

Noncholinergic Neurons in the Basal Forebrain: Often Neglected but Motivationally Salient

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Although noncholinergic neurons in the basal forebrain are known to contribute to cognition, their response properties in behaving animals is unclear. In this issue of *Neuron*, Lin and Nicolelis demonstrate that these neurons represent the motivational salience of sensory stimuli and may modulate cortical processing to direct top-down attention.

Directing attention to relevant sensory stimuli is critical for survival because attention can facilitate perception, learning, and action. But what makes a sensory stimulus relevant? One property that clearly contributes is the motivational salience of a stimulus; if a stimulus either predicts a reward or punishment, or if it is reinforcing in and of itself, by definition the stimulus may be labeled motivationally salient. Therefore, understanding how the brain represents motivationally salient stimuli may be fundamental to understanding the top-down control of attention. In principle, the brain need not explicitly encode motivational salience at the level of single neurons, as appetitive and aversive brain circuits could independently influence mechanisms for attention. Alternatively, individual neurons could represent motivational salience per se, and this response property could arise from the convergence of information carried by appetitive and aversive systems. Until recently, relatively few studies examined single-neuron response properties in the context of both rewards and punishments; progress on understanding the relationship between motivational salience and attention has therefore been limited. In this issue of *Neuron*, Lin and Nicolelis (2008) push the field forward by examining the neural responses properties of an oft-neglected member of the basal forebrain—the noncholinergic neurons—in the context of rewards, punishments, and attentional performance.

A large body of evidence supports the idea that projections from the basal fore-

brain are important for modulating cortical excitability and influencing different types of attention (Everitt and Robbins, 1997). Prior experimental work in these brain regions has largely focused on the neocortical cholinergic projections, in part because the neurons of origin in the nucleus basalis of Meynert selectively degenerate in Alzheimer's disease (Whitehouse et al., 1982). Improved lesioning techniques with greater selectivity for cholinergic neurons have helped demonstrate that cholinergic projections to cortical and subcortical structures are important for attending to salient sensory stimuli (Everitt and Robbins, 1997). Importantly, attempts to integrate these newer results with those using less selective excitotoxins suggest that the noncholinergic neurons in the basal forebrain also play important roles in learning, memory, and attention (Everitt and Robbins, 1997). The noncholinergic neurons are comprised of GABAergic neurons as well as neurons with the capacity to synthesize glutamate (Gritti et al., 2006). These neurons are intermingled with cholinergic neurons, and a sizable fraction project to cortex in parallel with cholinergic neurons (Gritti et al., 1997). Indeed, the GABAergic corticopetal component is equivalent or larger than the cholinergic component, which itself constitutes only about 5% of this diverse basal forebrain neuronal population (Gritti et al., 2006).

Previous attempts to understand the physiological properties of the different cell types in the basal forebrain during natural behaviors have been hampered by the

inability to determine neurotransmitter identity. Recently, however, Lee and colleagues (2005) used juxtacellular recording to immunohistochemically identify neurons and showed that cholinergic neurons change firing rates dramatically across sleep-wake states. Lin and Nicolelis (2008) capitalize on this work to study the more abundant noncholinergic neurons by recording from neurons that do not change average firing rate across sleep-wake states. They examined the response properties of these noncholinergic neurons in behaving rats performing a Go/Nogo task. Notably, they used both appetitive (sucrose) and aversive (quinine) reinforcers in order to determine whether neural responses covaried with motivational salience or with positive or negative reinforcement value. The ability to distinguish between these two response properties relies on the fact that receiving negatively valued outcomes can be as behaviorally motivating (or salient) as positively valued outcomes. Thus, neurons encoding reinforcement value will respond in proportion to the appetitive or aversive value of particular outcomes, but neurons encoding motivational salience will respond similarly when outcomes are similarly salient, irrespective of reinforcer valence.

Lin and Nicolelis (2008) report that noncholinergic basal forebrain neurons encode motivational salience in their task. These neurons exhibited a short-latency phasic increase in firing rate following stimuli which predicted the potential outcome for each trial. Furthermore, this population of neurons showed similar

bursts irrespective of whether a Go response would result in an appetitive or an aversive outcome. Three findings argue strongly against the possibility that these neurons simply encode sensory properties: (1) these neural responses were similar whether the predictive stimuli presented were visual or auditory, (2) these neurons did not respond to novel sensory stimuli that had not yet been associated with reinforcement, and (3) extinction of the stimulus-reinforcer associations led to a marked reduction in the bursting responses. Taken together, these findings indicate that noncholinergic basal forebrain neurons respond to stimuli that have been associated with reinforcers of either valence.

One potential concern about the motivational salience hypothesis arises from the fact that the Go/Nogo task is an avoidance task. That is, rats that withheld licking in response to a tone associated with quinine did not receive the aversive reinforcer (cf. a Pavlovian task where reinforcers follow cues regardless of operant responses). Thus, in one sense, outcomes on trials where rats avoided punishment were relatively rewarding. Perhaps noncholinergic neurons encode reward value after all? [Lin and Nicolelis \(2008\)](#) addressed this question by comparing those trials where quinine was available and the rat made a Go or a Nogo response (presumably reflecting expectation of sucrose and quinine avoidance, respectively). The burst response of noncholinergic neurons in both these trial types was remarkably similar, suggesting that these neurons likely were not encoding expected reward value (which was presumably different for the two responses), but rather were encoding motivational salience. Further support for the salience hypothesis comes from the observation that neural responses to reinforcement delivery were similar for both appetitive and aversive outcomes themselves.

Neurons encoding properties more similar to motivational salience, as opposed to reinforcement value, have also been identified in a number of other brain areas, including the premotor cortex ([Roesch and Olson, 2004](#)) and the amygdala ([Belova et al., 2007](#)). However, the amygdala contains neurons appropriate for mediating valence-specific processes, like fear or reward learning, as well as

valence nonspecific processes, such as motivational salience, arousal, and attention ([Belova et al., 2007](#); [Paton et al., 2006](#)). Of note, the central nucleus of the amygdala has projections to the cholinergic neurons of the basal forebrain and to midbrain dopamine neurons, and these connections have been proposed to link amygdala processing to neural circuits implementing two different forms of attention: attention for performance and attention for learning ([Holland and Gallagher, 1999](#)).

Based on the short latency of the initial bursting response in noncholinergic neurons, [Lin and Nicolelis \(2008\)](#) suggest a role for these neurons in directing top-down attention toward salient stimuli that are consistently associated with reinforcement. They suggest that this form of attention corresponds to attention for performance, which facilitates well-learned behavioral responses to stimuli that reliably predict reinforcement outcomes ([Holland and Gallagher, 1999](#)). They provide evidence linking the encoding of motivational salience to attention for performance by showing that these same noncholinergic neurons respond when auditory stimuli are successfully detected but are silent when stimuli are missed in a tone-detection task performed near psychophysical threshold. Moreover, burst responses to tones increase with the degree to which a tone predicts reward. Thus, noncholinergic neurons may be involved in directing behavioral responses toward stimuli in proportion to their reward value (only rewards were used in the detection task). [Lin and colleagues \(2006\)](#) have previously shown that noncholinergic neurons burst during transient increases in gamma oscillations measured in the prefrontal cortex, suggesting a role in enhancing cortical excitability. In theory, this effect could be due to the GABAergic corticopetal projection to prefrontal cortex from the basal forebrain, providing a mechanism for the top-down control of attention for performance ([Sarter and Bruno, 2002](#)). In order to elucidate the precise mechanisms by which these noncholinergic neurons exert their effects, future work must characterize these neurons by neurotransmitter identity and determine whether they directly (as projection neurons) or indirectly (as interneurons) modulate prefrontal processing.

Attention for performance may be contrasted with attention for learning, in which attending to surprising outcomes (reinforcement prediction errors) can enhance the speed of learning. As noted above, evidence suggests that a neural circuit involving the central nucleus of the amygdala and cholinergic neurons in the basal forebrain plays a role in both attention for performance and learning ([Maddux et al., 2007](#)). One counterintuitive result presented by [Lin and Nicolelis \(2008\)](#)—suggesting that noncholinergic neurons may play a role in attention for learning—is the fact that noncholinergic neurons exhibit the greatest response to reinforcement when reinforcement follows a tone least predictive of reward (as judged by average detection performance) and the smallest response to reward occurs when reinforcement follows the tone most predictive of reward.

The pattern of activity in response to predictive stimuli and to rewards (described in the previous two paragraphs) is strikingly similar to the activity observed in midbrain dopamine neurons (e.g., [Fiorillo et al., 2003](#)), which is thought to reflect a temporal difference error in predictions of future reward. Dopamine neurons project to both cholinergic and GABAergic neurons in the basal forebrain ([Gaykema and Zaborszky, 1997](#)), which suggests that the expectation-modulated reinforcement responses that [Lin and Nicolelis \(2008\)](#) observed may actually reflect reward prediction errors. Using behavioral paradigms employing aversive stimuli, it will be important to establish whether the activity of noncholinergic neurons is also correlated with punishment prediction errors, a result that [Lin and Nicolelis](#) might predict given their data suggesting that noncholinergic responses are correlated with motivational salience and not reinforcement value. This result would imply that noncholinergic neurons provide an unsigned prediction error, which is a signal that could facilitate the deployment of attention for learning. Indeed, even when performing a well-learned detection task that presumably engages attention for performance, rats may in fact continually adjust their behavior to update associations in accord with recent reinforcement history, a process that likely engages attention for learning.

Historically, basal forebrain lesions have been carried out using toxins that destroyed noncholinergic neurons in addition to cholinergic neurons. These lesions resulted in a broad array of learning and memory deficits, which for the most part are not observed when lesions are made using toxins targeting cholinergic neurons and sparing noncholinergic neurons (Everitt and Robbins, 1997). The novel contribution from Lin and Nicolelis (2008) reminds us that the often-neglected noncholinergic neurons of the basal forebrain may play a fundamental role in signaling motivational salience, which may be useful for directing top-down attention. Their results open a new avenue of research that promises to help unravel the mechanisms that link the processing of appetitive and aversive stimuli

to different forms of attention during learning and action.

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Cerebral and Peripheral Amyloid Phagocytes— an Old Liaison with a New Twist

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In this month's issue of *Nature Medicine*, Town et al. suggest that peripheral macrophages invading the brain reduce cerebral amyloidosis and thus may play a key role in the pathogenesis of Alzheimer's disease (AD). This observation intensifies the longstanding controversy of whether mononuclear cells such as macrophages and/or microglial cells are beneficial or detrimental in AD.

The current discussion is already some twenty years old: It was Henryk Wisniewski who argued that microglia in culture but not in vivo can phagocytose β -amyloid fibrils. His conviction was based on ultrastructural observations in Alzheimer's disease (AD) brains revealing an intimate relationship of β -amyloid plaques with microglia, which were, however, never found to harbor β -amyloid fibrils within their lysosomal compartments. In contrast, Wisniewski and colleagues described phagocytosed β -amyloid fibrils in macrophages of elderly patients suffering from fatal stroke—a rare complication in AD,

which certainly does not represent the usual course of disease (Wisniewski et al., 1991; Frackowiak et al., 1992).

During development, myeloid cells invade the brain and differentiate into microglia. Resident microglia in the adult brain are thought to monitor their local environment and—in contrast to their peripheral counterparts, namely monocytes and extraneural tissue macrophages, which are rapidly and efficiently repopulated (Kennedy and Abkowitz, 1998)—resident microglia appear to have a rather slow turnover (Asheuer et al., 2004; Priller et al., 2001).

In the brains of AD patients as well as the respective transgenic mouse models, microglia become activated and increase in number in response to cerebral β -amyloidosis. The extent to which peripheral macrophages/monocytes contribute to this amyloid-associated microgliosis and its significance for AD remains unclear (Wyss-Coray, 2006).

In the current issue of *Nature Medicine*, Town and colleagues (2008) crossed CD11c-DNR mice, in which TGF- β -Smad2/3 signaling is blocked in CD11c⁺ cells, to two distinct and widely used amyloid precursor protein (APP) transgenic