Cholinergic Mediation of Attention

Contributions of Phasic and Tonic Increases in Prefrontal Cholinergic Activity

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Contrary to the classic description of acetylcholine (ACh) as a slowly acting neuromodulator that influences arousal states, results from experiments that employed enzyme-selective microelectrodes for the real-time monitoring of ACh release in the cortex of attentional task-performing rats indicate that cholinergic signals manifesting on multiple timescales (seconds, tens of seconds, and minutes) support, and are necessary for, the mediation of defined cognitive operations. Specifically, in the prefrontal cortex, second-based cholinergic signals support the detection of behaviorally significant cues. In contrast to these prefrontal cholinergic transients, performance-associated cholinergic activity that manifested at lower temporal resolution also was observed elsewhere in the cortex. Although tonic cholinergic signal levels were correlated with the amplitudes of cue-evoked cholinergic transients, and the latter with response latencies, the interrelationships and interactions between the multiple cholinergic signaling modes remains unclear. Hypotheses concerning the afferent circuitry contributing to the regulation of second- versus minute-based cholinergic signals are discussed. The discovery of cholinergic transients and their crucial role in cue detection and attentional performance form the basis for new hypotheses about the nature of cholinergic dysfunction in cognitive disorders and offer new targets for the development of treatments for the cognitive symptoms of neuropsychiatric and neurodegenerative disorders.

Key words: **acetylcholine; attention; basal forebrain; detection; enzyme-selective microelectrodes**

Introduction

Research on the functions of the cortical cholinergic input system began over 40 years ago with the classic experiments by Celesia and Jaspers, Szerb, Pepeu, Phillis and others (for a recent review of the historical literature, see Ref. 1). It is of interest to note that early evidence suggested that the activity of cholinergic inputs to the cortex was related either to the state of the reticular activating system or, given the absence of information about the presence of cholinergic cell groups in the basal forebrain, assumed that these neurons originated in the brain stem and formed an integral component of the ascending reticular activating system.[2]

Cholinergic inputs to the cortex originate in the nucleus basalis of Meynert (nBM), substantia innominata (SI), the horizontal nucleus of the diagonal band (HDB), and the preoptic nucleus (collectively termed basal forebrain, BF).[3–8] The BF projections to the cortex also include GABAergic and possibly glutamatergic neurons, but little is known about their organization and function.[9–11]

The traditional description of the anatomical organization of BF cholinergic projections to the cortex corresponds with the common characteristics of ascending arousal systems, including the presence of a "diffuse" or undifferentiated projection system and a widespread, undifferentiated pattern of cortical innervation. Similarly, the available data concerning the distribution of high-affinity choline transporters and muscarinic (metabotropic) and nicotinic (ionotropic) acetylcholine receptors supported the view that cholinergic neurons innervate all cortical regions and layers and modulate practically most cortical neurons.[12–22] Collectively, the anatomical characteristics of the cortical cholinergic input system corresponded with, and directly supported, the unspecified "arousal" functions traditionally attributed to this neuronal system.[3,23–25]

The limited topographical organization of BF efferent and afferent projections indicated the absence of major BF subdivisions or modules. Tracing

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studies indicated a rough rostrocaudal/mediolateral topographic organization of BF cholinergic projections to the cortex.[26,27] In primates, cholinergic neurons from the anteromedial and anterolateral nBM preferentially project to the medial prefrontal cortex (PFC), while orbitofrontal and lateral PFC areas are innervated by projections from cholinergic neurons situated in the more intermediate and posterior BF regions.[28] In rodents, the primary source of neocortical cholinergic inputs to the pre/infralimbic and cingulated cortex stem from the HDB, as well as the ventral nBM and anterior SI.[7,29,30]

Basal forebrain cholinergic neurons receive inputs from numerous telencephalic, diencephalic, and brainstem regions, including mPFC, ventral hippocampus, amygdala, nucleus accumbens (NAc), thalamus, reticular formation, ventral tegmental area, laterodorsal tegmental nucleus, locus coeruleus (LC), and raphe nucleus.[31–37] Glutamatergic projections represent a major source of cortical projections to the BF.[37] The majority of these projections terminate on parvalbumin-immunoreactive, and therefore GABAergic neurons that have been speculated to be largely projection neurons.[37] This cortical feedback loop to the BF has been hypothesized to represent a major component in the prefrontal efferent circuitry that mediates top-down effects that act to optimize attentional performance under taxing conditions.[38,39]

The view that the cortical cholinergic input system acts as a neuromodulator system that activates the entire cortical mantle to promote cortical information processing in the awake brain and during REM sleep has been confirmed by previous studies indicating that a broad range of stimuli and behavioral manipulations, including novelty, stress, sensory stimulation, and feeding behavior all increase cholinergic activity in the cortex, with very little evidence for a dissociation between such increases across multiple cortical regions. However, studies assessing the behavioral and cognitive effects of BF lesions in the 1990s, first using nonspecifically acting excitotoxic amino acids and later the specific cholinotoxin 192 IgG-saporin, formed a major basis of the more specific hypothesis that the integrity of this cortical input system is required for a wide range of attentional functions and capacities.[25,40–43] Experiments using microdialysis confirmed that demands on attention are necessary to increase levels of cortical acetylcholine release.[44–50] The conclusions based on these experiments are not necessarily in conflict with the earlier results showing effects of novelty or stressors on cortical ACh release, as these relatively broad behavioral manipulations all cause attention responses. Research on the functions of the cortical cholinergic inputs systems using microdialysis perhaps reached a pinnacle by demonstrating that levels of cortical ACh release did not correlate with levels of attentional performance, but with the degree to which the task taxed the animals' ability to perform under challenging conditions or, in other words, with attentional effort.[50,51]

The collective results from this research continued to conform with the assumed properties of a neuromodulator system, including slowly changing levels in activity, over minutes, and the limited spatial resolution, indicative of the slow dynamics of a neuronal system that influences levels of arousal and cortical information processing and of the widespread if not ubiquitous actions of a neuromodulator across the entire cortical mantle, respectively. Thus, the temporal and spatial resolution of data that was generated by a particular and, for good reasons, dominating method in the behavioral neurosciences, microdialysis, happened to be consistent with, and therefore substantiated, the traditional views concerning the fundamental functional characteristics of this neuromodulator system.

However, behavioral as well as neuropharmacological evidence indicated that the functions of the cortical cholinergic input system could not be fully explained by the hypothesis that slowly changing levels of cholinergic activity modulate attentional functions and attentional effort. For example, the effects of selective cholinergic lesions on the performance of rats in an operant-sustained attention task were repeatedly demonstrated to manifest only with respect to trials that required the detection of signals, while sparing the animals' ability to "report" the absence of signals following nonsignal events.[40,52–55] It should be noted that "detection" refers to a broad process that involves the integration of a stimulus into ongoing cognitive and behavioral activity, including a shift in attention from ongoing activities toward stimulus-evoked behavior, response rule processing, outcome expectation, and outcome timing. In studies using microdialysis, a single data point reflects accumulated ACh release over 6–8 min and over tens of trials involving signal as well as nonsignal events, presented in random order. Thus, the special role of cortical cholinergic input in the performance of trials requiring signal detection, revealed by lesion studies, cannot be investigated in studies using standard microdialysis methods. The evidence from the lesion studies indicated that the cortical cholinergic input system contributes specifically to the detection process. We hypothesized that the switch from the associational processing that mediates the performance in nonsignal trials to the detection of signals following signal events requires a cholinergic signal.[39] In

other words, we predicted that a trial-related, transient (or phasic) cholinergic signal occurs and is necessary for signal detection.

A second major reason for assuming that slow, or tonic changes in cholinergic activity insufficiently describes cholinergic neurotransmission concerns the presence of a superbly potent metabolic enzyme for ACh, acetylcholinesterase (AChE). As this enzyme is among the most, if not the most potent enzyme present in mammalian bodies, in terms of its catalytic power, one would expect that it serves to support a highly phasically active neurotransmitter system. In this context, and although this is a debated issue, the presence of such an enzyme also suggests that ACh is transmitted within classic synapses, as opposed from other neuromodulators that are volume transmitted.

Phasic Cholinergic Signals and Cue Detection

Real-time monitoring of ACh release has become possible with the advent of enzyme-coated microelectrodes and the amperometric measurement of current produced by the oxidation of an electroactive reporter molecule of the analyte of interest. With respect to ACh, the method monitors choline that results from AChE-mediated hydrolysis of ACh. Choline is oxidized by choline oxidase, which is immobilized on the surface of platinum recording sites. The resulting hydrogen peroxide is oxidized on the platinum surface by applying a constant voltage, resulting in current (for details about the measurement scheme and results from validation experiments indicating that these currents indeed reflect ACh release from cholinergic synapses and as a result of depolarization, see Refs. 56–60).

As such amperometric recordings in performing animals are associated with substantial technical and experimental problems, including interference by static energy sources, our first set of experiments necessitated a relatively simple test of the hypothesis that phasic cholinergic signals are associated with, and are necessary for (see later paragraphs), shifts from endogenously generated behavior and associational processing to the detection of signals and signal-evoked cognitive and behavioral processes (see earlier for the definition of "detection"). These experiments utilized a relatively simple cued-appetitive response task involving long intertrial intervals (ITI; 90 ± 30 s). The long ITI fostered disengagement from task, as indicated by extensive and consistent grooming behavior. The cue, a ceiling light on for 1 s, predicted subsequent reward delivery (6 ± 2 s later) at one of two reward ports (randomly selected). Behaviorally, the cue generated a distinct shift from grooming behavior toward the monitoring of the reward ports, followed by port approach and reward retrieval in response to reward delivery.

Such a cue-evoked shift in behavior occurred in the majority of, but not all trials. In 30–40% of the trials the cue failed to evoke such behavior and animals continued grooming ("missed cue"). Importantly, in such trials, reward was also delivered, and because of the salient stimuli associated with reward delivery, animals approached the ports and retrieved the reward, albeit with longer latencies when compared with animals that detected the cue and therefore were already monitoring the ports (for details and behavioral data, see Ref. 61).

Amperometric recordings of cholinergic activity in the medial PFC indicated phasic signals evoked by cues that were detected, but not in trials involving missed cues.[61] Before further analyzing the timing and properties of these phasic signals, it should be noted that port approach, reward delivery, and reward retrieval did not confound and in fact did not generate phasic cholinergic signals (for a description of the multiple analyses and experiments substantiating this conclusion, see Ref. 61, including the Supplemental Materials).

FIGURE 1 depicts the averages ($\pm$ SEM) of cholinergic signals recorded from six animals during trials involving cue detection. Cholinergic signals are shown locked to the cue (FIG. 1A), the time of the peak amplitude (FIG. 1B), and the onset of the cue-evoked behavioral onset. Because of the variable timing of the cholinergic signal peak, the cue-locked presentation (FIG. 1A) suggests a broader, more lasting increase in cholinergic activity then apparent when inspecting individual spaces. Reflecting that this is the case, the peak-amplitude-locked depiction of these data (FIG. 1B) indicates a much tighter, bell-shaped distribution of cue-evoked cholinergic transients. The bottom graph indicates that the detected cue-evoked increase in cholinergic activity precedes the onset of the behavioral response. To reiterate, and as described in Parikh *et al.*,[61] such transients were not observed during trials in which the cue was not detected and although reward delivery-associated stimuli evoked postapproach and reward retrieval.

The onset of the cholinergic signal, defined as a 25% increase of precue levels, and the onset of the behavioral shift were highly correlated ($r = .79$). Furthermore, by the time reward was delivered, the cholinergic signals were already decaying. The time signals required to decrease by 50% from peak amplitude was 3.17 ± 0.27 s. Although we know that a significant

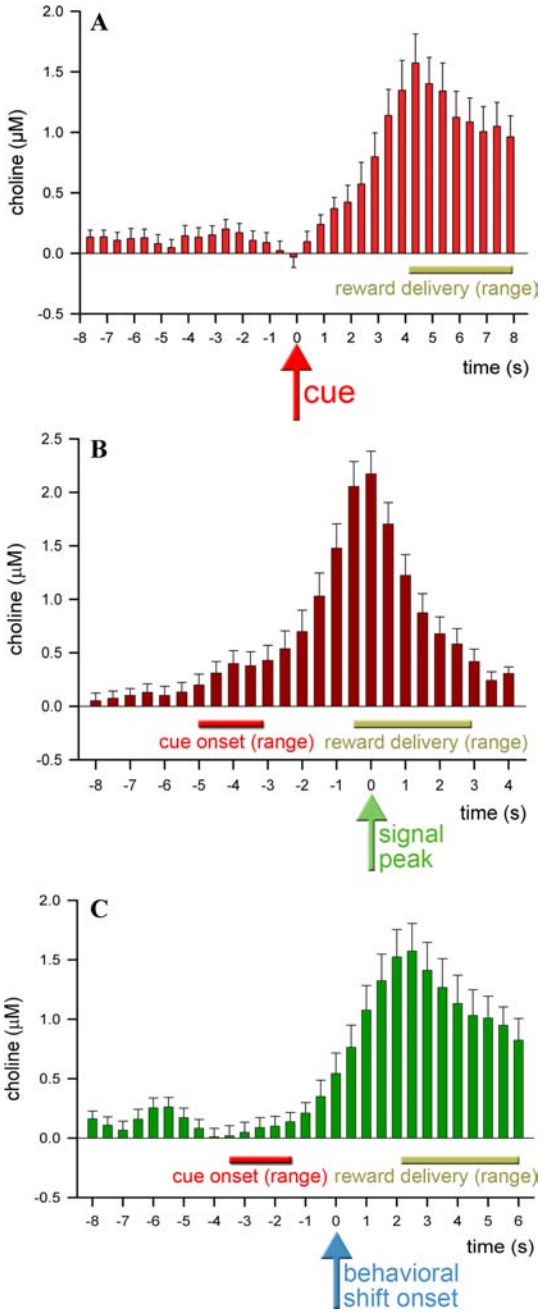

FIGURE 1. Cholinergic transients recorded in the medial PFC of rats performing a cued appetitive response task. The graphs depict cholinergic activity during trials involving cue detection (for the absence of increases in cholinergic activity during trials involving missed cues, and for details concerning the generation of the data shown in this figure, see Ref. 61). Following a light cue, reward was delivered 6 ± 2 s later at one out of two food ports. The *top graph* is taken from Reference 61 (reproduced with permission from Elsevier) and shows cholinergic activity locked to the cue. The relatively broad and persistent elevation of cholinergic activity reflects the variable peak time of cholinergic activity. Therefore, the *middle graph* (**B**) depicts the same data locked to the signal peak, indicating a tighter and more symmetric distribution of cue-evoked cholinergic activity. The *bottom graph* (**C**) plots these data locked to the onset of the cue-evoked shift in behavior, typically from grooming to port monitoring. This illustration indicates that increases in cholinergic activity coincide with and, in fact, precedes the onset of cue-evoked shifts in the animals' attention.

proportion of the decay rate of cholinergic signals reflects the capacity of the high-affinity choline transporter,[60] the decay rates observed in performing animals likely reflect diminishing ACh release.

Additional experiments, described in Reference 61, indicated that variation in the time interval between cue and reward delivery caused variation of the timing of the peak amplitude of cue-evoked cholinergic signals. This was an important observation, as it indicates that cholinergic transients do not merely reflect a postsensory epiphenomenon of the cue. If that was the case, variations of cue–reward intervals should not affect the timing of the cholinergic transients. The variation of the timing of cue-evoked cholinergic transients indicates that they are associated with a cognitive operation—cue detection—the timing of which is a function of cue–reward intervals.

We also demonstrated that bilateral removal of cholinergic inputs to the medial PFC decreased the rate of cue detection. Although this finding supports the necessity of the cholinergic input system for cue detection and suggests that cholinergic transients represent an essential mediator of cue detection, the effects of the cholinergic deafferentation on detection rate remained moderate and were transient. This result is in striking contrast to the robust and persistent impairments in the performance of more defined operant tasks for the measurement of attention,[40,62,63] and may reflect the limited demands on attention by the cued appetitive response task. Moreover, prefrontal cholinergic inputs are particularly active during challenges on performance involving the recruitment of top-down mechanisms (Refs. 40, 62, and 63), and therefore the limited effects of the deafferentation also reflects the absence of such demands on increased attentional effort while performing the cued appetitive response task.

To test the hypothesis that the cholinergic control of cue detection represents a specific function of the PFC, we recorded cholinergic activity in a neocortical control region, the motor cortex (forepaw region). This nonassociational region was selected because it cannot be excluded that cholinergic inputs to other associational regions, particularly the posterior parietal cortex, are directly influenced by and complement the cognitive functions of cholinergic inputs to the medial PFC.[64,65] Neither detected nor missed cues, nor any other task-related event, evoked reliable and robust cholinergic transients in the motor cortex. Additionally, and as would be expected, removal of cholinergic inputs to motor cortex did not affect the animals' performance of the cued appetitive response task. Thus, this finding indicates a clear dissociation between the role of cholinergic transients in medial PFC and motor cortex. The putative functions of cholinergic transients in the motor cortex remain unknown, but may contribute to the learning of fine motor skills.[66,67]

Tonic Cholinergic Activity and Attentional Performance

In addition to cue-evoked cholinergic transients we also observed, on a scale of tens of seconds, trends in cholinergic activity that occurred precue and predicted subsequent cue detection or misses and, on a scale of minutes, increases in cholinergic activity that began with the onset of the session and lasted throughout the session.[61] Since the role of the former remains poorly understood, we will focus on the nature and function of session-based tonic cholinergic activity.

These minute-based increases in fluctuations in cholinergic activity (FIG. 2) were not observed in trained animals that were placed into test chambers, but that were not allowed to perform. Therefore, tonic cholinergic activity was not evoked by the performance context and associated cognitive and motivational states and expectations. Rather, tonic changes represent, necessarily, a correlate of performance. Moreover, such tonic changes were observed in medial PFC and motor cortex, and therefore are hypothesized to manifest cortexwide (FIG. 2).

The functional contributions of these tonic changes to performance are not clear. On the one hand, a significant positive correlation between tonic signal levels and the amplitudes of cue-evoked cholinergic transients corresponds with the speculation that the level of tonic cholinergic activity modulates the general efficacy of cortical information processing. As already mentioned, the amplitude of the transients correlated with response latency, suggesting that indirectly, tonic levels likewise contribute to cue-evoked shifting in attention, processing of response rules, and, generally, cue-evoked behavioral operations. On the other hand, lesions of the cholinergic input to the motor cortex, which in fact spread dorsally and ventrally beyond the primary motor region, did not affect the animals' behavior. It is possible that these session-related, cortexwide tonic changes in cholinergic activity act in concert with other ascending arousal systems[68] to foster and maintain a general readiness for cortical information processing and that therefore the removal of individual contributions to "background" tonic activity has limited functional consequences. This view also corresponds with the observation that in order to disrupt attention performance by cortical cholinergic deafferentation, relatively extensive removal of

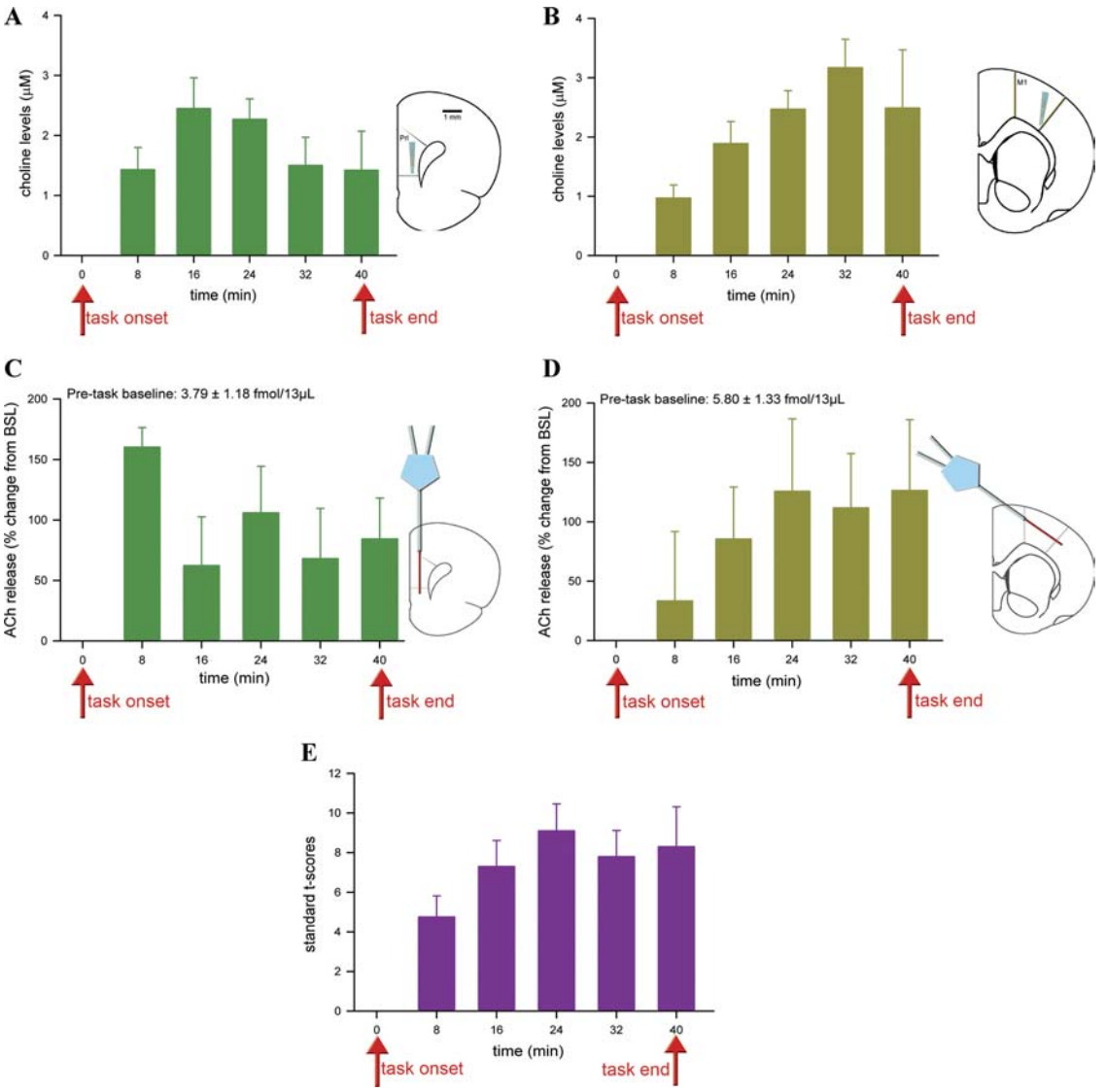

FIGURE 2. Performance session-related changes in ACh release determined by using amperometry (**A,B**) or microdialysis (**C,D**) in the medial prefrontal cortex (PFC) (**A,C**), or motor cortex (**B**,**C**) in animals performing the cued appetitive response task (taken from the supplemental materials;[61] reproduced from Parikh *et al.*[61] with permission from Elsevier). In both cortical regions and as measured by both methods, performance was associated with increases in cholinergic activity. In order to compare the data generated by two different methods, amperometric measures were expressed against a 3-min pretask baseline and averaged over 8-min blocks to match the dialysate collection intervals. Furthermore, data from both methods were transformed to indicate dimension-free expression of performance-associated changes in cholinergic activity. The analysis of these data indicated that session-related increases in cholinergic activity neither differed between the two cortical regions nor between the two methods, and there were no interactions between methods, regions, and time blocks. (**E**) Based on the absence of significant differences, this graph depicts transformed data averaged over the two regions and methods, and plotted by time block. Collectively, these results suggest that session-related (or tonic) increases in cholinergic activity may occur cortexwide and can be measured with both methods (microdialysis and amperometry).

cholinergic inputs from greater parts of the cortex is required to produce robust and persistent impairments in performance.[69] This is in striking contrast with the attentional performance under challenging conditions, such as during the presence of a distractor. Even moderate and highly restricted cholinergic deafferentation of the medial PFC increases the detrimental effects of distracters (Young, Howe, Parikh, and Sarter,

unpublished observations). We do not yet know whether the critical role of medial PFC cholinergic inputs in such conditions (see, also, Ref. 70) manifests with respect to transients and/or tonic cholinergic activity. As already mentioned, we know that increases in attentional effort evoked augmented increases in medial PFC cholinergic activity measured by using microdialysis.[50,51] However, the interactions between tonic and phasic cholinergic activity in the PFC and elsewhere in the cortex in the mediation of increases in attentional effort remain to be studied.

Tonic Cholinergic Activity: Interpretation of Acetylcholine Release Measured by Microdialysis

The pattern of these session-related changes in cholinergic activity resembled performance-associated ACh release measured by microdialysis in animals performing operant attention tasks. Therefore, we also measured ACh release in the medial PFC and motor cortex in animals performing the cued appetitive response task and treated the amperometric and microdialysis data so that their temporal resolution was identical and that statistical comparisons could be conducted. This analysis substantiated that there was no difference between tonic changes recorded using choline-selective microelectrodes and microdialysis. Furthermore, there were no regional differences. In other words, both methods recorded the same type of cholinergic activity in mPFC and motor cortex (FIG. 2).

This finding clarifies the component of ACh release measured by microdialysis, and therefore assists greatly in interpreting data from studies using this method. *In vivo* microdialysis studies measure performance-related changes in tonic cholinergic activity, on a scale of minutes. As tonic cholinergic activity did not differ between mPFC and motor cortex, this measure does not appear to be influenced by phasic signals that occurred only in medial PFC.

It should be reiterated that the functional significance of tonic changes remains unclear. As already mentioned, experiments using microdialysis revealed that levels of ACh release in task-performing animals reflect demands on attention effort, as opposed to levels of performance.[50,51,61] Thus, this measure is appropriately sensitive to variations of a fundamental cognitive determinant of attentional performance. While our prior experiment has substantiated the necessity of PFC cholinergic activity for the cue-detection processes, an exploration of the relative contributions of phasic versus tonic cholinergic changes requires experimental approaches that involve the individual manipulation of cholinergic signals at different timescales. It is entirely unclear, at this point, how this could be achieved. Collectively, the available evidence and these considerations suggest that studies employing microdialysis will continue to make important contributions to the analysis of cholinergic function, specifically and exclusively of the tonic component of cholinergic neurotransmission.

Neuronal Circuitry Orchestrating Phasic Versus Tonic Cholinergic Signals in the Medial Prefrontal Cortex

Our evidence collectively indicates that attentional performance-related cholinergic activity manifests on at least three timescales: cue-evoked transient of phasic signals on the scale of seconds; precue trends predicting cue detection or misses on the scale of tens of seconds; and session-based tonic changes on the scale of minutes. This evidence is consistent with conceptualizations that assume the presence of multiple cholinergic modules and a regulation of cholinergic activity in modality- and cortical area-specific manner.[71] However, the anatomical characteristics of the basal forebrain cholinergic efferent projections and basal forebrain afferent circuitries do not readily reveal the presence of such highly topographically organized modules or subdivisions.[11,23,25] Therefore, we can only speculate about the afferent systems that contribute to the manifestation of phasic and tonic cholinergic activity in the medial PFC.

Cue-evoked cholinergic transients, observed in trials in which the cue was detected, can be considered top-down signals for the following reasons. Cholinergic signals do not indicate the presence or absence of the cue in the sensory processing stream; even in trials in which the cue was missed, it is extremely likely that it did not enter this stream. This view is also supported by the observation that in missed-cue trials, animals exhibited a very short fluctuation in the grooming sequences in response to the cue, but continued, by definition, to engage in grooming behavior, as opposed to orienting toward, and switching orientation between, the food ports. Thus, the signal indicates and mediates the incorporation of the cue into ongoing behavioral and cognitive processes and the cue's subsequent control of the animals' behavior. Successful cue detection is a function of the subjects' readiness for input processing, including the allocation of attentional resources for the suppression of competing, task-irrelevant cognitive and behavioral activities and for the processing of

inputs expected within a given time frame and spatial location. Therefore, misses presumably reflect a low readiness for input processing and/or the failure to suppress competing associational activity and to switch PFC circuitry to input processing. It follows that in tasks involving highly practiced conditioned responses and the presentation of invariant cues, missed cues are not a function of the physical properties of the cue, but indicate phenomena described as inattentional blindness or attentional lapses.[72,73]

Top-down regulated cholinergic signals are likely to be a result of local prefrontal innervation of cholinergic terminals and the direct and indirect modulation of basal forebrain cholinergic projections to the medial PFC via direct prefrontal projections to the basal forebrain or via limbic stations, particularly the NAc. The NAc has privileged access to medial PFC cholinergic inputs.[74,75] Indeed, it is intriguing to speculate that phasic dopamine signals recorded in the NAc in response to cues predicting reward[76] contribute, via NAc projections to the basal forebrain, to the manifestation of cue-evoked prefrontal cholinergic transients. Thereby, reward prediction may be integrated with prefrontally controlled attentional shifts and response processing, collectively giving rise to the cholinergically mediated detection of cues. Research on the role of the PFC local or long-loop efferent projections, which contribute to the manifestation of cholinergic transients, may also deliver the experimental tool to selectively modulate transients without affecting tonic cholinergic activity (see earlier in this chapter).

The neuronal mechanisms regulating performance session-related levels of tonic cholinergic activity cortexwide are even less clear. Since tonic activity manifests in response to performance, and is not evoked by exposure to the training environment, it may reflect an interaction between telencephalic and brainstem projections recruiting the basal forebrain. It is intriguing to speculate that because of the cortexwide presence of tonic changes, an ascending neuronal system with access to all cortical regions and demonstrated influence on basal forebrain cholinergic neurons, particularly the ascending noradrenergic system,[77,78] is critically involved in the generation of minute-based changes in cortical cholinergic activity. Given the highly collateralized organization of noradrenergic projections, volume transmission of noradrenaline, and evidence indicating noradrenergic control of basal forebrain cholinergic neurons,[79] cholinergic activity may be profoundly influenced by noradrenergic afferents from the LC. The findings that cortical-evoked potentials involving noradrenergic activation are abolished by removal of basal forebrain cholinergic neurons[80] or by blocking noradrenergic $\alpha 1$ receptors in the basal forebrain,[81] confirm the potential significance of such noradrenergic–cholinergic interactions. These noradrenergic–cholinergic interactions could be at the core of Yu and Dayan's[82] postulated roles of the two neuronal systems in the mediation of different levels of uncertainty about the stimulus situation.

Attention and Multiple Cholinergic Signaling Modes: Translational Significance

The finding that prefrontal cholinergic transmission entails phasic and tonic modes to encode specific cognitive operations have major implications for our understanding of the role of cholinergic dysfunction in the development of the cognitive symptoms of neurodegenerative and neuropsychiatric disorders, and for drug development strategies focusing on the restoration or modulation of a dysregulated cholinergic transmission. Attentional impairments are core components of the cognitive deficits in schizophrenia[83] and contribute to the disruption of filtering capacities and attentional resource management in these patients. Dysregulation in forebrain cholinergic systems[84] has been hypothesized to contribute essentially to the attentional symptoms of schizophrenia. While prior theories concerning the role of transmitter abnormalities in cognitive disorders were largely confined to considerations about abnormally high or low levels of neurotransmitters (for a review of this issue, see Ref. 85), the demonstration of cholinergic signals manifesting on multiple timescales forms the basis for strikingly more sophisticated speculations about the escalating cognitive consequences of perhaps relatively minor abnormalities in the temporal orchestration, rise time, and decay dynamics of cholinergic transients, or concerning interactions between signal dynamics over seconds, tens of seconds, and minutes, respectively. It is obvious that we have extremely little knowledge about the type and nature of abnormalities in neuromodulator systems and their interactions[68] in schizophrenia, and much needed insights will come from research by recording cholinergic signals in animal models. Likewise, the dynamic properties of cholinergic neurons in patients with mild cognitive impairment or early Alzheimer's disease is quite unclear,[86] although such information appears to be of crucial importance for efforts to develop cognition enhancers. Because cholinergic mechanisms are likely to represent primary targets in such efforts or are necessarily involved in the downstream effects of

cognition enhancers acting primarily in noncholinergic systems, such efforts will have to characterize and discriminate between drug effects on phasic versus tonic components of cholinergic neurotransmission.

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Competing Interest

The authors declare no competing interest.

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