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Cell-specific modulation of plasticity and cortical state by cholinergic inputs to the visual cortex

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Abstract

Acetylcholine (ACh) modulates diverse vital brain functions. It innervates a wide range of cortical areas, including the primary visual cortex (V1), and multiple cortical cell types have been found to be responsive to ACh. Here we review how different cell types contribute to different cortical functions modulated by ACh. We specifically focus on two major cortical functions: plasticity and cortical state. In layer II/III of V1, ACh acting on astrocytes and somatostatin-expressing inhibitory neurons plays critical roles in these functions. Cell type specificity of cholinergic modulation points towards the growing understanding that even diffuse neurotransmitter systems can mediate specific functions through specific cell classes and receptors.

Keywords

astrocytes; inhibitory neurons; somatostatin interneurons; potentiation; decorrelation; desynchronization

1. INTRODUCTION

The primary visual cortex (V1) is a powerful model system for studying how ‘bottom-up’ sensory experience can be modulated by ‘top-down’ neurotransmitter processes. In particular, it is densely innervated by afferent cholinergic projections originating in the basal forebrain (BF) which includes the nucleus basalis and the nucleus of the diagonal band of Broca (Do et al., 2016; Kitt et al., 1994; Laplante et al., 2005; Luiten et al., 1987), an area conceptualized as a critical component of ‘top-down’ processes (Sarter et al., 2001). The

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distribution of cholinergic axons have been shown to be diffuse (Eckenstein et al., 1988; Rye et al., 1984) and vary in density across the cortical layers (Lysakowski et al., 1989; Mesulam et al., 1992; Raghanti et al., 2008; Satoh et al., 1983). This, coupled with differential expression of muscarinic (mAChRs) and nicotinic acetylcholine receptors (nAChRs) across cortical layers and cell-types (Clarke et al., 1985; Groleau et al., 2015; Zilles et al., 1989), can lead to specific modulation of distinct cortical circuits that orchestrate different brain functions.

Diverse vital brain functions known to be regulated by cholinergic modulation of the neocortex include arousal (Phillis, 1968), attention (Herrero et al., 2008), information processing (Bhattacharyya et al., 2013; Disney et al., 2007; Goard and Dan, 2009; Kosovicheva et al., 2012; Soma et al., 2013), learning and memory (Dotigny et al., 2008; Hasselmo, 2006) and cortical plasticity (Bear and Singer, 1986; Froemke et al., 2007; Kang et al., 2014a; Kang and Vaucher, 2009). The ability of a single cholinergic system to modulate such diverse brain functions, each occurring at specific and distinct timescales, can perhaps be attributed to its specific modulation of varied cell classes that form distinct cortical circuits.

Multiple cortical cell types have been found to be responsive to acetylcholine (ACh). These cells have complex functional interactions, as supported by observations of both hyperpolarizing and depolarizing responses in excitatory neurons (Arroyo et al., 2012; Bandrowski et al., 2001; Gulledge and Stuart, 2005; McCormick and Prince, 1986) and different subtypes of inhibitory neurons (Arroyo et al., 2012; Kawaguchi, 1997; Xiang et al., 1998) across distinct neocortical layers in multiple species. A recent study also reveals that ACh can elicit facilitatory and suppressive responses in non fast-spiking (FS) and FS cortical interneurons, respectively (Arroyo et al., 2012).

In the following two sections, we will review specific examples of how cortical circuits comprising excitatory neurons, various inhibitory neuron subtypes, and astrocytes, respond to cholinergic modulation. Specifically, we will focus on two major cholinergic functions: cortical plasticity and state-dependent temporal dynamics of cortical activity. We will discuss cell type specificity for each function and propose functional microcircuits by which ACh elicits these actions.

2. PLASTICITY

One of the earliest studies showing that ACh can induce long-lasting changes in the excitability of neurons was performed by pairing ACh iontophoresis with intracellular depolarization of cortical neurons in awake cats (Woody et al., 1978). Subsequent studies have shown that co-application of ACh or muscarinic agonists with glutamate can induce a prolonged increase in response to glutamate in somatosensory cortical neurons (Lin and Phillis, 1991; Metherate et al., 1987). When the application of ACh or electrical stimulation of BF is paired with sensory stimulation in the somatosensory (Donoghue and Carroll, 1987; Howard III and Simons, 1994; Lamour et al., 1988; Metherate et al., 1987; Rasmusson and Dykes, 1988; Tremblay et al., 1990a, b), auditory cortex (Bakin and Weinberger, 1996; Dimyan and Weinberger, 1999; Edeline et al., 1994; Kilgard and Merzenich, 1998a, b;

Kilgard et al., 2001), and visual cortex (Kang et al., 2014a; Kang et al., 2015), prolonged enhanced responses to the paired sensory stimuli are observed, often along with changes in behavior (Kang et al., 2014b). These studies have also revealed that cholinergic antagonists cannot reverse the prolonged changes, thereby confirming that the induction but not maintenance of prolonged changes requires ACh (Lamour et al., 1988). It is worth mentioning that cortical plasticity can occur at both single cell and cortical map levels (Bakin and Weinberger, 1996; Bao et al., 2003; Froemke et al., 2007; Kilgard and Merzenich, 1998a; Puckett et al., 2007). There are also other forms of cholinergic modulation of cortical responses, including nicotinic ACh receptor mediated experience dependent plasticity (Morishita et al., 2010), associative fear learning (Letzkus et al., 2011), and behavior state dependent gain control (Fu et al., 2014). In this section, we focus on BF-mediated cholinergic plasticity in adult cortex.

In V1, modulation by ACh and cholinergic drive from the BF in particular are known to result in an enhancement of direction and orientation selectivity in anesthetized animals (Murphy and Sillito, 1991; Sato et al., 1987; Sillito and Kemp, 1983; Zinke et al., 2006), increase in attentional modulation of V1 neurons in behaving monkeys (Herrero et al., 2008), and alteration in the reliability and synchrony of stimulus evoked spikes in V1 neurons (Goard and Dan, 2009). More broadly, responses of V1 neurons to specific visual stimulus features also exhibit pronounced plasticity, and in particular depend on the history of visual stimulation (Dragoi et al., 2000). The potential mechanisms underlying such stimulus-specific plasticity were not examined previously, but now our work and that of others has revealed a significant contribution from cholinergic inputs acting on astrocytes to influence prolonged changes in neuronal responses.

Cortical astrocytes are an integral component of V1 circuits because they are visually responsive and are capable of modulating visually driven neuronal responses (Schummers et al., 2008). Astrocytes are also involved in the regulation of the microvasculature (Girouard and Iadecola, 2006; Iadecola and Nedergaard, 2007; Vaucher and Hamel, 1995), and couple neuronal responses to hemodynamic signals that underlie functional imaging (Schummers et al., 2008). In the hippocampus, the circuitry of cholinergic modulation includes astrocytes (Haydon, 2001; Nedergaard et al., 2003), which have been discovered to be ACh-responsive (Araque et al., 2002; Perea and Araque, 2005; Shelton and McCarthy, 2000). *Ex vivo* studies implicate hippocampal astrocytes in synaptic potentiation [(Henneberger et al., 2010; Perea and Araque, 2007; Yang et al., 2003) compare with (Agulhon et al., 2010)], demonstrating that they can potentially provide a powerful mean of altering neuronal networks to induce response plasticity. More recently, our work (Chen et al., 2012), together with others (Navarrete et al., 2012; Takata et al., 2011), has revealed that BF-induced astrocytic activation can induce potentiation of local field potentials (LFP) recorded in the cortex and hippocampus.

To investigate the possible role of astrocytes in cholinergic plasticity of V1 responses, we measured neuronal as well as astrocyte activity while electrically stimulating the BF (Chen et al., 2012). Using cell-attached recordings *in vivo*, we demonstrated that electrical stimulation of the BF, paired with visual stimulation, can induce significant potentiation of visual responses in excitatory neurons of mouse V1 **(Fig. 1)**. We further showed with *in vivo*

two-photon calcium imaging, *ex vivo* calcium imaging, and whole-cell recordings that this pairing-induced potentiation is mediated by direct cholinergic activation of V1 astrocytes via muscarinic AChRs. In conditional inositol 1,4,5 trisphosphate receptor type 2 KO (IP_3R2-cKO) mice, which lack astrocyte calcium activation, the potentiation is absent, suggesting a critical contribution of astrocytes to this plasticity. The potentiation is also stimulus-specific, because pairing BF stimulation with a specific visual orientation revealed a highly selective potentiation of responses to the paired orientation compared with unpaired orientations. Collectively, these findings reveal a unique and surprising role for astrocytes in BF-induced stimulus specific plasticity in the cerebral cortex.

How do astrocytes evoke sensory stimulus specific cholinergic potentiation? Or, more specifically, how does IP_3R2 mediated Ca^{2+} pathway evoked by ACh through mAChRs in astrocytes induce synaptic plasticity in nearby neurons activated by a sensory stimulus? Possible mechanisms include: 1) astrocytic release of glutamate, D-serine, or other gliotransmitter (Parpura and Zorec, 2010; Volterra and Meldolesi, 2005), or 2) regulation of extracellular transmitters (Pannasch et al., 2014) or potassium (Wang et al., 2012), possibly through modulation of transporters in the astrocyte membrane (Bazargani and Attwell, 2016). Future investigation is required to dissect these possibilities, including interaction between astrocytic Ca^{2+} pathways in somata and processes (Bazargani and Attwell, 2016).

3. CORTICAL STATE

Another major function of cholinergic modulation is cortical state change, such as attention (Harris and Thiele, 2011). A wealth of studies using BF lesions, and BF electrical stimulation and pharmacology, have presented rich evidence in support of cholinergic modulation of the detection, selection and processing of stimuli, particularly during attention.

Some of the earliest evidence revealing the role of ACh in information processing came from BF lesion studies. In these studies, selective excitotoxic lesions of the BF neurons were performed by injecting excitatory amino acid agonists or immunotoxins into the BF (Wenk, 1997). Animals with their BF neurons impaired by this method showed reduced attentional functions (McGaughy et al., 2002; Muir et al., 1993; Robbins et al., 1989; Turchi and Sarter, 1997; Voytko et al., 1994) and stimulus processing abilities (Chiba et al., 1995), as reflected by lower accuracy and longer latencies in their response to attentional tasks. Pharmacological studies using cholinergic receptor agonists and antagonists as well as with cholinesterase inhibitors to enhance or suppress cholinergic action have provided further understanding of the mechanisms. Particularly, researchers have demonstrated that both nicotinic and muscarinic receptors can mediate the change in performance during cholinergic modulation of sensory processing (Hutchison et al., 2001; Stough, 1998; Stough et al., 1995; Thompson et al., 2000) and attentional tasks (Bauer et al., 2012; Furey et al., 2008; Herrero et al., 2008; Thienel et al., 2009).

The advent of single and multi-unit recording has allowed further understanding of cholinergic modulation of information processing at a single neuronal level. These studies typically involve recording of the spike responses of a population of single units before,

during and after local iontophoretic application of ACh or electrical stimulation of the BF. In sensory cortex, these studies have shown that cholinergic modulation can affect contrast gain (Bhattacharyya et al., 2013; Disney et al., 2007; Soma et al., 2013), orientation and direction selectivity (Herrero et al., 2008; Muller and Singer, 1989; Sato et al., 1987; Sillito and Kemp, 1983; Thiele et al., 2012), spatial integration (Roberts et al., 2005), receptive field size (Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998a) and attention (Herrero et al., 2008).

More recently, similar studies performed with more elegant analyses have also revealed that ACh can enhance information processing through interneuronal decorrelation of V1 responses (Goard and Dan, 2009; Thiele, 2009). Such decorrelation between V1 responses is particularly evident during execution of attentional tasks in behaving monkeys (Cohen and Maunsell, 2009; Mitchell et al., 2009).

Several studies have shown that the cholinergic system can control cortical states. ACh release in the cortex has been observed to co-vary with brain state changes (Marrosu et al., 1995), while increased BF neuronal firing has been found to occur during cortical desynchronization (Duque et al., 2000; Manns et al., 2000). The causal relationship between the cholinergic system and cortical states are further established in a range of studies. Lesions of the BF lead to increased low-frequency LFP power (Buzsaki et al., 1988), indicating more synchronized neural activities, while electrical and optogenetic stimulation of the basal forebrain or of cholinergic projections to the cortex induces mAChR-mediated cortical desynchronization, including decreased low-frequency and increased high-frequency LFP power (Kalmbach et al., 2012; Metherate et al., 1992). This ACh-induced desynchronization is similar to that observed during normal physiological changes (Kalmbach et al., 2012).

These related phenomena (Harris and Thiele, 2011), viz. neuronal decorrelation and LFP desynchronization, are proposed to enhance information processing in alert, active and attentive conditions (Cohen and Maunsell, 2009; Herrero et al., 2013; Herrero et al., 2008; Mitchell et al., 2009; Singer, 1993). Thus, ACh can change the temporal dynamics of cortex by shifting cortical state from a correlated or synchronized state to a decorrelated or desynchronized state, and consequently enhance cortical information processing. Recent computational studies have suggested that inhibitory neurons can drive decorrelation and sparse coding in the cortex (De La Rocha et al., 2007; King et al., 2013), and experimental evidence shows that inhibitory neuronal activity correlates with (Klausberger et al., 2003) and can induce (Avella Gonzalez et al., 2012; Cardin et al., 2009) specific neuronal activity patterns. Furthermore, subtypes of inhibitory neurons differentially express nicotinic and muscarinic ACh receptors, suggesting possible distinct cholinergic modulation of their microcircuits (Arroyo et al., 2014; Porter et al., 1999; Xiang et al., 1998).

To investigate the possible role of ACh inputs to cortex and inhibitory neurons in temporal activity modulation, we measured the neural activity of each inhibitory neuron type while optogenetically stimulating superficial cholinergic axons in mouse V1 (Chen et al., 2015). We found that intracortical cholinergic inputs specifically and differentially drive a defined functional cortical microcircuit in superficial layers of mouse V1 to cause ACh driven

desynchronization: they facilitate somatostatin-expressing (SOM) inhibitory neurons that in turn inhibit parvalbumin-expressing (PV) inhibitory neurons and pyramidal neurons. Selective optogenetic inhibition of SOM neurons blocks desynchronization of the LFP and decorrelation of neural responses induced by cholinergic stimulation **(Fig. 2a, b)**. This demonstrates that direct cholinergic activation of SOM neurons is necessary for this phenomenon. Furthermore, direct optogenetic activation of SOM neurons, independent of cholinergic modulation, is sufficient to induce desynchronization. Together, these findings demonstrate a crucial role of cholinergic drive to specific inhibitory-excitatory circuits in actively shaping the dynamics of neuronal activity **(Fig. 2c)**.

Among other subtypes of inhibitory neurons, vasoactive intestinal peptide-expressing (VIP) and layer 1 (L1) inhibitory neurons have also been reported to respond to cholinergic modulation (Alitto and Dan, 2012; Arroyo et al., 2014; Fu et al., 2014; Kawaguchi, 1997; Letzkus et al., 2011). These subtypes of inhibitory neurons respond to higher ACh concentrations compared to SOM neurons: in V1 slices, SOM neurons start to respond to ACh at lower concentrations (1-100 μM), consistent with their low-threshold spiking properties (Fanselow et al., 2008), whereas VIP and L1 neurons require higher concentration (10 mM) (Chen et al., 2015). In addition, they affect excitatory neurons differently during cholinergic modulation. Upon application of ACh in slices, excitatory neurons receive massive inhibitory input, which mostly arises from SOM neurons since these inhibitory inputs are abolished by suppressing activities of SOM neurons optogenetically. In contrast, suppression of VIP or L1 inhibitory neurons does not alter inhibitory inputs to excitatory neurons upon ACh application, despite these neurons being activated at high levels of cholinergic drive. Furthermore, optogenetic inhibition of VIP neurons *in vivo* does not block LFP desynchronization. These results indicate that, although VIP and L1 inhibitory neurons respond to cholinergic input, they do not play a major role in cortical functional circuits for desynchronization.

VIP neurons almost exclusively inhibit SOM neurons in layer II/III of mouse visual cortex, whereas SOM neurons strongly inhibit VIP neurons (Pfeffer et al., 2013). Some studies suggest suppressed responses of SOM neurons via inhibition from VIP neurons (Fu et al., 2014; Karnani et al., 2016; Pi et al., 2013), whereas others have reported that ACh activates SOM neurons (Chen et al., 2015; Kawaguchi, 1997; Kocharyan et al., 2008; Xu et al., 2013). Given the differential ACh concentration dependency between VIP/L1 neurons and SOM neurons, and mutual inhibition between VIP and SOM neurons, it is possible that these inhibitory neuron subtypes act as a switch between different functional microcircuits depending on cholinergic input level. While SOM neurons are activated by ACh and cause cortical state change such as arousal/attention, VIP/L1 neurons may contribute to functions requiring higher cholinergic drive such as gain control during locomotion (Fu et al., 2014) or associative fear learning (Letzkus et al., 2011).

4. CONCLUSIONS

We have reviewed how ACh can engage specific cortical circuits that operate at distinct timescales to modulate two different brain functions: response plasticity of single neurons, and response dynamics of neuronal populations. Specifically, ACh acts on circuits

comprising astrocytes and pyramidal neurons to modulate visual cortical plasticity that occurs at a prolonged timescale (tens of seconds to minutes). ACh acts on circuits comprising inhibitory neuronal subtypes and pyramidal neurons to modulate cortical state changes and information processing over a more transient timescale (milliseconds to seconds). These two functional microcircuits are distinguished by their distinct timescales and their recruitment of different cell types. However, while repeated pairing with BF and sensory stimulation is required for cholinergic plasticity, the microcircuit required for cortical state change will also be evoked at each BF stimulation. Thus, the functional microcircuit for desynchronization may affect cholinergic plasticity, probably through improvement of sensory stimulus selectivity. Furthermore, although the timescale of these brain functions seem to match respectively the slow timescale of astrocytes (Lopez-Hidalgo and Schummers, 2014) and fast timescale of inhibitory neurons (Butts et al., 2007), it may be possible for the engagement of astrocytes and inhibitory neurons to overlap and for both cell types to be involved in cholinergic modulated learning and plasticity: the ‘faster’ inhibitory neurons can initiate plasticity via disinhibition (Sur et al., 2013) while the ‘slower’ astrocytes can consolidate the phenomenon. For example, in gain modulation with associative fear learning (Letzkus et al., 2011) or during locomotion (Fu et al., 2014), VIP/L1 neurons modulate cortical gain via disinhibition through nicotinic ACh receptors, and such repetitive gain modulation can be further facilitated and consolidated by ACh-activated astrocytes through their muscarinic ACh receptors. Further investigation will be necessary to uncover the mechanisms that underlie possible interaction between astrocytes and inhibitory neurons during cholinergic modulation.

The proposed microcircuits described in our studies are derived from studies using the superficial layers of the mouse visual cortex as a model. The common principles derived from these findings can potentially apply to other cortical layers, brain regions and species. However, the exact mechanisms may differ across regions and species due to varying density and distribution of cholinergic axons across cortical layers (Lysakowski et al., 1989; Mesulam et al., 1992; Raghanti et al., 2008; Satoh et al., 1983), and differential expression of muscarinic and nicotinic ACh receptors across cortical layers and cell-types (Clarke et al., 1985; Groleau et al., 2015; Zilles et al., 1989). For example, VIP neurons inhibit PV neurons in the superficial layers of mouse auditory cortex (Letzkus et al., 2011; Pi et al., 2013), whereas such inhibition is not clearly observed in the visual cortex (Karnani et al., 2016; Pfeffer et al., 2013). Furthermore, cortical projections of BF are topographically organized (Zaborszky et al., 2015) and cholinergic modulation can be cortical area specific (Chaves-Coira et al., 2016; Golmayo et al., 2003; Rasmusson et al., 2007). Thus, cholinergic modulation can be task specific and also different tasks with varied cholinergic load could activate distinct cortical circuits (Chen et al., 2015).

The cholinergic system from the BF that innervates the neocortex was previously found to be implicated in arousal (Phillis, 1968) and attention (Arnold et al., 2002; Dalley et al., 2001; Herrero et al., 2008; Himmelheber et al., 2000; McGaughy et al., 2002; Parikh et al., 2007; Passetti et al., 2000) using rats, monkeys and cats as research models. However, a recent study (Hangya et al., 2015) has revealed that a non-cholinergic basal forebrain population (but not cholinergic neurons) was correlated with trial-to-trial measures of sustained attention in mice performing an auditory detection task. Furthermore, cortically

projecting PV neurons in BF may innervate cortical PV neurons and modify gamma band oscillations (Kim et al., 2015) or wakefulness (Anaclet et al., 2015; Zant et al., 2016). These studies open the question of whether there are differences between cholinergic modulation and BF modulation of the neocortex (Avila and Lin, 2014). Future detailed analysis of region, task, and species-specific cholinergic mechanisms is therefore important for revealing definitive answers to these questions.

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HIGHLIGHTS

- Calcium pathway in astrocytes play a major role in ACh-induced cortical plasticity
- ACh induces cortical desynchronization via direct action on SOM interneurons
- Different aspects of cholinergic modulation are mediated by distinct cell types

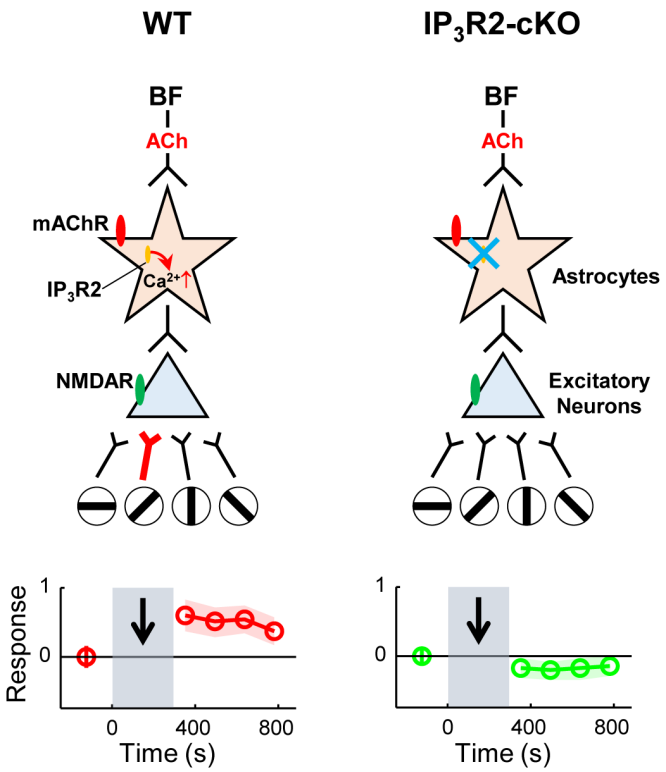

Figure 1.

Cholinergic modulation of plasticity. **(Left, Top)** Schematic illustrating BF-enabled, stimulus-specific plasticity in V1 of wild type (WT) mice (Chen et al., 2012). Pairing a visual stimulus (an oriented grating) with electrical stimulation of the basal forebrain (BF) leads to prolonged facilitation of V1 neuron responses to the specific visual stimulus but not other stimuli (denoted by thick red connections between 45 degree oriented stimulus and pyramidal neuron, depicted as triangle). BF stimulation also leads to increased calcium responses from astrocytes (depicted as star), which are mediated by muscarinic ACh receptors (mAChRs) and by IP_3 receptor type 2 (IP_3R2) on astrocyte calcium stores. Astrocyte-mediated effects on neurons engage NMDA receptors (NMDARs). **(Left, Bottom)** Neuronal responses (shown in red) were measured extracellularly before and after the pairing. Shaded area with black arrow indicates a period of pairing. Increased responses persist for 100s of seconds. **(Right, Top)** In mice specifically lacking IP_3R2 receptors in astrocytes (IP_3R2-cKO animals), BF stimulation does not evoke IP_3R2-mediated calcium increases in astrocytes (blue cross). **(Right, Bottom)** Pairing BF stimulation with a visual stimulus does not cause stimulus-specific potentiation of V1 neuronal responses (shown in green). Adapted from Chen et al. (2012).

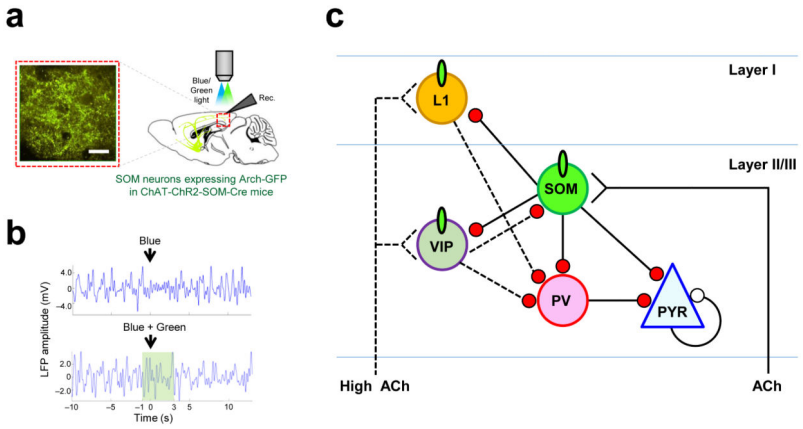

Figure 2.

Cholinergic modulation of cortical state. **(a)** Experimental setup for electrophysiological recordings to reveal the role of ACh in cortical desynchronization and decorrelation (Chen et al., 2015). In one experiment, the neuronal activator Channelrhodopsin (ChR2) is expressed in ChAT-expressing neurons of the basal forebrain and blue light stimulation over V1 is used to selectively release ACh in V1. In the same mice, the neuronal activity suppressor Archaerhodopsin (Arch) is expressed in somatostatin-expressing V1 neurons, and green light stimulation used to selectively suppress SOM neurons. Neuronal responses and LFPs are recorded in V1 before, during and after blue light, or simultaneous blue and green light, stimulation through the objective. ***(Inset)*** Image of Arch-GFP expression in V1. Scale bar, 50 μm. **(b)** LFP desynchronization during ChAT-ChR2 stimulation at t = 0 s (arrow) ***(top)*** is blocked by simultaneous SOM-Arch stimulation (green bar) ***(bottom)***. Traces were low-pass filtered (< 5 Hz). Thus, ACh release leads to desynchronization of responses, and activating SOM neurons is critical for mediating the effects of ACh. **(c)** Schematic illustrating the suggested circuit mechanisms underlying cholinergic modulated temporal dynamics in the superficial layers of V1. The various inhibitory neuron types (including SOM; parvalbumin-expressing, PV; vasoactive intestinal peptide-expressing, VIP; layer 1, L1) have complex inhibitory relationships with one another. PV and SOM neurons inhibit pyramidal (PYR) neurons, while SOM neurons also inhibit PV neurons. Desynchronization and decorrelation of pyramidal neuron responses following ACh release arises primarily due to the inhibitory-disinhibitory effects of PV and SOM neurons mediated through the action of ACh on SOM neurons. The effect of ACh on VIP and L1 neurons requires higher concentrations of ACh. Green ovals indicate cholinergic receptors. Red and white circles indicate inhibitory and excitatory synapses, respectively. Adapted from Chen et al. (2015).