Mini-Symposium

Optogenetic Dissection of the Basal Forebrain Neuromodulatory Control of Cortical Activation, Plasticity, and Cognition

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The basal forebrain (BF) houses major ascending projections to the entire neocortex that have long been implicated in arousal, learning, and attention. The disruption of the BF has been linked with major neurological disorders, such as coma and Alzheimer's disease, as well as in normal cognitive aging. Although it is best known for its cholinergic neurons, the BF is in fact an anatomically and neurochemically complex structure. Recent studies using transgenic mouse lines to target specific BF cell types have led to a renaissance in the study of the BF and are beginning to yield new insights about cell-type-specific circuit mechanisms during behavior. These approaches enable us to determine the behavioral conditions under which cholinergic and noncholinergic BF neurons are activated and how they control cortical processing to influence behavior. Here we discuss recent advances that have expanded our knowledge about this poorly understood brain region and laid the foundation for future cell-type-specific manipulations to modulate arousal, attention, and cortical plasticity in neurological disorders.

Key words: **nucleus basalis; GABAergic; reinforcement; reward timing; cortical state; motivational salience**

Significance Statement

Although the basal forebrain is best known for, and often equated with, acetylcholine-containing neurons that provide most of the cholinergic innervation of the neocortex, it is in fact an anatomically and neurochemically complex structure. Recent studies using transgenic mouse lines to target specific cell types in the basal forebrain have led to a renaissance in this field and are beginning to dissect circuit mechanisms in the basal forebrain during behavior. This review discusses recent advances in the roles of basal forebrain cholinergic and noncholinergic neurons in cognition via their dynamic modulation of cortical activity.

Introduction

The basal forebrain (BF) contains multiple major ascending arousal systems that promote wakefulness, awareness, and cortical low-voltage fast activity (Moruzzi and Magoun, 1949; Semba, 2000; Zaborszky, 2002; Jones, 2003, 2004; Brown et al., 2012; Zaborszky et al., 2015). The BF has also long been implicated in cognitive functions, including attention, learning, and motivational salience (DeLong, 1971; Richardson and DeLong, 1990; Wilson and Rolls, 1990a; Voytko et al., 1994; Voytko, 1996; Lin and Nicolelis, 2008). The degeneration of the BF is an early event in Alzheimer's disease (Whitehouse et al., 1982; Grothe et al., 2012) and forms of dementia (Cummings and Benson, 1984) and is associated with normal cognitive aging (Gallagher and Colombo, 1995). Deep brain stimulation targeting the BF is being evaluated as a novel therapy for dementia-related disorders (Freund et al., 2009; Hescham et al., 2013; Salma et al., 2014).

The BF is an extended structure situated at the base of the brain and classically defined by the presence of clusters of large cholinergic neurons (Meynert, 1872), which are found in the medial septum

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(Ch1), the vertical (Ch2) and horizontal (Ch3) limbs of the diagonal band, as well as in the substantia innominata/nucleus basalis (NB) (Ch4; Mesulam et al., 1983). These regions provide ascending projections to the hippocampus, thalamus (Parent et al., 1988; Jourdain et al., 1989; Bickford et al., 1994; Gritti et al., 1998), amygdala (Unal et al., 2015), and neocortex (Zaborszky et al., 2015), as well as descending projections to the hypothalamus (Gritti et al., 1994). Here we focus on recent optogenetic studies conducted by the authors that targeted the Ch3/Ch4 regions and their projections to the neocortex. We note that other recent studies also addressed postsynaptic cell-type-specific mechanisms of cholinergic activation in the cortex (Arroyo et al., 2012; Bennett et al., 2012; Saunders et al., 2015) and important subcortical projections (Unal et al., 2015) that our review does not cover.

Although the BF is best known for, and often equated with, acetylcholine-containing neurons that provide most of the cholinergic innervation of the neocortex (Jones, 2004), it actually contains projection neurons with a diversity of neurotransmitters. In addition to cholinergic neurons, the BF houses two other, parallel projection systems to the cortex, one releasing GABA and the other glutamate as their main neurotransmitter (Mesulam and Van Hoesen, 1976; Brashear et al., 1986; Freund and Gulyás, 1991; Freund and Meskenaite, 1992; Gritti et al., 1993; Hur and Zaborszky, 2005; Henny and Jones, 2008). The anatomical heterogeneity and cell-type diversity of the BF have hampered research into how it functions. The availability of new transgenic mouse lines to specifically target cholinergic, GABAergic, and glutamatergic BF projections is rapidly changing the field (Hippenmeyer et al., 2005; Rossi et al., 2011; Vong et al., 2011; Zhao et al., 2011). When used together with other technological advances, such as optogenetics and pharmacogenetics, these new mouse lines have allowed researchers to perform critical experiments that could only be dreamt about until recently (Boyden et al., 2005; Zhang et al., 2007; Nawaratne et al., 2008).

In this review, we aim to provide an overview of recent advances grouped around three major topics. First, although the role of the BF in cognitive functions has long been associated with its cholinergic modulation, until recently it has not been possible to determine when and how cholinergic BF neurons are specifically activated in behavior. Second, although the study of the BF has traditionally focused on cholinergic neurons, cortical projections from the BF contain equally if not more prominent noncholinergic components, and their functions are poorly understood. Third, the circuit mechanisms by which cholinergic and noncholinergic BF neurons dynamically modulate cortical activity to mediate cognitive functions remain unclear. Together, these new studies advance our understanding of the BF and begin to reveal the rich temporal dynamics and diverse functions served by distinct components of this neuromodulatory hub. We begin with new studies focused on the BF cholinergic projection and then move on to discuss noncholinergic BF neurons.

BF cholinergic neurons are activated by reward and punishment with remarkable speed

Most of our knowledge about central cholinergic function in cognition has come from lesions and pharmacological studies (Everitt and Robbins, 1997; McGaughy et al., 2000; Hasselmo and Sarter, 2011). However, when are cholinergic neurons recruited during behavior and what cognitive variables do they signal? Progress in answering this long-standing question has been stalled by the lack of tools for cell-type-specific recordings. A handful of identified cholinergic neurons have been recorded across sleep–wake states using a juxtacellular approach with *post hoc* identification, a challenging technique that is difficult to combine with behavior (Lee et al., 2005; Hassani et al., 2009). Unfortunately, cholinergic neurons cannot be identified definitively using extracellular recordings based on anatomical landmarks, pharmacological approaches, or distinct action potential waveforms. As a consequence, until recently, there have been no recordings of identified BF cholinergic neurons in behaving animals. This challenge was taken up in a recent study that used optogenetics-assisted cell-type identification to extracellularly record cholinergic neurons (Hangya et al., 2015).

To determine which aspects of cognition cholinergic activity might support, these authors trained mice on an auditory detection task requiring sustained attention. Correct responses were rewarded with a drop of water, whereas false-alarm responses triggered a mild puff of air directed to the face as punishment. This task was designed to test the long-standing hypothesis that the cholinergic system is involved in attentional functions on a fast timescale (Everitt and Robbins, 1997; Sarter et al., 2005, 2009; Herrero et al., 2008). Sustained attention might fluctuate in time, and its momentary level is expected to modulate behavioral performance, such as accuracy and reaction time (Coull and Nobre, 1998; Barnes and Jones, 2000). Thus, attentional modulation can be defined operationally as neural activity before stimulus onset that predicts facets of behavior, such as reaction time or accuracy. Surprisingly, not the cholinergic but the activity of a population of unidentified neurons predicted reaction time and performance accuracy, behavioral measures classically associated with attention. These results supported the view that the BF serves attentional functions, albeit controlled by some noncholinergic neurons.

To motivate behavioral performance, mice were rewarded and punished based on their choices, which enabled the authors to test whether cholinergic responses are related to reinforcers. Indeed, nearly all cholinergic neurons responded with strong, short-latency activation to primary reinforcers: water reward and air-puff punishment. Punishment elicited uniform and reliable activation at remarkably short latencies (18 ± 2 ms) in cholinergic neurons. Reward-elicited responses were larger when the signal-to-noise ratio of the preceding auditory stimuli was lower. These responses were consistent with a model according to which graded reinforcement surprise recruits cholinergic neurons. The remarkable speed and precision of cholinergic activation provides a key piece of evidence complementing *in vitro* studies showing that the millisecond timing of acetylcholine can control the strength and even the sign of plasticity at hippocampal synapses (Gu and Yakel, 2011; Gu et al., 2012). In addition, cholinergic neurons appear to recruit specific subtypes of cortical inhibitory interneurons that generate disinhibition (Letzkus et al., 2011).

Interestingly, the response properties of cholinergic neurons were similar across two different nuclei within the BF, the prefrontally projecting horizontal diagonal band (Ch3) and the auditory cortex projecting NB (Ch4), despite the fact that these nuclei are often implicated in different functions and have a different topography of cortical projections (Zaborszky et al., 2015). These results reveal that the BF cholinergic system broadcasts a precisely timed signal to large areas of the brain and thereby could support learning and plasticity as a reinforcement signal (Hangya et al., 2015), as suggested by previous nonspecific electrical stimulation studies (Kilgard and Merzenich, 1998).

A BF cholinergic signal conditions reward timing activity in the primary visual cortex

Converging evidence supporting the idea that BF cholinergic neurons convey a reinforcement signal comes from studies of reward timing activity in the primary visual cortex (V1) of rodents. Reward timing activity in V1 emerges as a consequence of pairing visual stimuli with delayed reward, leading to stimulus-evoked activity in V1 that predicts the timing of expected future reward (Shuler and Bear, 2006; Zold and Hussain Shuler, 2015). Thus, reward timing activity exemplifies a core function of the brain: predicting the timing of future events of behavioral importance based on past experience. This ability to appreciate the predictive qualities of environmental cues affords a means by which the organism may subsequently evaluate the relative worth of options, inform the timing of future actions, and govern future learning in response to changes in the experienced environment. Indeed, visually cued, interval timing activity in V1 has been shown to report the target interval to reward, informing the decision of when to time the action on a trial-by-trial basis (Namboodiri et al., 2015).

A formal reinforcement-based model was proposed to address how reward timing activity may form within V1 (Gavornik et al., 2009; Huertas et al., 2015). A key aspect of the formal computational model is the provision of a reinforcement signal conveying behavioral outcome. Indeed, Weinberger and colleagues have long advanced the hypothesis that BF cholinergic innervation conveys a signal conducive to engendering physiological memories in cortex. Their programmatic investigation has demonstrated that a tone paired with direct acetylcholine application to the auditory cortex or NB electrical stimulation results in receptive field modification toward the paired frequency, mimicking that induced by behavioral conditioning, an effect blocked by cortical application of atropine (Metherate and Weinberger, 1989; Bakin and Weinberger, 1996; Miasnikov et al., 2001). Furthermore, conditioning by NB pairing leads to behavioral associative memories (McLin et al., 2002) by acting as a teaching, rather than as a motivational, signal (Miasnikov et al., 2008). Given these and related observations (Bear and Singer, 1986; Gu and Singer, 1989; Froemke et al., 2007), BF cholinergic input was postulated as a potential signal carrying a reinforcement signal affecting plasticity in V1. Therefore, to test the necessity of the cholinergic system for learning reward timing activity, Chubykin et al. (2013) selectively lesioned cholinergic BF input to V1 via injections of 192-IgG-saporin into V1 and assessed whether new cue-reward delays could be learned and expressed neurally within V1. This study showed that BF cholinergic innervation to V1 is indeed required for reward timing activity to be learned in V1. Importantly, cholinergic innervation was not necessary for already learned reward timing to be expressed.

To test the sufficiency of BF cholinergic input for reward timing activity in the visual cortex, another study examined directly whether BF innervation of V1 in general, and cholinergic innervation of V1 in particular, is sufficient to condition cued-interval timing activity mimicking reward timing activity as observed after behavioral conditioning (Liu et al., 2015). By optogenetically driving BF input within V1 at fixed temporal delays after predictive visual cues, Liu et al. demonstrated that cue-evoked "reward" timing activity is indeed elicited by selective activation of BF input. Their results also demonstrated that optogenetically entrained timing activity in V1 can be bidirectionally tuned to represent new conditioning intervals and is subject to experience-dependent refinement. Interestingly, the distributions of neural reports to given delays exhibit a scale invariance with respect to the delay. Such multiplicative scaling may be a neural correlate of the scalar timing property—a version of Weber's law in the time domain—wherein the distributions of behaviorally timed responses are superimposable after multiplicative scaling (Gibbon, 1977). Finally, by conditioning visually evoked responses with selective activation of cholinergic fibers within V1, Liu et al. advanced the case that cholinergic innervation within V1 is indeed sufficient for cued interval-timing activity, in addition to it being necessary (Liu et al., 2015). Together with the study by Hangya et al. (2015) showing that BF cholinergic neurons respond acutely to behavioral outcome (reviewed above), these studies advance the case that BF cholinergic innervation acts as a reinforcement signal shaping cortical circuits to generate behaviorally relevant activity.

BF cholinergic signaling controls cortical states during whisking

In addition to its role in plasticity, the cholinergic BF projection to the cortex is also involved in modulating cortical network state (Jones, 2004). Cholinergic input to the cortex has long been considered to act as a global activating system (Buzsaki et al., 1988; Metherate et al., 1992; Jones, 2005; Brown et al., 2012; Pinto et al., 2013), but until recently, there were no direct measurements of cholinergic signaling and cortical state changes on rapid timescales with behavioral relevance in awake mice.

Cortical states in the primary somatosensory barrel cortex (S1) in awake animals shift between quiet wakefulness and active whisking. During quiet wakefulness in head-restrained mice, slow, large-amplitude fluctuations in membrane potential of layer 2/3 excitatory neurons in S1 are common. These fluctuations are highly synchronized in nearby neurons and can be observed readily in the local field potential and the electroencephalogram (Poulet and Petersen, 2008). However, when mice are actively exploring their immediate environment by rhythmically moving their whiskers backwards and forwards, the slow membrane potential fluctuations are suppressed. This active cortical state is characterized by depolarized membrane potential, decreased membrane potential variance, and reduced correlation of membrane potential fluctuations in nearby neurons (Poulet and Petersen, 2008).

Sensory processing depends strongly on cortical state, with smaller and more localized responses to whisker deflection during the active desynchronized cortical state (Ferezou et al., 2007). The active cortical state appears to be generated by internal brain mechanisms, because it is essentially unaffected by cutting the sensory nerves. Key determinants of the active whisking cortical state include increases in thalamic (Poulet et al., 2012) and cholinergic (Eggermann et al., 2014) input to the barrel cortex. Firing rates in the somatosensory thalamus increase strongly during whisking compared with quiet wakefulness, and this increased glutamatergic input drives depolarized and desynchronized activity in S1 (Poulet et al., 2012). Inactivation of the thalamus increases slow, large-amplitude fluctuations in membrane potential during quiet wakefulness, but during whisking after thalamic inactivation, S1 is hyperpolarized with low membrane potential variance (Poulet et al., 2012).

A recent study found that the hyperpolarized state of the neocortex during active whisking after thalamic inactivation appears to be mediated by release of acetylcholine by neurons located in the BF and projecting to S1 (Eggermann et al., 2014). Calcium signals in cholinergic axons in S1 are prominent during whisking, suggesting that acetylcholine is being released (Eggermann et al., 2014). Injection of pharmacological antagonists of cholinergic

receptors into S1 blocked the whisking-related hyperpolarization of the cortex after thalamic inactivation (Eggermann et al., 2014), with the strongest effects mediated by muscarinic antagonists. Finally, optogenetic stimulation of cholinergic neurons in the BF could mimic the effects of whisking on membrane potential dynamics in S1, and these effects could also be blocked by local injection of cholinergic antagonists (Eggermann et al., 2014).

Therefore, these results demonstrate prominent cholinergic signals during whisking in S1 and suggest that the active state of mouse S1 during whisking is driven by at least two different signals: increased thalamic firing and increased cholinergic signaling. The released acetylcholine suppresses slow spontaneous activity accompanied by hyperpolarization during whisking, which likely counteracts the increased thalamic input during whisking (Poulet et al., 2012). Cholinergic input to S1 might also contribute to the reduced amplitude and spread of whisker-deflection-evoked sensory responses during whisking compared with quiet wakefulness (Crochet and Petersen, 2006; Ferezou et al., 2007).

Control of cortical arousal by parvalbumin-containing GABAergic BF neurons

In addition to cholinergic neurons, there are multiple other types of cortically projecting neurons in the BF, many of which, like the cholinergic neurons described in the previous sections, exhibit increases in activity associated with cortical activation (Hassani et al., 2009). Among these, GABAergic neurons are particularly numerous and important in behavioral state control (Brown and McKenna, 2015; Kim et al., 2015). In fact, in mice, there are approximately seven times (3.9–12 times depending on the BF subregion) as many GABAergic neurons as cholinergic neurons (McKenna et al., 2013; Yang et al., 2014). A significant minority of these BF GABAergic neurons are long-range projection neurons with targets in the neocortex, hippocampus, thalamus, and lateral hypothalamus (Freund and Meskenaite, 1992; Gritti et al., 1994, 1997, 2006; Henny and Jones, 2008; McKenna et al., 2013). A subset of the neocortically projecting BF GABAergic neurons contains the calcium-binding protein parvalbumin (PV) (Gritti et al., 2003). In mice, PV is contained in approximately one-quarter of large (>20 μm), putative long-range projecting, GABAergic neurons (McKenna et al., 2013). Other neocortically projecting BF GABA neurons express the potassium channel Kv2.2 (Hermanstyne et al., 2010) or the neurokinin-3 receptor (Furuta et al., 2004).

In vitro whole-cell recordings in GAD67–GFP knock-in mice or PV–tdTomato mice allowed the first characterization of the intrinsic membrane properties of identified GABAergic and PV neurons (McKenna et al., 2013). These recordings revealed many similarities but also important differences between BF GABAergic/PV projection neurons and cortical fast-spiking PV interneurons. Like cortical PV interneurons, BF GABAergic/PV projection neurons are very fast firing, with brief action potentials and electrical coupling (McKenna et al., 2013). However, unlike their cortical counterparts, they are spontaneously active in the absence of injected current and exhibit prominent hyperpolarization-activated cation currents that resist prolonged hyperpolarization and may play a role in promoting the rhythmic cluster/burst activity of identified BF GABAergic and PV neurons observed *in vivo* (Duque et al., 2000; Hassani et al., 2009).

What effect do cortically projecting BF GABAergic neurons have on cortical function? Clues to the answer of this question came from juxtacellular recordings *in vivo* that showed that a significant minority of identified GABAergic neurons exhibit fast firing during wakefulness and rapid eye movement sleep (Hassani et al., 2009), as well as from anterograde tracing studies that showed that BF GABAergic neurons preferentially target cortical interneurons, including fast-firing PV neurons involved in cortical gamma oscillations (Freund and Meskenaite, 1992). Thus, it was postulated that BF GABAergic neurons may exert a state-dependent control over cortical gamma oscillations.

A recent study (Kim et al., 2015) tested this hypothesis using an optogenetic approach targeting the subset of BF GABAergic neurons containing PV. Indeed, selective optical stimulation of BF PV neurons preferentially enhanced cortical EEG power in the gamma range, whereas optical inhibition reduced the power of cortical 40 Hz oscillations induced by a 40 Hz auditory stimulus train (Kim et al., 2015). Thus, although many GABAergic neurons in the BF are sleep active/sleep promoting (Hassani et al., 2009), a significant subset project to the cortex and promote the fast gamma-band activity typical of conscious states, likely through entrainment of the firing of cortical interneurons. Cholinergic neurons strongly excite BF GABAergic and PV neurons through local release of acetylcholine (Yang et al., 2014). Thus, under normal conditions, the BF cholinergic and GABAergic systems likely work synergistically to generate cortical activation and promote wakefulness.

Studies of BF noncholinergic neurons in rodents have opened up a new vista in our understanding of BF control of cortical activation. Given that GABAergic and PV neurons are similarly present in primates (Walker et al., 1989; Côté et al., 1991), a challenge for the future will be to determine whether these are also cortical-projecting neurons with similar functions and apply this knowledge to the treatment of human disorders affecting the BF, such as coma and Alzheimer's disease.

Another group of noncholinergic BF neurons encodes motivational salience and modulates the speed of decision making

In addition to cholinergic neurons and PV-containing GABAergic neurons described above, another group of presumably noncholinergic BF neurons has been studied extensively in recent years (Lin et al., 2006; Lin and Nicolelis, 2008; Avila and Lin, 2014a,b; Nguyen and Lin, 2014). This population of BF neurons shares homogeneous physiological properties, including low tonic baseline firing rates (<10 Hz) and intermittent phasic bursting activity that is highly correlated among neurons in this group (Lin et al., 2006; Avila and Lin, 2014b). Their large, broad and complex action potential waveforms (Avila and Lin, 2014b) and short latencies in modulating cortical activity (Nguyen and Lin, 2014) are consistent with these neurons being long-range projection neurons. These neurons represent a distinct population in the BF that encodes reward and motivational salience information using phasic bursting responses (Lin and Nicolelis, 2008; Avila and Lin, 2014b; Nguyen and Lin, 2014) and have been referred to as "salience-encoding" or "bursting" BF neurons. The bursting BF neurons are unlikely to be the cholinergic neurons (Lee et al., 2005; Hangya et al., 2015) or PV-containing GABAergic neurons (Kim et al., 2015) because, in addition to differences in firing properties, the bursting BF neurons do not modulate their average firing rates across sleep–wake states (Lin et al., 2006; Lin and Nicolelis, 2008). These observations suggest that salience-encoding BF neurons represent yet another group of noncholinergic and non-PV BF neurons whose neurochemical identity remains to be determined.

The response profile of this group of BF neurons has, in fact, been described widely in the BF literature. Among the first studies of the substantia innominata region in behaving monkeys, DeLong (1971) described how BF neurons have low tonic firing rates and respond to reward and reward-predicting cues. Such response profiles have since been characterized widely in behaving monkeys (Richardson and DeLong, 1990, 1991; Wilson and Rolls, 1990a,b) and rodents (Tindell et al., 2005, 2009; Smith et al., 2011; Thomson et al., 2014; Tingley et al., 2014). Despite the prevalence of this neuronal population in BF recording studies, this activity pattern has been mostly misinterpreted in the literature as representative of BF cholinergic neurons.

The encoding of motivational salience by bursting responses of noncholinergic neurons appears to play a key role in some decision-making processes. The BF bursting activity is not required for sensory detection because clearly perceptible sensory cues do not elicit any BF response before associative learning (Lin and Nicolelis, 2008). Rather, as demonstrated in an auditory near-threshold detection task, the BF bursting activity is tightly correlated with and potentially enables the animal to properly respond to a detected cue based on its motivational salience (Lin and Nicolelis, 2008). These observations led to the hypothesis that BF bursting activity serves to enhance the cortical representations of detected stimuli for the purpose of reinforcement-guided behavior (Lin and Nicolelis, 2008). In support of this hypothesis, stronger BF bursting responses to motivationally salient cues are tightly coupled with, and causally linked to, faster and more precise decision speed (Avila and Lin, 2014a). Furthermore, the recruitment of the BF motivational salience signal enhances processing in the frontal cortex by generating an event-related potential response (Nguyen and Lin, 2014). Therefore, the BF motivational salience signal likely serves as a gain-modulation mechanism to modulate the speed of the decision-making process, which facilitates behavioral responding to sensory cues based on their motivational, but not perceptual, salience.

These findings highlight the need to determine the neurochemical identity of salience-encoding BF neurons to test whether they correspond to BF glutamatergic projections to the cortex (Hur and Zaborszky, 2005) or, alternatively, BF GABAergic projections that preferentially innervate cortical interneurons and may enhance cortical processing through disinhibition (Freund and Gulyás, 1991; Freund and Meskenaite, 1992; Henny and Jones, 2008).

Conclusions

Classic studies of the BF neuromodulatory system using selective cholinergic immunotoxic lesions, pharmacology, and electrical stimulation, among other techniques, have been of great importance in relating BF, at the mechanistic level, to cortical activation and plasticity and, at the behavioral level, to arousal, learning, and attention (Metherate et al., 1992; Everitt and Robbins, 1997; McLin et al., 2002; Sarter et al., 2005; Disney et al., 2007; Herrero et al., 2008; Goard and Dan, 2009; Baxter and Bucci, 2013). New techniques for genetically targeting distinct neuronal types, observing their activity, and manipulating them using optogenetic tools enables entirely new types of experiments that have revitalized the field. We can now record the activity of specific types of projection neurons during behavior, and then, informed by these observations, we can attempt to "reinject" the patterns of activity observed. These new tools are allowing the field to test directly the causal role of distinct pathways using gain- and loss-of-function experiments.

After decades of focus on the putative general arousal role of cholinergic BF neurons, recent studies exploiting cell-type-specific targeting and optogenetics reviewed here are beginning to provide novel insights on the behavioral function of cholinergic neurons and their circuit-level mechanism, as well as revealing the functional significance of diverse noncholinergic neuronal populations in the BF. These results show that cholinergic BF neurons broadcast a fast reinforcement signal to the cerebral cortex (Hangya et al., 2015) that is capable of inducing plastic changes in V1 to produce a reward timing signal (Chubykin et al., 2013; Liu et al., 2015), as well as powerfully modulating the membrane dynamics in cortical circuits to generate active brain states (Eggermann et al., 2014). Conversely, noncholinergic BF neurons appear to play equally powerful roles in enhancing cortical activity, especially in the frontal cortex, through generating gamma oscillations (Kim et al., 2015) and an event-related potential response (Nguyen and Lin, 2014). The results reviewed here suggest that both cholinergic and noncholinergic BF neurons enhance cortical activity, but the timing of their modulation during behavior may differ: cholinergic BF neurons primarily respond to reinforcers (Hangya et al., 2015) whereas subsets of noncholinergic BF neurons respond phasically to motivationally salient cues that predict reinforcement (Lin and Nicolelis, 2008; Avila and Lin, 2014a) and correlate with operational measures of attention (Hangya et al., 2015). Therefore, cholinergic and noncholinergic BF neurons might play complementary and synergistic functions in arousal and cognition. Together, these studies are rapidly changing the face of the BF neuromodulatory system away from a monolithic and slow cholinergic modulatory action and begin to unveil the full rapid temporal dynamics of heterogeneous elements in the BF circuit.

These results mark just the beginning of a new era in the study of the BF, and much remains to be explored in this anatomically and neurochemically heterogeneous region. For instance, cholinergic and noncholinergic neurons are segregated topographically, each neuron projecting to a relatively small cortical region (Wu et al., 2014; Zaborszky et al., 2015); thus, it will be important to determine whether there are conditions under which certain subpopulations are selectively recruited, in addition to the apparently global recruitment of BF cholinergic neurons by reinforcers (Hangya et al., 2015). It is also important to determine whether the functions of BF neurons are mediated by direct projections to the neocortex or via indirect projections to other subcortical targets, such as the thalamus (Parent et al., 1988; Jourdain et al., 1989; Bickford et al., 1994; Gritti et al., 1998), amygdala (Unal et al., 2015) and hypothalamus and brainstem (Freund and Meskenaite, 1992; Gritti et al., 1994, 1997, 2006; Henny and Jones, 2008; McKenna et al., 2013). Future studies will need to define the behavioral correlates of distinct neuronal populations in the BF, as well as address how different types of information arrives at the BF, how the information is processed locally in the BF circuit, and how such information influences downstream activity in the cerebral cortex. These endeavors will help us understand how information about attention, learning, motivational salience, and arousal converge and interact in this underexplored nexus of the brain. Ultimately, this information will be crucial in designing specific treatments for disorders that affect BF function, such as coma (Brown et al., 2010), sleep disorders (Brown et al., 2012), dementia (Cummings and Benson, 1984), Alzheimer's disease (Whitehouse et al., 1982; Grothe et al., 2012), and normal cognitive aging (Gallagher and Colombo, 1995).

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