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Invited Review

# What do phasic cholinergic signals do?

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ABSTRACT

In addition to the neuromodulatory role of cholinergic systems, brief, temporally discrete cholinergic release events, or "transients", have been associated with the detection of cues in attention tasks. Here we review four main findings about cholinergic transients during cognitive processing. Cholinergic transients are: (1) associated with the detection of a cue and influenced by cognitive state; (2) not dependent on reward outcome, although the timing of the transient peak co-varies with the temporal relationship between detection and reward delivery; (3) correlated with the mobilization of the cue-evoked response; (4) causal mediators of shifts from monitoring to cue detection. We next discuss some of the key questions concerning the timing and occurrence of transients within the framework of available evidence including: (1) Why does the shift from monitoring to cue detection require a transient? (2) What determines whether a cholinergic transient will be generated? (3) How can cognitive state influence transient occurrence? (4) Why do cholinergic transients peak at around the time of reward delivery? (5) Is there evidence of cholinergic transients in humans? We conclude by outlining future research studies necessary to more fully understand the role of cholinergic transients in mediating cue detection.



## 1. Introduction

Cholinergic neurons originating in the nucleus basalis of Meynert, substantia innominata and the diagonal band (henceforth termed basal forebrain; BF) project to virtually all cortical areas and layers. In the last decade, anatomical research has greatly revised traditional views about the organization of this projection system. Long-held notions of a "diffuse" or "reticular" projection system have been replaced by descriptions of BF cholinergic cell clusters, cluster-specific dendritic organization, and a highly topographic organization of BF cholinergic projections (Zaborszky, Csordas, et al., 2015; Zaborszky, Duque, et al., 2015; Zaborszky, van den Pol, & Gyengesi, 2012). Important anatomical aspects of this projection system remain undetermined and even disputed, such as the organization of inputs to individual BF cell clusters, the synaptic space of individual BF neurons, and the ultrastructural characteristics of cholinergic synapses and the identity of their neuronal targets. However, future research is expected to reveal the circuit-specificity of the organization of individual BF cells, which would reject notions of redundancy, overlap and diffuseness in the organization of the BF cholinergic projection system. The anatomical descriptions of other putatively "diffusely" organized ascending projection systems originating in brain stem have the potential to follow suit and undergo a similar revision (e.g., Helboe, Egebjerg, & de Jong, 2015; Schwarz & Luo, 2015).

A similar evolution is taking place in the description and conceptualization of presynaptic cholinergic signaling. The traditional focus on slow and regionally non-specific changes in extracellular and extrasynaptic (or "volume-transmitted") "ambient" basal acetylcholine (ACh) levels (for review see Sarter, Parikh, & Howe, 2009) has been challenged by our more recent demonstration of regionally-specific phasic cholinergic signaling in cortex ("cholinergic transients"; below). The present review focuses on those transients, though it should be noted that the larger body of evidence supports a multi-modal, multi-timescale view of cholinergic function. That is, in addition to the transients, cholinergic terminals also support a more canonical neuromodulatory component of cholinergic neurotransmission, varying perhaps at the scale of tens of seconds to minutes and being particularly active in association with demands on attentional control (e.g., St Peters, Demeter,

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Lustig, Bruno, & Sarter, 2011). Interactions between cholinergic neuromodulation and transients are discussed in Sarter, Lustig, Howe, Gritton, and Berry (2014) and Sarter (2015). Importantly, the neuromodulatory and transient components of cholinergic neurotransmission are dissociable. The modulatory component, measured by microdialysis, can be relatively high while cholinergic transient frequencies are relatively low, rejecting the possibility that methodological (i.e., analytical) limitations have confounded the conclusion that a cholinergic neuromodulatory component is present. In other words, ACh levels in minute-based dialysate collections are unlikely to represent integrated transients (for more discussion of measurement issues see Sarter & Kim, 2015). Below we will focus on the functions of cholinergic transients.

## 2. Cholinergic transients: technical and conceptual origins

The measurement scheme underlying choline-sensitive amperometric biosensors and their potential usefulness for the neurosciences has long been proposed (e.g., Garguilo & Michael, 1994, 1996; Kawagoe, Niehaus, & Wightman, 1991). However, not until the work of Gerhardt and colleagues were sensors available with adequate sensitivity and responsivity, as well as ceramic bases equipped with multiple recording sites that afford important analytical control measurements (Burmeister, Moxon, & Gerhardt, 2000; Parikh et al., 2004). Our original interest in searching for phasic cholinergic responses was largely based on the observation that acetylcholinesterase (AChE) has one of the highest catalytic powers ever reported for an enzyme (Quinn, 1987). Thus, contrary to the traditional slow neuromodulatory conceptualization of cholinergic function, cholinergic synapses appear to be specifically suitable for rapid, highly phasic and spatially selective synaptic signaling. Although the regulation of AChE remains poorly understood (e.g., Dobbertin et al., 2009), results from our experiments using sensors with choline oxidase and AChE co-immobilized onto recording sites suggest that even after large and likely non-physiological ACh release events *in vivo*, endogenous AChE hydrolyzes all detectable ACh so rapidly that the process cannot be detected (Giuliano, Parikh, Ward, Chiamulera, & Sarter, 2008). For this reason, choline currents, measured with amperometry and biosensors, have been interpreted as indicating newly released ACh, although it is important to remain mindful that new insights into the regulation of AChE may complicate the interpretation of brain choline currents.

We originally hypothesized that phasic ACh release events (henceforth termed "transients") are associated with the detection of cues. "Detection" here concerns a cognitive process as defined by Posner and colleagues. It is worth quoting their full definition because of the important distinction made between detection and orienting: "By *detection*, we will mean 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. We mean to distinguish detection in this sense from more limited automatic responses that may occur to the event. *Orienting*, as we will use the term, involves the more limited process of aligning sensory (e.g., eyes) or central systems with the input channel over which the signal is to occur. Thus it is possible to entertain the hypothesis that subjects may orient toward a signal without having first detected it. This would mean simply that the signal was capable of eliciting certain kinds of responses (e.g., eye movements or shifts of attention) but has not yet reached systems capable of generating responses not habitual for that type of signal" (Posner, Snyder, & Davidson, 1980, p. 162). Thus, detection involves execution of a previously acquired response to a cue (or signal). For example, monitoring traffic lights and orienting towards the switch to green *per se* does not constitute detection. However, using this signal (the switch to green) to activate the signal-associated response rule ("go") and executing it fulfills this definition.

This definition appears almost hopelessly complex as it encompasses steps ranging from perception to working memory operations, response preparation and response execution. However, signal–response relationships need to be established, and outcomes need to be integrated into this associative framework in order to increase the efficacy of subsequent detection operations and facilitate the revision of response selection based on the results of previous choices. To extend Posner's definition to encompass the entirety of processes described above: ***By detection, we mean the entirety of information concerning the presence of a signal into a system that allows the subject to report the existence of the signal (or cue) by an arbitrary response specified by the experimenter, and that provides feedback about the adequacy/accuracy of the response based on response outcome***.

Our original hypothesis that cholinergic transients mediate signal detection was derived from the effects of selective lesions of the cortical cholinergic input system on detection performance. In this research in rodents (McGaughy & Sarter, 1995; St Peters, Cherian, Bradshaw, & Sarter, 2011), and later also in humans (Demeter, Sarter, & Lustig, 2008), we have used a task, originally designed as a sustained attention task (SAT), that consists of a random sequence of signal (with variable salience) and nonsignal trials, each of which requires the reporting of the presence or absence of the signal via separate response keys. In signal trials, reporting the signal is a "hit" and leads to reward while reporting that there was no signal ("miss") leads to no reward and triggers the intertrial interval (ITI). In nonsignal trials, operating the no-signal response key is counted as a "correct rejection" and rewarded, while claiming that a signal was present ("false alarm") is not. Importantly, the SAT rewards both signal- and non-signal-linked responses. As we discuss below, this eliminates the possibility that cholinergic transients encode reward *per se*. The cognitive and perceptual demands of SAT are optimized by successive (as opposed to simultaneous) discrimination, event asynchrony, and variable event rate and signal saliency (Davies & Parasuraman, 1982).

Following immunotoxin-induced selective lesions of BF cholinergic cell groups projecting to cortex, rats permanently missed the majority of signals, with only ~30% residual hits regardless of signal duration. In contrast, their correct rejection rate remained high (~80%) and unaffected (McGaughy, Kaiser, & Sarter, 1996). This finding indicates the necessity of cholinergic activity for signal detection but it does not identify the essential component of cholinergic neurotransmission (neuromodulatory or transient). Halorhodopsin photoactivation-induced silencing of cholinergic activity specifically during signal presentation reproduced the effects of cholinergic lesions (Gritton et al., 2016). This suggests that the primary cause of signal detection impairments in lesioned animals was the absence of cholinergic transients.

## 3. Cholinergic transients during signal detection performance

Because amperometric recordings of choline currents are in the low pA-range, our initial experiments designed to record currents during signal detection necessitated the use of a simplified cued appetitive response task that could be performed in an environment devoid of devices that generate electrostatic energy (Parikh, Kozak, Martinez, & Sarter, 2007). Rats were trained to respond to a signal by approaching two response ports for retrieval of the reward. Detection was defined as orienting towards the signal *and* approaching the ports. If signals failed to elicit food port approach these trials were counted as a miss. Trials were separated by 90 ± 30 s. During misses, brief orienting responses, triggered by