination or delayed response tasks (e.g., Refs. [148,192]) and thus were not designed to document changes in activity that would reflect top-down regulation. However, Wilson and Rolls [192] observed neurons whose activity was determined in part by the learned reinforcement value of stimuli. These data may be interpreted as reflecting a memory-based activation of the cholinergic system to mediate a biasing toward the processing of such stimuli [192]. Likewise, the data by Richardson and DeLong [149] indicate that activity in the primate basal forebrain reflects stimulus-based cognitive operations which presumably are modulated top-down. While direct evidence concerning the role of cortical cholinergic input systems in the top-down regulation of attention remains scarce, the effects of prefrontal manipulations, in interactions with manipulations of task parameters, on attention performance correspond well with predictions derived from the present model (see Section 3.1. below).

Interactions between signal-driven and cognitive cholinergic modulation of detection: As illustrated in Fig. 1, activation of cortical cholinergic inputs is proposed to reflect both signal-driven and top-down recruitment of this modulatory system. Prefrontal cholinergic inputs may play a distinct role in the cholinergic meditation of signal detection, as they act to recruit the 'anterior attention system' as a function of signal characteristics [140]. Additionally, prefrontal cholinergic inputs are also modulated top-down, based on prefrontal feedback to the basal forebrain neurons. The neuronal mechanisms involved in this feedback remain unclear because of uncertainties concerning intrabasalis circuitry [158] and because of the absence of data characterizing prefrontal–basal forebrain interactions in task-performing animals.

The hypothesis that cortical cholinergic inputs mediate both signal-driven and top-down mechanisms of attention may necessitate the assumption that different branches of this neuronal system can be individually modulated depend-

ing on the attentional context and on signal characteristics. Although anatomical conceptualizations have been put forward that describe this system as consisting of modules that can be separately driven by afferent projections [197,199], the demonstration of such a mode of operation has been hampered by the present limitations in the spatial and temporal resolution of in vivo measures of ACh release [72,79]. Obviously, this issue is of substantial importance and will need to be investigated in behaving animals using evolving methods that are capable of monitoring cholinergic transmission at a temporal resolution of seconds or less [131].

The present model suggests that activation of cortical cholinergic inputs, as a function of signal properties and cognitive context, optimizes the signal detection[1] process. Yu and Dayan [41,196,195] postulated, based on their computational model, that cortical cholinergic activity specifically reflects the interactions between bottom-up and top-down mechanisms. Furthermore, their model suggests that cortical cholinergic activity reflects top-down uncertainty, meaning the degree to which top-down information mediated by fast glutamatergic transmission in cortical circuits disagrees with bottom-up glutamatergic transmission of sensory input and thus the degree to which cognitive variables governing top-down processes require adjustment [41,196,195]. As we will see below, the available evidence corresponds readily with their model and also with the present view that the activity of cortical cholinergic transmission reflects the combined contributions of signal-driven and cognitive cholinergic modulation of signal detection.

3.1. Exemplification: cholinergic mediation of sustained attention performance

To illustrate the role of the cortical cholinergic input system in attentional performance, as depicted in Fig. 1, sustained attention performance is used as an example, primarily because relevant neurobiological data generated by experiments involving this task are available. Issues concerning the validity of this operant task, and data in support of the claim that animals' performance in this task reflects sustained attention performance, are discussed elsewhere [4,98,160]. This task typically consists of the presentation of two types of trials, signal trials (signals are typically presented via a panel light illuminated for 25–500 ms) and nonsignal trials (no panel light illumination). Levers are inserted into the operant chamber to signal the response period. As correct responses to the two trial types (hits and correct rejections) are required on opposite levers, the animals cannot solve the task by adopting a complete side- or lever-bias, as such a bias would generate 100% hits and false alarms, or 100% correct rejections and misses, respectively (for details see Refs. [4,27,98]). The presentation of a range of stimuli, variable intertrial intervals, and of a randomized sequences of signal and nonsignal trials is designed to tax the sustained attentional capacity of the subject (e.g., Refs. [28,30,89,129]).

3.1.1. Signal-driven cholinergic modulation: effects of cortical cholinergic deafferentation on attention performance

Animals with cortex-wide loss of cortical cholinergic inputs, produced by bilateral infusions of the immunotoxin 192IgG saporin into the nucleus basalis of Meynert/substantia innominata region of the basal forebrain, exhibit a specific and extremely reliable pattern of impairment when tested in a task designed to assess sustained attention performance. Such lesions result in a decrease in the number of correct responses to signal trials, yielding low (<30%) and signal duration-independent hit rates. In contrast, loss of cortical cholinergic inputs does not affect the animals' ability to respond correctly in nonsignal trials (correct rejections; [25,26,99–102]. Importantly, restricted cholinergic deafferentation of the primary and secondary visual cortex, by multiple injections of 192 IgG-saporin into these regions, failed to affect the rats' performance in the sustained attention task described above, and also failed to affect the animals' ability to discriminate between simultaneously presented visual stimuli flashing (on–off) at 5 Hz versus 1.25–4.17 Hz [76]. In contrast, cortex-wide cholinergic deafferentation appears necessary to produce these impairments in the detection of signals [99–101]. These data indicate that the cholinergic deafferentation-induced impairments in attentional performance cannot be explained in terms of disrupting the cholinergic modulation of the primary representation of sensory input. Rather, the impairments in attention performance that result from cortical cholinergic deafferentation reflect a dysfunctional detection process (as defined in Footnote 1).

The selective decrease in the ability to respond correctly to signal trials that results from cortical cholinergic deafferentation cannot be interpreted in terms of overt changes in performance, specifically because the increase in misses in signal trials typically is not associated with an increase in correct rejections in nonsignal trials (or, vice versa, the decrease in hits is not associated with a decrease in false alarms). Likewise, if the deafferentation-induced decrease in hits was due to changes in the thresholds and criteria that control 'detection'-rates, the animals' criterion for rejecting nonsignal trials would also be expected to be affected by the lesion, but such changes were never observed. Thus, there is little evidence or interpretational context to suggest that the lesion-induced impairments in the animals' ability to respond correctly to signal trials were due to the disruption of primary sensory mechanisms, or that such impairments could be effectively captured by the constructs derived from signal detection theory (see also Ref. [172]).

Cortical cholinergic deafferentation disrupts both the signal-driven and cognitive modulatory mechanisms normally mediated by this neuronal system. However, top-down, cognitive modulation may play a negligible role

during standard task performance and in the absence of unexpected variations concerning signal type, signal sources, signal presentation parameters, distractors, and so forth. Thus, the selective decrease in hits following cortex-wide cholinergic deafferentation is hypothesized to be largely due to the disruption of signal-driven recruitment of the cholinergic system. The ability of more salient stimuli to counteract moderate deafferentation-induced impairments in accuracy [103] appears to correspond with this view, as the detection[1] of more salient signals may depend less on cholinergic modulation. Finally, such an interpretation also corresponds with data indicating that the basal forebrain cholinergic system mediates incremental but not decremental attentional processes [33].

3.1.2. Signal-driven cholinergic modulation: signal duration-dependent hit rates

Even following extended training in this task, the detection of signals remains signal duration-dependent (e.g., Refs. [99–102,182,183]). Furthermore, as the task parameters (such as the variability of intertrial intervals, event rate, signal probability, signal duration) typically are held stable for extended periods, little demand on cognitive modulation of signal detection may be associated with standard task performance. Thus, in this situation, the cholinergic modulation of signal duration-dependent signal detection presumably is a result of signal-driven recruitment of the cholinergic system. Recent recordings from the posterior parietal cortex in animals performing the sustained attention task indicate that signal-triggered neuronal activity is not present in signal trials resulting in a 'miss' response (J. Broussard and B. Givens, unpublished results). Thus, the relatively higher rate of misses in trials with shorter signals may reflect the failure of weaker signals to activate the cholinergic system and thus a lower likelihood for detection[1].

3.1.3. Signal-driven cholinergic modulation: attention performance-associated increases in cortical ACh release

During standard task performance, cortical cholinergic activity is hypothesized to be largely signal-driven, and thus increases in cortical ACh release would be expected to occur specifically in response to signals but not during nonsignal trials. Although robust increases in ACh efflux in animals performing attentional tasks were demonstrated, and although such increases are not observed in various control procedures [39,74,73,71,103], the temporal resolution of present microdialysis methods prevents the determination of trial type-specific changes in ACh efflux. Evolving amperometric techniques for the assessment of ACh release [131] may be capable of testing the hypothesis that presentation of signals in tasks assessing attentional functions selectively are associated with increases in cortical cholinergic transmission. In line with the PPC recording data mentioned above, and possibly also with the lack of effect of decreases in signal duration on cortical ACh efflux [132], signal-driven cortical cholinergic activity can also be hypothesized to predict the detection[1] of the signal, rather than indicating its physical presence.

3.1.4. Cognitive cholinergic modulation: effects of distractors

Presentation of distractors is expected to trigger top-down modulation as they need to be identified as such and discriminated from signals. Top-down mechanisms further act to suppress or filter the processing of distractors. Distractor-induced impairments in performance also contribute to the recruitment of top-down mechanisms to counteract the effects of loss of stimulus control and reward on performance. Our hypothesis suggests that the cortical cholinergic input system is part of the prefrontal efferent circuitry mediating such top-down effects. Indeed, prefrontal neuronal activity increases specifically in association with the presentation of distractors, and this increase in neuronal activity is mediated via cholinergic inputs to the recording area [56]. The present hypothesis also predicts that cortical cholinergic deafferentation that is restricted to prefrontal regions does not affect standard task performance (during which cortical cholinergic activity is entirely signal-driven; above), but that the effects of such restricted lesions interact with the detrimental effects of distractors on performance, reflecting a dysfunctional recruitment of top-down mechanisms. Indeed, infusions of the immunotoxin into the medial prefrontal cortex did not affect standard sustained attention performance. However, the presentation of a distractor resulted in a significantly greater impairment in performance in deafferented when compared to sham-operated animals [57]. These data correspond with the model described in Fig. 1, specifically with the idea that cholinergic innervation of the prefrontal cortex is necessary to initiate the cognitive mechanisms that support performance under changing task condition, such as the presentation of distractors.

3.1.5. Cognitive cholinergic modulation: attentional "*effort*"-associated increases in cortical ACh efflux

While the sustained attention performance of animals recovered from the detrimental effects of a distractor, Himmelheber et al. [73] observed additional increases in frontoparietal ACh release. Recovery of performance while a distractor is presented could be speculated to be due to increased top-down effects, acting to amplify the detection process and to suppress the processing of the distractor. Thus, as the animals regain performance, or as performance requires attentional "effort", further increases in cortical ACh release may be conceptualized as reflecting increased top-down activity. As we already know that cholinergically driven prefrontal activation occurs during distractor presentation [56], the demonstration of "effort"-associated increases in ACh efflux is predicted to be attenuated by blocking cholinergic activation of the prefrontal cortex, or by blocking the activation of

prefrontal efferent projections which mediate top-down effects (see Fig. 1; see also Refs. [37,83,85]).

The hypothesis that increases in attentional "effort" are mediated via increases in cortical ACh release corresponds precisely with Yu and Dayan's model [196]. In their terms, the effects of a distractor augment the uncertainty associated with a top-down model, and cholinergic transmission reflects the degree of disparity between the top-down model and bottom-up information. The development of additional experimental avenues designed to vary this type of uncertainty may be key to test this hypothesis and to determine the general function of cortical ACh.

3.2. Switching between signal and nonsignal trials

The conceptualization of cortical cholinergic inputs as mediating signal-driven and cognitive modulation of the detection process corresponds well with the neurophysiological evidence discussed above. The latter suggests further that increases in cholinergic transmission, mediated by feedback interactions within cortical circuits, suppress the processing of associational (e.g., mnemonic) information, thereby reducing the impact of potentially interfering information on input processing (see also Refs. [66,67]). The strong formulation of this hypothesis suggests that cortical ACh mediates the switching of the cortical processing mode from an intracortical to an input-processing mode. The sparing of the performance in nonsignal trials by animals with loss of cortical cholinergic inputs supports this hypothesis, as the performance of such trials does not require switching the processing mode. This hypothesis also predicts that in tasks that do not require such switching by, for example, exclusively presenting signal trials, loss of cortical cholinergic inputs results in limited effects on performance. A test of this hypothesis using the sustained attention task is not straightforward as such a version of the task would produce overwhelming side- and lever-biases. (Signal detection-type tasks as used in the older literature may be more useful for this purpose [112]). However, the more limited effects of basal forebrain lesions on cued target detection [34]—where cues and targets are always illuminated and thus switching to an input processing mode is not taxed—could be interpreted as support for the idea that switching to an input processing mode represents an essential component of the cholinergic modulation of attentional performance. Furthermore, the limited effects of such lesions on the accuracy of rats tested in the five-choice serial reaction time task [150], although depending on the degree of the deafferentation [103], may be due to the absence of nonsignal trials, thereby limiting the switching between input processing and other modes of processing (e.g., associational, mnemonic, top-down), and thus the degree to which the integrity of cortical cholinergic inputs is necessary for performance in this task. Finally, the lack of effect of basal forebrain cholinergic lesions on the performance in traditional learning and memory tasks (e.g., Refs. [13–15,46,174,191]), which has been suggested to be due to the restricted attentional functions and capacities required to perform these tasks [164], more specifically may also be explained by the negligible degree to which the performance of such tasks requires the switching between input and other processing modes.

To the degree that attentional performance depends on a cholinergically mediated switching to input processing, attentional performance-associated increases in ACh release would be predicted not to correlate with levels of attentional performance but rather with the frequency of switches to the input mode. Evidence indicating that variations in five-choice performance did not covary with cortical ACh release [132], or that within-session decreases in the demands on attention performance did not trigger significant decreases in cortical ACh efflux [75], correspond with this hypotheses.

4. Conclusions and clinical significance

The present model describes the role of cortical cholinergic inputs in the mediation of attention performance in terms of interacting signal-driven and cognitive mechanisms which, collectively, act to optimize the detection (as defined in Footnote 1) of signals. Signal-driven and cognitive cholinergic modulation of signal detection may not always be clearly separated at the level of cortical cholinergic transmission; rather, corticopetal cholinergic activity reflects the interactions between both mechanisms, and the relative contribution of signal-driven versus cognitive cholinergic modulation to attentional performance depends on the nature of the task and the properties of the signals and signal presentation characteristics.

This hypothesis explains the effects of cortical cholinergic deafferentation and of manipulations of the excitability of cortical cholinergic inputs on attentional performance, and it provides relatively specific predictions concerning attentional performance-associated increases in cortical ACh release. Furthermore, this hypothesis integrates evidence, suggesting that cortical ACh suppresses associational information and amplifies the processing of thalamic inputs [64], and the fact that activation of the cortical cholinergic input system is not readily achieved but requires the presentation of novel or salient stimuli, or stimuli that act as signals in attention-taxing tasks [3,70,118].

The symptoms of two major disorders have been hypothesized to develop and escalate as a result of abnormalities in the integrity or dysregulation of cortical cholinergic inputs. The hypothesis illustrated in Fig. 1 provides the basis for a relatively detailed description of the consequences of different abnormalities in cortical cholinergic transmission for attention performance and, in the long-term, cognitive functions.

4.1. Alzheimer's disease

Although the discussion of the significance of the decline in the integrity of cortical cholinergic neurons for the manifestation of senile dementia continues, an overwhelming amount of evidence supports the general hypothesis that, compared to other neurotransmitter systems, dysregulation and loss of corticopetal cholinergic projections are most closely associated with, and may even account for, the decline in cognitive abilities [9,53,54,106,107,115,116,124–126]. The model illustrated in Fig. 1 predicts dramatic impairments in attention performance in subjects with a disintegrating basal forebrain cholinergic system (e.g., Refs. [10,130,128,134,161]). As loss or dysregulation of the cortical cholinergic input system weakens both the signal-driven activation of cortical cholinergic inputs necessary for effective detection, and the cholinergic mediation of top-down effects in situations where task parameters or contextual variables change, attentional input processing becomes fundamentally disrupted. If persistent, such impairments attenuate learning and thus foster the manifestation of expanding cognitive impairments in senile dementia [124,126,164].

The enhancement of stimulus detection and the early steps of stimulus encoding produced by acetylcholine esterase inhibitors in animals and humans (e.g., Refs. [17,18,51,151,186] correspond well with the present hypothesis. However, the relatively limited beneficial cognitive effects resulting from the treatment of patients with Alzheimer's disease with cholinesterase inhibitors indicate unsettled complexities, specifically in light of the possibility that the activity of cortical cholinergic transmission may be correlated with "attentional effort" or the strength of top-down effects rather than with actual levels of performance (above). However, there are several neuropharmacological limitations in the ability of such drugs to reinstate the functions of a degenerating cholinergic system that are beyond the scope of the present discussion (e.g., Refs. [99,159]). Furthermore, as discussed above, complex interactions between cholinergic activity in prefrontal regions and elsewhere in the cortex may mediate the dynamic interplay between signal-driven and top-down effects (see also Ref. [196]); however, systemic drug-induced increases in cholinergic transmission may have a limited potency in optimizing such interactions. Likewise, if the functions of cholinergic inputs can be reduced to mediating the switching to a cortical input processing mode (see Section 3.2.), drug-induced persistent increases in cholinergic transmission obviously would impede such an elementary function.

The data by Bentley et al. [17], generated by using event-related fMRI, support this cautionary discussion about potential beneficial effects of conventional cholinomimetic drugs. They reported that, in healthy subjects, administration of physostigmine resulted in the attenuation of the differential responses to attended versus unattended stimuli observed in extrastriate cortex. Moreover, this effect depended on the stimulus (faces versus houses). These results indicate that the cholinergic modulation of input functions indeed may be highly region-specific, and they suggest that systemic increases in cholinergic transmission may have very limited beneficial cognitive effects.

4.2. Schizophrenia

Abnormally reactive cortical cholinergic inputs have been proposed to contribute to the mediation of the attentional impairments in schizophrenia and thus to the development of psychosis (for review see Ref. [165]). This hypothesis is based in part on evidence indicating that mesolimbic dopaminergic neurons regulate, via multisynaptic pathways, the activity of cortical cholinergic inputs, that repeated administration of psychostimulants (that represents a psychotogenic manipulation) augments drug-induced increased in cortical ACh efflux, and that administration of antipsychotic drugs attenuates abnormal increases in cortical ACh release [114,119,120,122,159].

In animals tested in the sustained attention task described above, systemic or intracranial pharmacological manipulations which disinhibit and/or increase the excitability of cortical cholinergic inputs were found to spare the animals' ability to respond correctly to signals but increased the number of false alarms in nonsignal trials [43,77,113,122,183]. The increases in the number of false alarms could not be attributed to a side- or lever-bias because the animals' hit rates remained unchanged and signal duration-dependent. Likewise, changes in 'sensitivity' or 'criterion', such as the adoption of a 'riskier' criterion for signal detection, do not readily explain these findings as, for example, a riskier criterion would also be expected to result in increases in hit rates. Recent analyses of the effects of repeated administration of amphetamine—which "sensitizes" cortical ACh release [122]—on the response latencies of animals exhibiting such increases in false alarms suggested that these animals failed to switch from the processing of signal trials to that of nonsignal trials [95]. The present discussion (see Fig. 1) predicts that the performance of animals with an abnormally reactive cortical cholinergic input system is characterized by increases in the number of false alarms, that is, 'claims' for signals in nonsignal trials. Such increases in "false detections" may reflect an abnormal state of input processing or, in Yu and Dayan's terms [196], a state characterized by a decreased significance of top-down information and a relative overprocessing of inputs. Abnormally reactive cholinergic inputs may limit the shifting the cortical processing mode persistently toward (thalamic) input processing, thereby subjecting 'noise', which normally would be filtered, to cholinergically mediated amplification. As a result, attentional significance would be attributed to irrelevant or normally unattended stimuli (see also the discussion of the data by Bentley et al. [17] above). Such an interpretation of the effects of an

abnormally reactive cortical cholinergic input system on attentional performance is of obvious relevance with respect to hypotheses about the role of this system in the development of the symptoms of schizophrenia [165].

4.3. Acetylcholine, attention, and consciousness

Posner [139] suggested that awareness is a function of the attention network in the brain. Although attention and awareness may not describe completely overlapping constructs [93], the present discussion suggests that the integrity of cortical cholinergic inputs is crucial for the mediation of signal-driven and cognitive modulation of attention, of the interactions between these two modes of attentional information processing, and thus of awareness [135].

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