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Review article

Monoaminergic control of brain states and sensory processing: Existing knowledge and recent insights obtained with optogenetics

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ABSTRACT

Monoamines are key neuromodulators involved in a variety of physiological and pathological brain functions. Classical studies using physiological and pharmacological tools have revealed several essential aspects of monoaminergic involvement in regulating the sleep-wake cycle and influencing sensory responses but many features have remained elusive due to technical limitations. The application of optogenetic tools led to the ability of monitoring and controlling neuronal populations with unprecedented temporal precision and neurochemical specificity. Here, we focus on recent advances in revealing the roles of some monoamines in brain state control and sensory information processing. We summarize the central position of monoamines in integrating sensory processing across sleep-wake states with an emphasis on research conducted using optogenetic techniques. Finally, we discuss the limitations and perspectives of new integrated experimental approaches in understanding the modulatory mechanisms of monoaminergic systems in the mammalian brain.

Contents

Abbreviations: 5-HT, 5-hydroxy tryptamine, serotonin; aPC, anterior piriform cortex; CCK, cholecystokinin; ChR2, channelrhodopsin; DPGi, dorsal paragigantocellular reticular nucleus; DRN, dorsal raphe nucleus; EEG, electroencephalogram; EPSC, excitatory post-synaptic current; EPSP, excitatory post-synaptic potential; GABA, gamma amino butyric acid; GPCR, G protein-coupled receptor; GRIN, gradient index; IPSC, inhibitory post-synaptic current; IPSP, inhibitory post-synaptic potential; I_{CAN}, Ca^{2+} activated nonspecific cation current; I_h, hyperpolarization activated cyclic nucleotide gated nonspecific cation current; I_{Kleak}, leak K^+ current; I(Nap), persistent sodium current; $I_{Twindow}$, T-type Ca^{2+} channel mediated window current; LC, locus coeruleus; LCNA, locus coeruleus noradrenergic; MnPN, median preoptic nucleus; MRN, median raphe nucleus; M/T, mitral/tufted (cell); NA, noradrenaline; NREM, non- rapid eye movement (sleep); OB, olfactory bulb; PFC, prefrontal cortex; PV, parvalbumin; REM, rapid eye movement (sleep); SK channels, small conductance (K^+) channels; SOM, somatostatin; TMN, tuberomamillary nucleus; TRN, thalamic reticular nucleus; VGAT, vesicular GABA transporter; VGLUT, vesicular glutamate transporter; VIP, vasoactive intestinal peptide; vlPAG, ventrolateral periaqueductal gray; VLPO, ventrolateral preoptic area; VMAT, vesicular monoamine transporter; VTA, ventral tegmental area; YFP, yellow fluorescent protein.

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1. Introduction

The way an animal adapts to its ever-changing environment relies heavily on perceiving sensory information including filtering, coding and building internal representations from it. Although sensory information processing relies mainly on classical fast (glutamate/GABA) neurotransmission in a variety of complex cortical and subcortical neuronal circuits, neuromodulatory systems can have a pronounced influence on its dynamics on multiple stages and timescales. Neuromodulatory systems of the brain are characterized by diffuse projections originating from small clusters of cells located classically in the brainstem and hypothalamic/basal forebrain structures. These cells release neuro-modulators (peptides, amines) that activate G protein-coupled receptors (GPCR). The receptor activation affects the excitability and synaptic inputs to multiple target neurons. Interestingly, a recent study has found that neuromodulators can alter the extracellular concentration of various ions even in the absence of neuronal activity in cortical slices while imposing the same ionic changes *in vivo* resulted in local brain state transitions (Ding et al., 2016). In contrast to fast synaptic neurotransmission, neuromodulation occurs mostly, but not exclusively through volume conduction (van den Pol, 2012). As it mostly involves effects mediated via GPCRs the timescale of neuromodulatory action is considerably slower compared to fast neurotransmission. Although fast neurotransmitters are contained into small vesicles that are released upon single action potential or tonic firing, neuromodulators are found in large dense core vesicles that are released upon a volley of synaptic activity or burst firing (Ford et al., 2009; van den Pol, 2012). Neuromodulatory neurons contain both type of vesicles and exhibit tonic, as well as burst firing patterns, which appears consistent with communication through transmitters and modulators. Interestingly, the cellular activity of modulatory systems of the brain, including monoaminergic systems, is strongly modulated across sleep-wake states (Brown et al., 2012; de Lecea et al., 2012; Fort et al., 2009; Hassani et al., 2009; Lee and Dan, 2012; Saper et al., 2010). The relatively slow time-course of brain state changes makes neuromodulation suitable for behaviorally-relevant adaptation/flexibility (e.g., acquisition of a task, memory consolidation, attention, stress, etc.) and brain state (e.g., sleep-wake cycle) regulation, both phenomena that extend over long periods of time. For instance, long timescale processes influenced by neuromodulators include dopamine in vigor and motivation (Cohen et al., 2012; Hamid et al., 2016; Panigrahi et al., 2015), learning (Rossato et al., 2009), acetylcholine in attention (Goard and Dan, 2009; Parikh et al., 2007; Pinto et al., 2013; Sarter et al., 2009), NA in learning (Martins and Froemke, 2015) and 5-HT in value processing (Nakamura et al., 2008).

In addition to these slow effects, the activity of neurons in various neuromodulatory nuclei can show rapid (less than a second) changes in their activity that are phase-locked to various events including sensory stimuli (Liu et al., 2014; Martins and Froemke, 2015; Ranade and Mainen, 2009), motor responses (Liu et al., 2014; Ranade and Mainen, 2009), reward processing (Liu et al., 2014; Ranade and Mainen, 2009) or brain state changes (Joshi et al., 2016). Due to their widespread anatomical projections, neuromodulatory systems have profound effects on a number of neural targets in various structures of the brain, while acting at multiple timescales. This review focuses on recent progress in elucidating the role of monoaminergic regulation of brain states and sensory information processing with a particular emphasis on studies using optogenetic techniques.

2. New ways to probe monoaminergic systems

When aiming to elucidate the role of different monoamines in various brain functions one can either study the neuronal correlates of a given event (i.e. sensory stimuli or various behavioral events) in monoaminergic neurons or study the causal relationship between their selective control (i.e., activation or inactivation) and various neuronal and/or behavioral readouts. Embarking on such a quest requires to anatomically and functionally disentangle the cellular components of modulatory circuits and their intricate network of projections that can be excitatory or inhibitory depending on their presynaptic vesicular content and the presence or absence of monoaminergic receptor subtypes on the target neurons. All of the evidence supporting a functional role for these circuits in brain state control and sensory processing stems from various *in vitro* and *in vivo* techniques – electrical stimulation, agonist infusion, gene overexpression, lesion, antagonist injection, gene targeting, cell ablation, single unit recording, local field potential recording, immuno-detection of immediate early genes – that have inherent limitations, including low spatial and temporal resolution and possible involvement of compensatory mechanisms. The recent advent of actuator technologies including pharmaco-genetics (Rogan and Roth, 2011) or opto-genetics (Yizhar et al., 2011) can overcome these limitations and offer completely new perspectives on experimental design which has already significantly advanced our understanding of the roles of these systems (Adamantidis, 2015). Both correlative and causal approaches are extremely informative, as correlative experiments provide important information on the endogenous activity of monoaminergic neurons while activation/inactivation experiments provide causal links and assess their sufficiency and necessity in spontaneous brain states, related recurrent oscillations and sensory information processing.

2.1. Correlative studies

Monitoring the activity of monoaminergic neurons during different brain states and behavioral tasks has established strong correlations between neuronal activity or forebrain concentration of monoamines and various aspects of sensory acquisition/processing. The somata of monoaminergic neurons in various nuclei are intermingled in a neurochemically heterogenous neuronal network (Allers and Sharp, 2003; Esclapez et al., 1994; Fu et al., 2010; Iijima and Ohtomo, 1988; Margolis et al., 2010; Sapin et al., 2010). Therefore, revealing the neurochemical identity of the neurons recorded is of pristine importance when attempting to relate neuronal activity to the release of monoamines in various

target areas. Information regarding the neurochemical identity of the recorded neurons can be obtained using a variety of strategies, including post-mortem immunohistochemistry combined with juxtacellular recording/labeling, but usually with a trade-off between reliability and difficulty. Indeed, various parameters of the recorded physiological signals is thought to provide information about the cell type being recorded, for example the shape and duration of action potentials, but the reliability of this simple method to define the neurochemical identity of the targeted neuron remains debatable (Allers and Sharp, 2003; Hajos et al., 2007; Sapin et al., 2010). Pharmacological tools can also provide information on the identity of the neurons being recorded, for example the purportedly selective expression of inhibitory autoreceptors on serotonergic (Courtney and Ford, 2016) and noradrenergic (Schlicker and Gothert, 1998) neurons or SK channels on dopaminergic neurons (Koulchitsky et al., 2012) makes them identifiable using a systemic drug administration while recording single unit activity. A more reliable method for identifying the neurons recorded is juxtacellular labeling using biotinylated amines (Pinault, 1996). This method has the advantage of providing anatomical information on the neurons recorded including morphology and output preferences and can be combined with post hoc immuno-histochemistry. Although this approach has high temporal and spatial resolution, only few neurons can be labeled in a single animal, thus limiting high-throughput analysis of neuronal network in anesthetized or awake head restrained preparations. Optogenetic tools can also be used to provide information about the neurons recorded (e.g., "opto-tagging" of recorded cells) (Herrera et al., 2015; Lima et al., 2009), yet the need for cautious interpretation remains. Using this approach, the neurochemical identity of the recorded neuron can be revealed by combining single unit recordings with photo-stimulation of neurons which express channelrhodopsin (ChR_2) in a cell-type specific manner, however, the possibility of ectopic ChR_2 expression as well as the presence of false negative neurons should be considered. Unlike juxtacellular recording/labeling this method does not provide morphological information on the neurons recorded. Of note, ChR2-assisted circuit mapping – using the membrane location of the transgene protein to reveal cellular projection – has revealed the presence of unexpected circuits, in particular long-range GABA neurons (Basu et al., 2016; Herrera et al., 2015; Melzer et al., 2012). In some cases in addition to confirming that the recorded neuron responds to photo-stimulation and therefore expresses ChR_2 the projection preference can also be revealed using antidromic photostimulation (Ciocchi et al., 2015). The advantage of using optogenetic tools to reveal the neurochemical identity of the neurons recorded is that many identified neurons can be recorded in a single animal making this method amenable for quantitative analysis.

2.2. Causal studies

In an effort to draw more causal evidence, genetic-engineering, pharmacology and electrical stimulation approaches have been used to unravel molecular/cellular mechanisms of monoaminergic systems that still support current hypothesis to date (Carter et al., 2010). However, achieving high temporal and spatial resolutions simultaneously has been quite challenging due to the inherent limitations of the existing techniques. For instance, genetic-engineering leads to single gene mutation (high spatial resolution) from early embryonic ages and in the whole organism. Although conditional approaches or viral targeting can be applied to reduce the temporal windows of action, the timescale of operation remains long and outside the range of physiological dynamics of neural circuits in the brain during sleep-wake states or sensory processing. Finally, transient pharmacological approaches can target selective receptors in restricted brain nuclei, however, the compound is often delivered in non-physiological concentrations and induces long and persistent (in)activation of the targeted receptors, as well as to a lesser extent other non-selective targets. The advent of optogenetic technologies to both image and control the activity of neural circuits has overcome most of those limitations through high temporal (millisecond timescale) and spatial (genetic targeting) resolution offering temporally precise activation/silencing of cellular compartments of a given circuit, but biological systems can still offer substantial challenges. Indeed, in this respect, in neuromodulatory systems previously considered homogenous evidence for extraordinary heterogeneity in their anatomical and functional features has been revealed. Since the afference to monoaminergic systems shows different topography, it requires one to restrict its manipulation to a subset of cells through optical stimulation of axons, retrograde viral targeting or intersectional approaches (see Future directions). Furthermore, an interesting feature revealed by the use of optogenetics is the co-transmission of several transmitters/modulators by single monoaminergic neurons. Two recent studies showed that most median raphe nucleus (MRN) 5-HT neurons are vesicular glutamate transporter (VGLUT) 3 positive, suggesting that they also use glutamate for co-transmission (Sos et al., 2016; Szonyi et al., 2016). Physiological experiments are in line with these anatomical findings (Amilhon et al., 2010; El Mestikawy et al., 2011; Kapoor et al., 2016; Liu et al., 2014; Varga et al., 2009). Similarly, a subset of dopaminergic neurons has been found to co-release glutamate and/or GABA (Borisovska et al., 2013; Tritsch et al., 2016; Vaaga et al., 2014), possibly through $VMAT_2$ vesicular upload of GABA. This phenomenon further highlights the need for a cellular/circuit level understanding of the effects observed *in vivo*, because even if neurochemical specificity can be achieved when targeting one class of monoaminergic neurons a certain effect attributed to monoamine release can in fact be mediated by classical fast neurotransmission. It will be of pristine importance to reveal the conditions and rules under which the release of either monoamines or co-transmitters happens.

3. Monoaminergic systems: few cells, broad projection & multiple functions

Monoaminergic systems participate in the modulation of several brain functions including sleep, arousal, attention, stress, sensory processing and cognition. Interestingly, the average firing rates of noradrenergic, serotonergic and dopaminergic neurons greatly varies across this behavioral repertoire similarly to the neurons of the cholinergic system. In particular, their firing is reduced during non-rapid eye movement (NREM) sleep relative to wakefulness (Brown et al., 2012). During subsequent rapid eye movement (REM) sleep, catecholamine-producing neurons remain quiescent, while cholinergic neurons fire at their highest rates (Brown et al., 2012; Lee and Dan, 2012). Due to their diffuse projections monoaminergic neuromodulator systems are thought to globally affect all brain areas they project to, however, they may exert more local effects via pre/post-synaptic modulation of synaptic transmission, based on each circuit's properties and state. Indeed, a recent study has found differences between both the absolute levels and the rate of state dependent changes in NA concentration at two different cortical sites (Bellesi et al., 2016). Interestingly, neurons in various monoaminergic nuclei are affected by other neuromodulator substances (Brown et al., 2002, 2006). An interplay between various neuromodulator substances including monoamines, their effects on multiple pre- and post-synaptic receptors expressed in a brain area and cell-type specific manner may in principle enable spatially and temporally coordinated neuromodulatory effects. In addition, heterogeneity

among a given monoaminergic neuronal population has been described (Calizo et al., 2011; Schwarz et al., 2015) leading to additional complexity of monoaminergic effects. Here, we propose that these state-dependent changes provide a significant modulatory action on sensory processing during wakefulness and/or NREM or REM sleep in various brain areas and on multiple timescales.

Monitoring the activity of identified monoaminergic neurons during different states and sensory processing in behaving animals and testing their causal involvement in behavior is an important step, however, identifying the cellular targets, locus of action and receptor sub-types involved in monoaminergic modulation will be much more informative for understanding the underlying cellular and network mechanisms. This could be accomplished using optogenetic approaches combined with molecular/cellular and behavioral analysis to eventually lead the way to novel therapeutic approaches for the numerous pathological conditions linked to monoaminergic systems.

Using pharmacological tools, a vast amount of studies have shown various cellular effects of different monoaminergic systems in multiple brain areas. However, bath-application of neuromodulators or their agonists fails to reproduce the temporal and spatial aspects of monoamine release, the direct reflection of tonic and phasic firing of parent neurons. Importantly, exogenous monoamines or their agonists may recruit receptors that are not normally activated by endogenous release. An important function of neuromodulation is thought to control the influence of various input sources to a given brain area. Some neuromodulator substances can suppress feedback inputs carrying information about internal representation but leave feed-forward inputs unaltered therefore increasing the relative influence of external representation over existing models, a useful strategy in an ever-changing environment (Hasselmo et al., 1992, 1997; Lottem et al., 2016). In agreement with this both NA (Foote et al., 1975) and 5-HT (Lottem et al., 2016) can suppress spontaneous cortical activity while leaving sensory evoked responses relatively unaffected.

3.1. Noradrenaline

The LC_{NA} system mediates several aspects of arousal including (hyper-)attention, alertness, cognition during many innate and acquired behaviors and alterations in LC neuronal discharge is associated with distinct changes in behavior, cognition, sensory processing and regulation of the sleep-wake cycle. Similar to other monoaminergic systems LC_{NA} neurons are thought to have broad, "diffuse" projections throughout the forebrain. To what extent can LC_{NA} projections in particular and monoaminergic projections in general be considered diffuse is an important question. A recent study using trans-synaptic viral tracing methods confirmed that LC_{NA} neurons innervating various brain areas receive relatively similar synaptic inputs and LC_{NA} neurons projecting to one output region also project to all other LC_{NA} brain regions, in line with a homogenous input/output organization (Schwarz et al., 2015). At the same time evidence for specificity and heterogeneity was also apparent highlighting a role for LC_{NA} sub-circuits.

There are relatively few causal investigations on the role of noradrenergic transmission in the brain. *In vitro*, noradrenaline increases the excitability of pyramidal cells by depolarizing their membrane potential and decreasing spike frequency adaptation (Wang and McCormick, 1993). Noradrenaline, acting on α1 adrenoceptors can increase the frequency of IPSCs in pyramidal neurons and depolarize several types of GABAergic interneurons in the neocortex (Kawaguchi and Shindou, 1998) and thalamic reticular nucleus (McCormick and Wang, 1991). Noradrenaline can shift the balance between dendritic and perisomatic inhibition (Salgado et al., 2011), increase the frequency of miniature inhibitory postsynaptic currents, and the release probability of unitary IPSCs, effects mediated by presynaptic α2 and β-adrenoreceptors on PV-positive neurons, but depresses GABAergic currents through the activation of postsynaptic α1 adrenoceptors (Salgado et al., 2012). Noradrenaline induces persistent firing in pyramidal neurons of the prefrontal cortex (PFC), through both pre- and post-synaptic mechanisms involving α1 and α2 adrenoceptors, respectively (Zhang et al., 2013) and by inhibiting I_h (Wang et al., 2007). This mechanism could provide a noradrenergic control over cortical information processing, as cortical persistent activity is the cellular substrate of working memory (Major and Tank, 2004).

In vivo, LC_{NA} neurons are tonically active during wakefulness, while their activity decreases during NREM sleep (Aston-Jones and Bloom, 1981a). Noradrenaline mediated tonic depolarization of cortical circuits is necessary for the tonic depolarization associated with locomotion (Polack et al., 2013). A recent elegant study showed that pairing sounds with LC single neuron depolarization can lead to the emergence of sensory responses in previously unresponsive neurons and this LC plasticity induced long term changes in the auditory cortex leading to improved auditory perception (Martins and Froemke, 2015).

3.2. Serotonin

Originating from a small cluster of neurons located in the brainstem raphe nuclei 5-HT is an important neurochemical implicated in a wide variety of behavioral, cognitive and emotional processes and is an important pharmacological target in the treatment of many psychiatric and neurological diseases including depression, anxiety, panic disorder and chronic pain (Michelsen et al., 2007). Theoretical and experimental work suggested 5-HT can regulate aversive learning (Daw et al., 2002; Dayan and Huys, 2009; Soubrié, 1986), can signal reward states (Daw et al., 2002) and promotes waiting (Fonseca et al., 2015; Miyazaki et al., 2012; Miyazaki et al., 2014). Two recent studies have shown that identified 5-HT neurons can signal information about reward and punishment on various timescales (Cohen et al., 2015; Liu et al., 2014).

The cellular and network effects of 5-HT are diverse affecting excitability of various cortical neurons and synaptic transmission through multiple receptors. Exogenous application of 5-HT to cortical brain slices has been shown to elicit hyperpolarizing and depolarizing effects on pyramidal and non-pyramidal cells as well as to modulate synaptic transmission. However, care must be taken when interpreting the results of some studies, which have used very high concentrations of bath applied 5-HT (tens of μM) whereas physiological levels of 5-HT in target areas is at the order of tens of nM (Bunin and Wightman, 1998). The most obvious direct effect of 5-HT on cortical pyramidal neurons is a hyperpolarization mediated by 5-HT_{1A} receptors (Araneda and Andrade, 1991) by opening of Kir3 channels (Hibino et al., 2010). A subset of pyramidal neurons also express 5-HT_{2A} receptors that, when activated by 5-HT, induce a slow membrane depolarization that results from the inhibition of the slow calcium-activated afterhyperpolarization (Villalobos et al., 2005). Consistent with these effects, 5-HT increases spontaneous excitatory postsynaptic currents (EPSCs) in pyramidal neurons through the activation of 5-HT(2A) receptors (Zhou and Hablitz, 1999a). In the medial PFC pyramidal neurons projecting to the contralateral cortex are excited by 5-HT via 5-HT2a receptors, but dorsal raphe nucleus (DRN) projecting neurons are inhibited by 5-HT via 5-HT1a receptors (Avesar and Gulledge, 2012), implying some functional separation among cells expressing different 5-HT receptors. However, numerous pyramidal cells express both of these receptors, as administration of 5-HT to these neurons results in

a biphasic (depolarizing/hyperpolarizing) response (Araneda and Andrade, 1991). 5-HT can also reduce the amplitude of action potentials backpropagating into the apical dendrite of pyramidal neurons by blocking dendritic Na^+ channels (Carr et al., 2002) and can inhibit voltage-dependent Ca^{2+} channel currents (Day et al., 2002). 5-HT induces a massive enhancement of spontaneous inhibitory postsynaptic currents (sIPSCs) in pyramidal neurons (Zhou and Hablitz, 1999a). 5-HT2a and 5-HT3 receptor mediated depolarizing and 5-HT1 receptor mediated hyperpolarizing responses to 5-HT have also been observed in different types of GABAergic interneurons with some consistency regarding different morphological classes (Ferezou et al., 2002; Foehring et al., 2002; Lee et al., 2010; Xiang et al., 1998). Interestingly, some cortical interneurons expressing vasoactive intestinal peptide (VIP)/cholecystokinin (CCK) but not parvalbumin (PV) or somatostatin (SOM) express the ionotropic 5-HT3 receptor and pharmacological activation of these receptors leads to massive membrane depolarization and action potential output (Ferezou et al., 2002; Lee et al., 2010).

In addition to these post-synaptic effects 5-HT can also affect synaptic transmission. Specifically, 5-HT potently suppresses excitatory synaptic transmission via 5-HT1A receptors in layers II and III of the medial entorhinal cortex by a presynaptic mechanism (Schmitz et al., 1998) and also inhibits GABA release from fast spiking neurons in the neocortex (Kruglikov and Rudy, 2008). 5-HT can shift the excitatory-inhibitory balance in favour of more excitation (Moreau et al., 2010). There is evidence for a cell type specific modulation of synaptic transmission by 5-HT (Komlosi et al., 2010; Winterer et al., 2011). Specifically, *in vitro* studies suggest that in human neocortical circuits bath applied 5-HT suppresses pyramidal neuron-interneuron connections but leaves the output of GABAergic cells unaffected (Komlosi et al., 2010). In the hippocampus 5-HT can reduce synaptic excitation of CCK expressing interneurons but not PV expressing basket cells (Winterer et al., 2011).

3.3. Histamine & GABA

Histaminergic neurons are involved in mediating specific aspects of wakefulness (Anaclet et al., 2009; Parmentier et al., 2002; Takahashi et al., 2006). Unlike the hypocretin/orexin cells that release glutamate (Schöne et al., 2014), the wake-promoting histamine cells from the posterior hypothalamus possess all the machinery necessary to synthetize GABA and this mode of transmission had not been tested until recently. Optogenetic activation of histaminergic neurons *in vitro* disinhibits tuberomamillary nucleus (TMN) cells themselves, while indirectly suppressing the activity of sleep-promoting cells from the anterior hypothalamus through local GABA interneurons (Williams et al., 2014). Furthermore, *in vivo* optogenetic activation of histaminergic neuron terminals in the striatum and cortex evoked tonic (extrasynaptic) GABAA receptor chloride currents onto medium spiny neurons and pyramidal neurons, respectively. Importantly, these currents were abolished following genetic deletion of VGAT from histamine cells, suggesting an inhibitory mode of action (Yu et al., 2015). At the cellular and network level histamine has diverse effects (Haas et al., 2008). Histamine can depolarize cortical and thalamocortical neurons while increasing their input resistance via H_1 receptors (McCormick and Williamson, 1991; Reiner and Kamondi, 1994) and can increase I_h in thalamocortical neurons (McCormick and Williamson, 1991). Antagonists of H_1 receptors, which have a well-known sedative effect can block the M-current in cortical neurons (Sato et al., 2005). Histamine can reduce the firing accommodation in hippocampal pyramidal neurons (Haas and Panula, 2003), can inhibit GABAergic neurons in the hippocampus (Atzori et al., 2000) and the thalamic reticular nucleus via H_2 receptors (Lee et al., 2004). Pharmacological activation of H_4 receptors hyperpolarizes mouse cortical neurons, increases their input resistance and does not affect thalamocortical synaptic transmission (Connelly et al., 2009). Altogether, these studies confirmed the inhibitory nature of the histaminergic cells, while the precise synaptic mechanism involved and the role of specific histamine receptor in mediating these responses await further investigation.

3.4. Dopamine

The function of the dopaminergic system and its involvement in reward processing (Schultz et al., 1997) has been reviewed extensively in the past years focusing on transient dopaminergic signals (Bermudez and Schultz, 2014; Paladini and Roeper, 2014), optogenetic strategies for studying VTA circuits (Pupe and Wallen-Mackenzie, 2015), the diversity of midbrain dopaminergic neurons (Roeper, 2013), the role of dopamine in plasticity (Pignatelli and Bonci, 2015) among others. Briefly, dopaminergic neurons show bidirectional coding of reward-prediction errors signaling the difference between the predicted and actual rewards. The majority of midbrain dopaminergic neurons show transient increases in their activity upon conditioned stimuli including visual, auditory and somatosensory stimuli predicting reward (Schultz, 1998). Dopaminergic neurons also respond to salient novel stimuli (Horvitz, 2000; Ljungberg et al., 1992) recently characterized as neuronal responses to real and potential reward (Kobayashi and Schultz, 2014). Interestingly, whereas VTA dopaminergic neurons are associated with reward outcomes a recent study found that dopaminergic neurons in the DRN undergo synaptic changes following acute social isolation, show increased activity upon rebound social contact and their optogenetic activation increases social preference but causes place avoidance (Matthews et al., 2016). This study further highlights the importance of heterogeneity in a given circuit and also the advantage of using cell-type specific optogenetics to monitor and control the activity of a subset of neurochemically defined neurons.

At the cellular and network level the effects of dopamine are very diverse, consistent with the general properties of neuromodulatory systems. Iontophoretic applications of dopamine or electrical stimulation of the VTA leads to the suppression of spontaneous and evoked firing of PFC neurons (Bernardi et al., 1982; Ferron et al., 1984; Godbout et al., 1991; Mantz et al., 1988; Pirot et al., 1992; Sesack and Bunney, 1989). Dopamine has been shown to increase the excitability of PFC pyramidal cells (Ceci et al., 1999; Gorelova and Yang, 2000; Henze et al., 2000; Penit-Soria et al., 1987; Yang and Seamans, 1996) and thalamocortical neurons (Govindaiah et al., 2010). Dopamine can decrease the spike AHP (Malenka and Nicoll, 1986) and this effect might underlie the increased gain in the frequency-current relationship of pyramidal neurons recorded in vitro in response to noisy input currents (Thurley et al., 2008). In the mouse PFC pyramidal neurons expressing D1 receptors possess distinctive morphological and physiological properties including compact dendritic arborization and burst firing activity, respectively while pharmacological activation of D1 receptors can substantially boost their action potential output (Seong and Carter, 2012). In contrast, some studies have shown a decrease in the excitability of rat PFC pyramidal neurons upon dopamine application (Geijo-Barrientos and Pastore, 1995; Gulledge and Jaffe, 1998, 2001; Zhou and Hablitz, 1999b) suggesting a more complex mode of modulatory action on these cortical targets.

Indeed, in layer 5 pyramidal neurons of the PFC activation of D1 receptors decreases, activation of D2 receptors increases axonal K^+ currents, suggesting an important role for dopaminergic regulation of neuronal signaling via axonal voltage gated K^+ channels (Yang

et al., 2013). D1/D5 receptor activation can increase the I(Nap) generated in the proximal axon initial segment (Gorelova and Seamans, 2015). Dopamine modulates K_{IR} currents in pyramidal neurons via cAMP and PKA signaling (Dong et al., 2004; Dong and White, 2003) and Ih in interneurons regulating the resting membrane potential (Rosenkranz and Johnston, 2006; Wu and Hablitz, 2005), depolarizes fast spiking interneurons by suppressing a voltage-independent 'leak' K^+ current (via D1/D5 receptor mechanism), a K_{IR} current and a slowly inactivating K^+ current resulting in an increased firing in response to depolarizing current steps in these neurons (Gorelova et al., 2002), this could lead to a net increase in overall action potential output (Trantham-Davidson et al., 2008).

In addition dopamine can also affect synaptic transmission. In the PFC, dopamine can increase extracellular GABA concentrations via D1 and/or D2 receptors (Bourdelais and Deutch, 1994; Del Arco and Mora, 2000; Grobin and Deutch, 1998; Retaux et al., 1991). Dopamine decreases IPSCs in layer II–III PFC neocortical pyramidal cells by activating presynaptic D1-like receptors (Gonzalez-Islas and Hablitz, 2001), but increases inhibition via a presynaptic, action potential–dependent mechanism (Kroner et al., 2007). Dopamine also suppresses inhibition in pyramidal neurons mediated by perisomatic targeting fast spiking interneurons via a D1 mediated presynaptic mechanism but enhances inhibition between non-FS interneurons and pyramidal cells (Gao et al., 2003). Dopamine enhances EPSCs in layer 2/3 pyramidal neurons in rat PFC cortex via D1 mediated post-synaptic effect (Gonzalez-Islas and Hablitz, 2003), but decreases the efficacy of unitary EPSPs between simultaneously recorded layer V pyramidal cells in primate neocortical slices maintained in vitro via a presynaptic D1 mediated mechanism (Gao et al., 2001).

Dopamine can influence an mGluR5-mediated depolarization essential for persistent activity in the PFC (Sidiropoulou et al., 2009) and can block cortical UP states in the medial entorhinal cortex via a D1 receptor mediated mechanism (Mayne et al., 2013). As mentioned in the case of 5-HT care must be taken when interpreting the results of experiments using relatively high concentrations of exogenously applied substances. A failure to replicate the spatiotemporal profile of endogenously released neurotransmitters and modulators is only one caveat of pharmacological receptor activation. An important aspect relies in the possible activation of receptors located at sites distal from dopaminergic axon terminals. Thus pharmacological activation of receptors can lead to different effects when compared to the physiological release of these substances. In agreement with this, local optogenetic stimulation of VTA dopaminergic fibers in the hippocampus leads to contrasting results to exogenous bath application of dopamine *in vitro* (Rosen et al., 2015).

4. Monoamines and brain states

Since the seminal experiment in the 30s which identified the brainstem as a critical area for sleep-wake control (Moruzzi and Magoun, 1949) and suggested sleep as a default, or passive, behavioral state, investigation over the last decades have progressively defined a new framework where sleep is now considered an active brain state that results from the coordinated activity of multiple neuronal circuits distributed across the brain (Fig. 1). In this view, the neural underpinnings of the sleep-wake state involve interactions between sleep-promoting areas such as the anterior hypothalamus, and arousal systems (most are wake-promoting) located in the posterior hypothalamus, the basal forebrain and the brainstem (Fort et al., 2009; Hobson and Pace-Schott, 2002; Weber et al., 2015). The arousal systems include the histaminergic and the hypocretinergic neurons in the hypothalamus; the cholinergic neurons, located in the pons and the basal forebrain, the noradrenergic neurons of locus coeruleus (LC), the dopaminergic and serotonergic raphe neurons of the brainstem

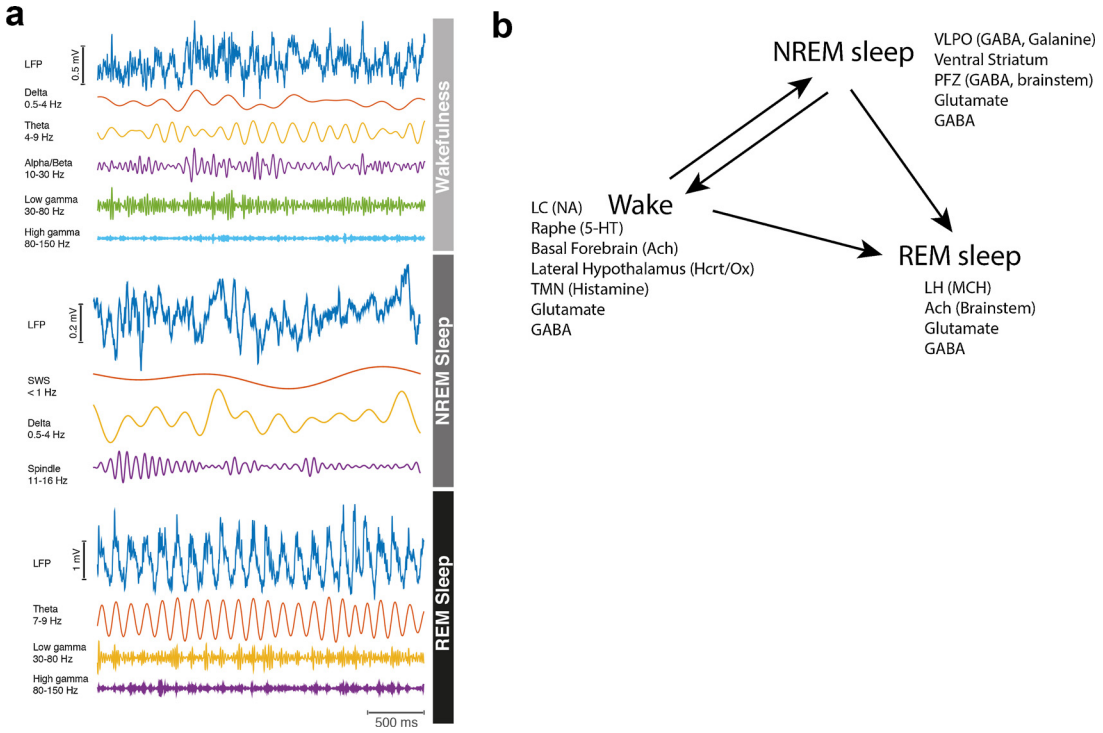

Fig. 1. Sleep-wake states in the rodent brain. (A) Filtering decomposition of LFP/EEG signals recorded from cortical layer 5 (Wakefulness and NREM sleep) and Hippocampus (pyramidale layer, REM sleep) across sleep-wake states in freely-moving mice. (B) Temporal organization of the successive recurrence of sleep-wake states. After prolonged wakefulness, the animal transitions to NREM sleep, from which it either wakes up or falls into "deeper" REM sleep. Termination of REM sleep is signaled by wakefulness in non-pathological states.

(Aston-Jones and Bloom, 1981a; Dahan et al., 2007; Hassani et al., 2009; Takahashi et al., 2008).

The state dependent concentration changes of monoamines has been extensively studied using microdialysis and voltammetry/amperometry. Forebrain extracellular concentrations of most monoamines drop during sleep compared to wakefulness (Mochizuki et al., 1992; Portas and McCarley, 1994; Shouse et al., 2000; Trulson, 1985). Interestingly, in addition to showing state dependent concentration changes NA levels can vary in a cortical area specific manner: the absolute levels of NA being higher, but the occurring changes slower in the PFC compared to motor cortex (Bellesi et al., 2016).

The advent of optogenetics (considering here the actuators, rather than the indicator of cellular activity) are recently providing new experimental ways to manipulate these circuits, with unprecedented temporal and spatial resolution, and establish solid functional links between (in)activity of single circuit elements and selective brain sates or behavior. Importantly, such "causal" approaches are only possible thanks to the tremendous data previously and currently acquired with more classical technologies. Indeed, to be considered as such, a sleep or a wake circuit must exhibit state-dependent activity across spontaneous behaviors: not only does their activity increase when an animal is awake compared to asleep, but their activity also increases during states of enhanced arousal, such as alertness, stress and sensory processing (Carter et al., 2010). Arousal centers described above send widespread ascending projections to subcortical and cortical structures, where they promote high frequency gamma and theta oscillations (Steriade et al., 1993). In addition, their descending projections modulate physiological activity including muscle tone, autonomic and sensory systems.

At the thalamocortical level, the resting membrane potential of thalamic relay neurons is kept elevated by neuromodulators including noradrenaline, dopamine, 5-HT and acetylcholine resulting in tonic firing mode (McCormick and Bal, 1997). As the level of arousal decreases the excitatory influence of wake-promoting systems on thalamic and cortical neuronal populations progressively diminishes. A reduction of noradrenaline, dopamine, 5-HT release leads to hyperpolarization of the resting membrane potential of thalamic cells and burst firing (Hirsch et al., 1983). Hyperpolarization of thalamocortical neuron membrane potential leads to de-inactivation of T-type Ca^{2+} channels (Leresche et al., 1990) and rhythmic low frequency burst firing. An interplay between T-type Ca2+ channels and various intrinsic currents (I_h, I_{CAN}, $I_{Twindow}$, I_{Kleak}) can lead to either delta oscillation (1–4 Hz) or UP states resulting in a slow (<1 Hz) oscillation (Hughes et al., 2002; Williams et al., 1997). These bursts can be synchronized among thalamocortical neurons leading to the expression of robust low frequency/high amplitude (<4 Hz) oscillations in the thalamocortical network which characterize the electroencephalogram (EEG) during NREM sleep (Steriade et al., 1993). Thalamocortical networks thus represent a core element for generating slow (<1 Hz) and delta (1–4 Hz) oscillations (Steriade et al., 1993) and faster rhythms during NREM sleep. Although these latter have been quite ignored in the quest for sleep-wake control in experimental sleep research, recent studies highlighted their importance in relaying sub-cortical sleep-wake signals (Herrera et al., 2015) and their possible role in modulating hippocampus-cortex information transfer during sleep states (Crunelli et al., 2014; Halassa et al., 2011; Logothetis et al., 2012; Lőrincz et al., 2015).

According to the current hypothesis sleep-promoting neural populations include inhibitory neurons (GABA, galanin) of the ventrolateral preoptic area (VLPO), the median preoptic nucleus (MnPN) located in the preoptic area (hypothalamus), which are active during NREM (Alam et al., 2002; Gallopin et al., 2000; McGinty et al., 2004). Recent studies identified additional sleep active neural populations located in the brainstem parafacial nuclei (Anaclet et al., 2014), a subset of GABAergic cortical cells expressing neuronal NOS (Gerashchenko et al., 2008) and the ventral striatum (Lazarus et al., 2012). These sleep-promoting neurons project to arousal-promoting cell groups where they are thought to inhibit noradrenergic, serotonergic, cholinergic, histaminergic and hypocretinergic neurons (Suntsova et al., 2007) as suggested by the "reciprocal inhibitory" model (Pace-Schott and Hobson, 2002).

Brain structures whose activity correlates with REM sleep onset and maintenance include cholinergic neurons of the pedunculopontine and latero-dorsal tegmental nuclei (Pace-Schott and Hobson, 2002) and GABAergic neurons located in the dorsal paragigantocellular reticular nucleus (DPGi) and the ventrolateral periaqueductal gray (vlPAG) (Fort et al., 2009; Weber et al., 2015). Note that additional sleep-promoting neuronal populations in the cortex and hypothalamus have recently been identified (Hassani et al., 2009; Morairty et al., 2013; Verret et al., 2003) but their participation to NREM or REM sleep requires further investigation. To date, causal evidence support a role for melanin-concentrating hormone producing neurons in the lateral hypothalamus in REM sleep induction and maintenance, while their optical silencing during REM sleep promotes reverse REM sleep-to NREM sleep transitions (Jego et al., 2013). Of note, sustained optical stimulation of LH_{MCH} cells, increased NREM sleep duration (Jego and Adamantidis, 2013; Konadhode et al., 2013). Importantly, the activity of GABAergic neurons in the ventral medulla correlate with REM sleep episode, (Fort et al., 2009; Luppi et al., 2016) was shown to causally induced REM sleep episode (Weber et al., 2015).

At the thalamo-cortical network level, the raise of cholinergic tone depolarizes thalamic cells leading to inactivation of I_T and I_h (McCormick, 1992a), resulting in a switch from LTCP mediated burst firing to either tonic firing or high threshold burst firing mode (Hughes et al., 2004; Lőrincz et al., 2008, 2009), seen at the EEG level by the disappearance of low frequency/high amplitude (<4 Hz) oscillations.

Next, we will focus on the role of noradrenaline, 5-HT, histamine and dopamine systems on brain states and sensory integration (Fig. 2).

4.1. Noradrenaline

The LC_{NA} neurons project extensively to the neocortex and thalamus (Vazey and Aston-Jones, 2014) where noradrenergic receptors (predominantly alpha 1, beta and alpha 2) are also expressed (McCormick, 1992a). Activation of noradrenaline neurons from the locus coeruleus (LC_{NA}) correlates with states of arousal and wakefulness in rats (Aston-Jones and Bloom, 1981a) in which they exhibited a slow, tonic, basal discharge rate with brief phasic responses to novel sensory stimuli (visual, auditory, somato-sensory and gustatory) (Aston-Jones et al., 1994; Clayton et al., 2004). Upon transition to NREM sleep, their tonic firing show a progressive decrease in frequency until they become silent during REM sleep, however LC neuron firing in NREM sleep is still locked to some extent to UP/DOWN states (Eschenko et al., 2012). Accordingly, we and others have demonstrated a causal evidence supporting a role for LC_{NA} in arousal (Carter et al., 2010; Vazey and Aston-Jones, 2014). In monkeys, LC_{NA} neurons are selectively associated with attended cues in a vigilance task (Aston-Jones and Bloom, 1981a). Therefore, arousal induced by stimulation of the LC may occur from direct activation of the cortex or indirect activation of the thalamus or other sub-cortical structures. Consistent with this anatomical distribution, bath application of NE on TC cells induces a switch from burst (typical of NREM sleep) to tonic firing, mediated by a slow depolarization (alpha 1) and an enhancement of the Ih current during hyperpolarization (beta receptors) and

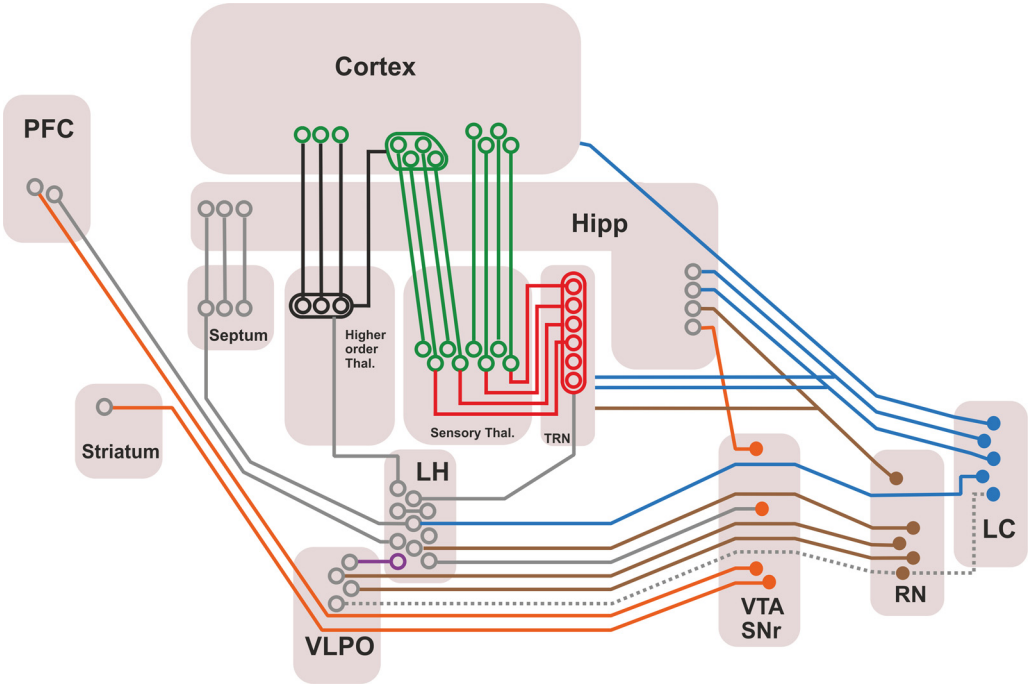

Fig. 2. Schematic representation of cortical and sub-cortical sleep-wake circuits. Noradrenaline (blue), acetylcholine (green), 5-HT (brown), dopamine (orange) neurons send widespread projections to the forebrain and cortical structures, thalamo-cortical circuits, hypothalamus (both anterior and posterior). Thalamic structures are divided into thalamic reticular nucleus (TRN, red), sensory thalamus (green) and higher order thalamus (Black). Additional circuits associated to brain states, sensory processing and cognitive processing are shown in grey (septum-hippocampus, lateral hypothalamus, striatum). Local and long-range GABA, glycinergic and glutamatergic neurons are not shown, except for the putative VLPO inhibitory inputs to brainstem modulatory systems (grey dashed line). Abbreviations: Hipp, hippocampus; LH, lateral hypothalamus; PFC, prefrontal cortex; RN, raphe nuclei; SNr, substancia nigra pars reticulata; LC, Locus coeruleus; VLPO, Ventro-lateral pre optic nucleus; VTA, Ventral tegmental area.

correspond to the onset of wakefulness (or REM-like state) or the emergence from anesthesia (McCormick, 1992a; Vazey and Aston-Jones, 2014). In addition, LC_{NA} fibers also innervate the TRN, where the alpha 1 receptor is densely expressed (McCormick, 1992b) and the hypocretin neurons of the hypothalamus where their depolarizing effect is converted to a hyperpolarizing one following sleep deprivation (Grivel et al., 2005; Uschakov et al., 2011). Bath application of NE or electrical activation of LC area results in a depolarizing effect in TRN neurons resulting in suppression of burst firing (Rogawski and Aghajanian, 1980, 1982). According to the model described above, once NE concentration diminishes (or washes out) burst firing slowly reappears. According to the current model of sleep-wake control, it has been suggested that weak LC_{NA} activation promotes burst firing while strong activation inhibits it (McCormick et al., 1991), suggesting that LC_{NA}-thalamus circuit itself strongly influences both sleep and awake states.

As proposed previously (Aston-Jones and Bloom, 1981a; Aston-Jones and Cohen, 2005), during wakefulness the LC_{NA} neurons control "adaptive gain and optimal performance". In their view, phasic LC activation is driven by the outcome of task-related decision processes and is proposed to facilitate subsequent behaviors and to help optimize task performance. In turn, when the subject's engagement in the task wanes, LC_{NA} neurons revert to a slow tonic firing.

4.2. Serotonin

5-HT is produced by group of cells that are exclusively found it the raphe nuclei of the brainstem. Similarly to LC_{NA} neurons, dorsal raphe neurons are strongly activated during wakefulness and progressively decrease their firing rate during NREM sleep to become silent during REM sleep (Trulson and Jacobs, 1979) and the forebrain 5-HT levels vary accordingly (Portas et al., 2000). However there are no recordings of identified serotonergic neurons during the sleep-wake cycle, and recordings from unidentified dorsal raphe neurons revealed considerable heterogeneities (Urbain et al., 2006).

Based on electrophysiological, neurochemical, genetic and pharmacological studies, it is currently accepted that 5-HT predominantly promotes wakefulness and inhibits REM sleep, however, it contributes to the increase in sleep propensity under certain conditions (Monti, 2011). Although the precise underlying mechanism remains unclear dorsal raphe 5-HT neuron innervation reaches brain areas involved in controlling the sleep-wake cycle including the cerebral cortex, amygdala, basal forebrain, thalamus, hypothalamic areas, LC and pontine reticular formation, where subtypes of the seven type 5-HT receptors (5HT1-7) are expressed (Paul and Lowry, 2013). In the thalamus, serotonergic afferents from the median and dorsal raphe target midline and intralaminar nuclei, and, more generally, the higher order nuclei, where they have heterogeneous effects on membrane potential depending on cell types and species considered (Varela and Sherman, 2009).

4.3. Histamine

The TMN of the hypothalamus contains all the neurons that produce and release histamine in the brain. Consistent with neuromodulatory system features, TMN_{Hist} neurons project widely throughout the brain including sleep and wake centers and nuclei. Although the direct and causal effects of histamine neuron activity on wakefulness remains unclear, its release in the brain correlates with wakefulness (Mochizuki et al., 1992) and TMN_{Hist} neurons are characterized by high firing rates during wakefulness – similar to hypocretin/orexin neurons, another wake-promoting system from the lateral hypothalamus – in particular immediately after sleep-to-wake transitions (Takahashi et al., 2006). Histamine acts through several histamine receptors, some of which being the target of anti-histaminergic (H1 blocker) that induced sleep as a

side-effect to their anti-allergenic properties (Ikeda-Sagara et al., 2012).

Selective siRNA knockdown or genetic ablation of the vesicular GABA transporter (VGAT) in histaminergic neurons produced hyperactive mice with unusual period of long consolidated wakefulness (Yu et al., 2015). The long range of histamine-GABA axonal projections suggests that extra-synaptic inhibition will be coordinated over large neocortical and striatal areas (Yu et al., 2015).

4.4. Dopamine

A recent study found strong evidence for the involvement of the VTA dopaminergic system in regulating arousal (Eban-Rothschild et al., 2016). By performing bulk calcium imaging using fiber photometry the authors recorded brain state dependent activity in VTA dopaminergic neurons. Following these correlative observations, chemogenetic and optogenetic activation and incativation of VTA dopaminergic neurons turned out to be both necessary and sufficient for arousal and the effects might be target specific. These results could have important functional implications since stimulus-responsive VTA neurons were shown to be reactivated during quiet wakefulness and sleep periods following a task that involved those stimuli (Valdés et al., 2015).

5. Monoaminergic modulation of sensory processing across various brain states

During wakefulness external inputs are first encoded in various sensory circuits and then consolidated through plastic changes during a "consolidation window" that starts few minutes after sensory learning and last for few hours (i.e., 4–5 h). Interestingly this consolidation may span across different brain states including wakefulness, NREM or REM sleep. The precise underlying mechanism of such consolidation remains unclear, yet monoaminergic systems are thought to play a major role since they are involved in the regulation of both brain states and sensory processing. Indeed, as described above, the discharge rates of neurons in various monoaminergic nuclei are usually reduced during NREM sleep relative to wakefulness. This (slow) change in modulatory tone may provide an "internal environment" that favors certain forms of plasticity required for the consolidation of sensory processing. Since these monoaminergic systems send massive projections to sensory thalamic and cortical structures, they could modulate sensory circuits during both learning (=acquisition) and consolidation of sensory processing.

Interestingly, firing rates of LC_{NA} neurons are enhanced during slow wave sleep after new learning in the preceding wakefulness period during an olfactory discrimination task, providing a possible off-line memory processing (Eschenko et al., 2012) and increase their phase-locking to cortical UP state during NREM sleep (Eschenko and Sara, 2008). Consistent with these results, pharmacological enhancement of noradrenergic tone during human sleep improves next-day task performance, whereas its reduction has the opposite effect (Gais et al., 2011). Similarly, available data indicates that after learning, a reduced cholinergic neurotransmission during NREM sleep is critical for the next-day improvement in performance (Gais and Born, 2004; Rasch et al., 2006). Although no direct effect of histamine has been described on sensory processing *per se*, experimental evidence suggests that an intact histaminergic system is required for maintaining appropriate levels of attention during wakefulness (Parmentier et al., 2002). In addition, histamine receptors are the targets for cognitive enhancement drugs (Kohler et al., 2011), suggesting that histaminergic neurons may participate in the general arousal required for optimal sensory processing.

The effect of 5-HT and NA on sensory information processing has been reviewed in detail elsewhere (Hurley et al., 2004). Here we focus on recent advances in the field obtained by using optogenetic tools to study the role of monoamines in sensory coding. Studying the effects of monoamines in sensory coding has been hampered by the lack of specific and temporally accurate tools. Electrical stimulation, a gold standard for causal studies has excellent temporal resolution, but completely lacks neurochemical specificity, as a stimulating electrode inserted in any brain area will indiscriminately activate proximal neurons and fibers of passage (Histed et al., 2009). Pharmacological tools can have relatively good specificity (although in vivo administration of drugs in the desired concentrations is usually challenging) but fail to replicate the temporal profile of the released monoamines. In addition, all receptors expressed will be activated not only the ones situated close to monoaminergic fibers. Optogenetic tools can be targeted to neurochemically defined neuronal populations, have excellent temporal specificity and can be used both for boosting or suppressing neuronal activity (Yizhar et al., 2011), although some constrains exist (Mahn et al., 2016). But even photostimulation of a neurochemically homogeneous neuronal population using ChR_2 might not take into account the heterogeneity within a given neuromodulatory system. In this respect only targeting subsets of neurons within a population of defined neuromodulatory cells by adding output specificity, wavelength-specific activation of opsins or using intersectional methods (Fenno et al., 2014; Klapoetke et al., 2014; Madisen et al., 2015; Schwarz et al., 2015; Yizhar et al., 2011) will lead the way to better understand the organization and function of monoaminergic systems.

Generally, the state dependent firing rate changes of various monoaminergic neurons and the resulting changes in forebrain monoamine levels is thought to be, at least partly, the cause of the state dependence of sensory responses. The mean firing rate of presumed monoaminergic neurons is higher during the awake state compared to NREM sleep. In the noradrenergic system, the remaining activity of LC_{NA} neurons during NREM sleep (Eschenko et al., 2012) suggests processing of sensory input in primary sensory regions or memory pathways during sleep (Aton, 2013; Nir et al., 2015). In addition to these slow state dependent activity changes, more rapid and transient activity changes phase locked to various sensory events characterize the activity of various neurons in monoaminergic nuclei of behaving animals (Aston-Jones and Bloom, 1981a, 1981b; Aston-Jones et al., 1994; Joshi et al., 2016; Liu et al., 2014; Montagne-Clavel et al., 1995; Ranade and Mainen, 2009; Waterhouse et al., 2004). This suggests that monoamines can affect their targets on several timescales. Although the latency of activity changes in response to sensory stimuli in MA neurons is variable, it can be remarkably rapid (i.e. 20-ms click responses in DRN neurons) (Ranade and Mainen, 2009). Taking into account the latency, duration and the relatively slow conduction velocity of monoaminergic fibers, the potential role of these transient sensory related activity changes could be to affect a forthcoming decision or motor program (Aston-Jones and Cohen, 2005). Therefore, monoamine activity could link sensory processing to higher order cognitive processes and motor components during animal behavior. One interesting aspect of olfactory related activity in the DRN of behaving animals is that the activity of some neurons is transiently altered before the odor presentation after the animal has entered the odor port (Ranade and Mainen, 2009), suggesting a context-dependent top-down modulation of DRN neuronal firing which not only influences forthcoming decisions or motor programs but sensory information processing as well. This context-dependent top-down input to the DRN may originate from the PFC and/or orbitofrontal cortices (Warden et al., 2012). In different sensory modalities the enhanced sensitivity of cortical neurons can be caused by higher order thalamic inputs. Specifically, in the

somatosensory system, optogenetic stimulation of the posteromedial thalamic nucleus resulted in the amplification and temporal extension of L5 barrel cortex pyramidal neuron responses to whisker stimulation (Mease et al., 2016).

Concerning the effect of monoamines on sensory coding on a rapid timescale two recent studies have revealed that transient activation of DRN 5-HT neurons can drastically affect the activity of both OB (Fig. 3) (Kapoor et al., 2016) and anterior piriform cortex (aPC) neurons (Fig. 4) (Lottem et al., 2016). Specifically, switching on 5-HT neurons in anesthetized mice leads to suppression of action potential output in the majority of the recorded aPC neurons (Fig. 4C). This prominent suppression of firing by 5-HT photostimulation was divisive, i.e. scaled with the baseline activity of the recorded neurons (Fig. 4D). Importantly, responses to various odorant molecules were unaffected by the activation of DRN 5HT neurons (Fig. 4E and F) suggesting 5-HT could play a peculiar role in olfactory coding. The mechanisms of the observed effects remain to be elucidated, but it is tempting to speculate on the possible mechanism that would cause the observed drastic suppression of firing and action potential output. Firstly, it remains to be tested whether the observed effects are the consequence of a direct action within the aPC as DRN 5-HT photostimulation could affect circuits outside the aPC and these could affect aPC neuronal activity. Indeed, in the OB brief DRN 5-HT photostimulation results in excitation of tufted cell spontaneous activity and potentiation of their odor responses whereas mitral cell spontaneous activity is excited but, their odor responses bidirectionally modulated (Kapoor et al., 2016). A second question is whether the effect on aPC spontaneous activity is mediated by 5-HT. If 5-HT is involved in the observed effects the suppression of firing could either result from a direct inhibitory effect through one of the 5-HT receptors coupled to inhibitory signaling or alternatively, 5-HT could excite aPC GABAergic interneurons which would in turn inhibit principal neurons. It is noteworthy to note in this respect that a small subset of aPC neurons increased their spontaneous firing upon 5-HT photostimulation (Fig. 4C). Whichever might be the underlying

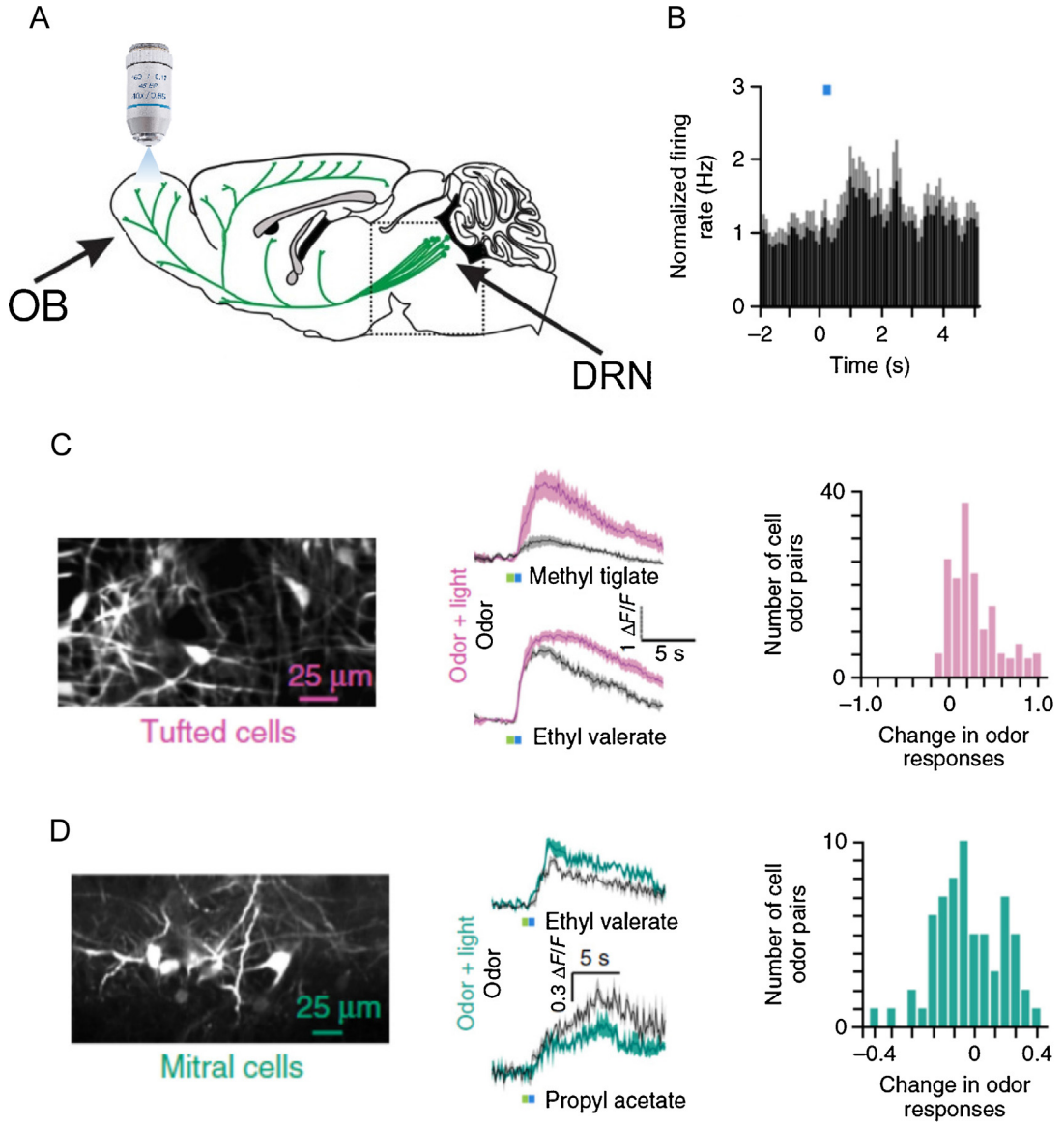

Fig. 3. DRN 5-HT neurons can affect the activity of OB neurons. (A) Recording configuration: OB neurons expressing GCAMP are imaged while the DRN is eclectically stimulated or OB neurons recorded while ChR2-expressing tryptophan hydroxylase (TPH) axons are locally photostimulated. (B) PSTH of activity of all putative mitral/tufted (M/TC, n = 17 cells) in the TPH2-ChR2-YFP mouse exhibiting excitation from rest when raphe fibers are activated with blue light. (C) Optogenetic stimulation of DRN leads to an increase in tufted cell spontaneous and odor evoked activity. (D) Electrical stimulation of DRN leads to an increase in mitral cell spontaneous activity and bidirectional modulation of odor evoked activity. Adopted from (Kapoor et al., 2016).

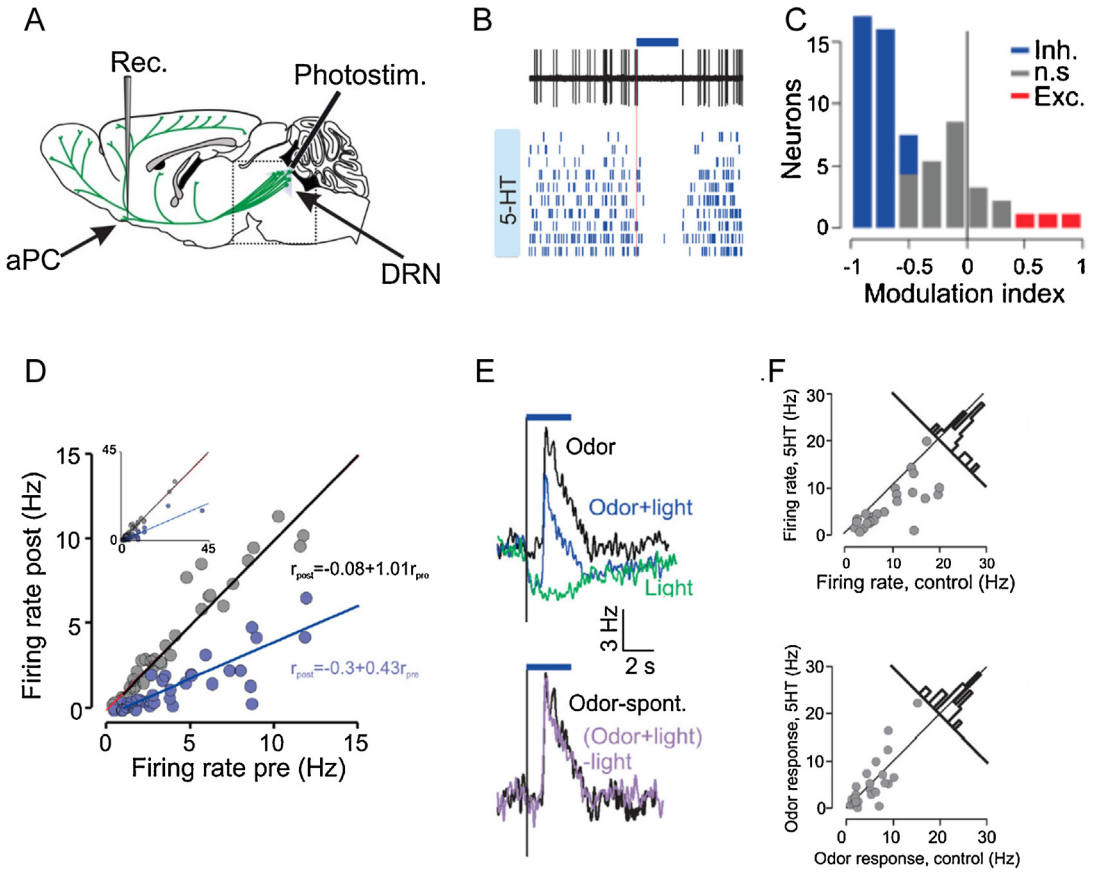

Fig. 4. DRN 5-HT neurons can rapidly affect the activity of aPC neurons. (A) Recording configuration: a recording electrode (Rec.) was inserted in the aPC to monitor single-unit activity and its modulation by photostimulation (Photostim.) of ChR2 expressing DRN 5-HT neurons. (B) Example baseline activity of an aPC unit and its response to DRN photostimulation. Top, Single-trial raw data (blue bar marks photostimulation, red line its onset), middle, raster plot in which each tic is a single-unit spike and each row a single trial. (C) Modulation indices for all recorded neurons. Blue bars: significantly inhibited units (Inh.), red significantly excited (Exc.), and gray not significantly modulated. (D) Scatter plot comparing firing rates under control and photostimulated trials for all significantly suppressed units indicates divisive inhibition, linear regression fit superimposed, equations indicated. (E) (Top) Averaged PSTHs of all neurons with significant odor responses and light modulations in the absence (black line) and presence (blue line) of DRN photostimulation, green line: average PSTH after DRN photostimulation in the absence of odorant presentation. (Bottom) Mean PSTHs of all neurons showing significant odor responses and light modulations in the absence (black line) and presence (purple line) of DRN photostimulation after subtraction of the corresponding baselines (spontaneous PSTHs). (F) (Top) Scatter plot comparing firing rates of activity during odor presentation in the absence and presence of photostimulation. Each point corresponds to a single unit. Bar histogram shows the distribution of differences between photostimulated and control firing rates across the population. The distribution is shifted away from the main diagonal toward the bottom right, indicating inhibition during photostimulation. (Bottom) Scatter plot comparing odor responses (difference between firing rates and baseline) in the absence and presence of photostimulation. Each point corresponds to a single unit. Bar histogram shows the distribution of differences between photostimulated and control firing rates across the population. The distribution is centered around the main diagonal, indicating no effect of photostimulation on odor responses after accounting for the effect of DRN activation alone. Adopted from (Lottem et al., 2016).

mechanism, the pronounced suppression of spontaneous firing by DRN 5-HT photostimulation and the lack of effect on the odor responses will have important functional implications for sensory coding. These rapid effects of a slow neuromodulator are relatively surprising but one must take into account that the optogenetic stimulation of a group of neurochemically homogenous neurons most likely triggers synchronous release from the axons of most ChR_2 expressing neurons stimulated. This might both overestimate the magnitude and homogenize the effects observed, while masking subtle, more naturalistic, local release.

One can only speculate about the exact functional roles of 5-HT and these predictions depend on the interpretation of spontaneous activity. If on one hand spontaneous activity represents noise (Shadlen and Newsome, 1994) then the effect of DRN 5-HT photostimulation (i.e. suppressing spontaneous activity but leaving sensory evoked firing unaffected) will lead to an increase in signal-to-noise ratio. On the other hand, if spontaneous activity caries information like expectation (Berkes et al., 2011; Fiser et al., 2010), DRN 5-HT activation will increase the contribution of sensory data against old existing models. This strategy could have several advantages in a novel environment where old models are malfunctioning. The exact functional consequence of this dual effect on spontaneous and sensory evoked activity and whether this is restricted to the olfactory system or reflects a general *modus operandi* in other sensory systems remains to be tested.

Iontophoretic application of dopamine can affect the response of medial PFC neurons to their preferred stimulus (Williams and Goldman-Rakic, 1995). Using optogenetics to identify the neurochemical identity of the neurons recorded it was recently found that a marked homogeneity characterizes reward prediction error signals in individual dopamine neurons (Eshel et al., 2016) and the underlying mechanism is a subtractive form of inhibition mediated by local GABAergic in the VTA (Eshel et al., 2015; Cohen et al., 2012).

6. The thalamo-cortical network: a hub for brain state-dependent sensory processing?

Both monoaminergic systems and peripheral inputs of nearly all sensory modalities converge onto thalamic relay nuclei before reaching primary sensory cortices. Importantly, the activity of thalamo-cortical networks is strongly modulated across sleep-wake states (see above). Therefore, thalamo-cortical cells are ideal

candidates for state-dependent modulation of sensory processing during wakefulness, but also sleep, in particular in sleep-related plastic changes (Aton, 2013).

Spontaneous and sensory-evoked neuronal activity in the thalamocortical system is heavily influenced by brain states (Renart et al., 2010; Steriade et al., 2001). Although this has been the subject of extensive research the underlying cellular and network mechanisms are far from being fully understood, but it is generally agreed that neuromodulation plays a dominant role. Brain states can alter the ratio between excitation and inhibition in the neocortex with the awake state being dominated by inhibition (Haider et al., 2013; Rudolph et al., 2007). Importantly, in addition to these slow (minutes or tens of minutes) state dependent modulations as apparent between different stages of the sleep/wake cycle, more rapid state dependent fluctuations (a few seconds) have been described within the awake state (McGinley et al., 2015b). Specifically, both neuronal activity and task performance are under the influence of transient brain state changes as reflected in various physiological readouts like the neocortical local field potential or pupil diameter (McGinley et al., 2015a).

Cortical cells show higher burst firing prevalence during a sleep episode that immediately followed an extended period of wakefulness, suggesting a possible change in synaptic plasticity, consistent with experiments described above (Vyazovskiy et al., 2009). Recent molecular studies showed a strong increase in protein synthesis and molecules related to synapse formation and stabilization during both NREM (Vecsey et al., 2012) and REM sleep (Luppi et al., 2016), suggesting a possible molecular mechanism for sleep-dependent consolidation of sensory inputs, through spine formation (Yang et al., 2014). Accordingly, waking leads to an overall increase in the number of cortical spines, whereas sleep is associated with net spine loss (Maret et al., 2011), suggesting a local regulation or a dependence to sensory modality and the need to consider those mechanism as distinct processes.

7. Future directions

By providing bidirectional control of genetically-defined populations of neurons with unprecedented temporal resolution and neurochemical specificity, optogenetic methods have already contributed substantially to neuroscience research. A few studies have used optogenetic techniques for elucidating the modulatory actions of monoaminergic systems or identifying the neurochemical identity of the recorded cells (e.g., opto-tagging). In the present review we summarized recent studies elucidating the involvement of monoamines in brain states and sensory information processing using optogenetic approaches, yet many challenges remain where both the imaging and control features of optogenetics will synergize.

First, monitoring the activity of identified monoaminergic neurons during stages of vigilance and various behavioral tasks will provide important information about the population dynamics and function amongst a specific monoaminergic system. However, given the cellular heterogeneity of monoaminergic nuclei, recordings from identified neurons, using opto-tagging methods or live imaging of cellular activity based on genetically encoded calcium/voltage indicators (Fosque et al., 2015) will be crucial in order to correlate monoaminergic functions with specific behaviors (sensory, motor, attention, learning etc.). Ideally, such identification will unravel function-specific subset of monoaminergic cells within a single nucleus that will further be causally investigated using either input/output characteristics (Schwarz et al., 2015) or intersectional methods (Fenno et al., 2014; Madisen et al., 2015). In addition, performing somatic Ca2+ imaging using either gradient index (GRIN) lenses (Andermann et al., 2013) or fiber photometry (methods collecting bulk fluorescence from a GCAMP expressing neurons or axons using an optical fiber) (Cui et al., 2013) or single bouton imaging as has been done for acetylcholine (Eggermann et al., 2014) will further our understanding of specific monoaminergic functions.

Second, since monoaminergic neurons are often intermingled within a heterogeneous network of cells and fibers of complex neurochemical identity, it will be important to unravel their distinct dynamics, synaptic interactions and mode of action – classical neuro-transmission or neuro-modulation? – with a particular emphasis on their unique roles in modulating brain states and/or sensory processing. A great deal of physiological, anatomical and theoretical work has focused on various aspects of synaptic organization of microcircuits in highly organized structures including cerebellar, hippocampal and neocortical circuits. Unlike these areas, the brainstem, as well as the hypothalamus, lack a laminar structure, which renders their functional dissection quite difficult and resistant to typical network features built from cortical and cerebellar investigations. However, the study of synaptic connections, vesicular release properties and functional connectivity has been possible by combining *in vitro/vivo* electrophysiology and optogenetics. For instance, a recent study has revealed that LC_{NA} neurons receive synaptic inputs from proximal GABAergic neurons (Jin et al., 2016), which may relay sub-cortical inputs and provide a tonic inhibition of LC_{NA} neurons (during REM sleep) and a rapid disinhibition during transition to wakefulness or conditions during which when elevated arousal or attention is needed, as shown recently for hypothalamic inhibition of reticular thalamus nuclei and NREM-to-wake rapid transitions (Herrera et al., 2015). This microcircuit level knowledge will provide useful information when interpreting the results of neuronal activity recordings from monoaminergic nuclei performed in behaving animals.

Third, although traditionally a particular monoaminergic system is considered homogeneous and thought to broadcast a general signal to every brain area it projects to evidence for sub-circuits is emerging (as discussed in section 3). If a particular monoaminergic neuron population consists of multiple sub-types the signals broadcasted by them can be asymmetrical. However, the definition of cell-types is far from resolved even for neuron types which have received extensive attention throughout decades of research, like cortical interneurons (Ascoli et al., 2008). New viral-genetic methods enable the analysis of input/output organization of a genetically defined neuron type. Specifically, using Rabies-virus-based circuit mapping one can reveal the synaptic inputs of neurons defined by both their output connections and neurochemical identity as has been elegantly demonstrated for the LC_{NA} system (Schwarz et al., 2015). However, in addition to input/output preferences of a monoaminergic neuron with known neurochemical identity other important aspects remain to be revealed in order to further our understanding of monoaminergic functions. These include, but are not limited to characterizing intrinsic cellular properties, synaptic activity and its plasticity, activity during various controlled behavioral events and brain states, response to sensory stimuli of different modalities.

Last, but not least understanding how action potential output in various monoaminergic neurons leads to the release of monoamines and/or other co-transmitted substances is important for a full mechanistic understanding of monoaminergic functions. If co-transmitters are involved (Tritsch et al., 2016; van den Pol, 2012), which are the activity patterns that favour either monoamine or co-transmitted substance release and how does this activity relate to the firing of identified neurons in behaving animals? Once this circuit-level information will become available, further knowledge about endogenous firing of various circuit elements and mechanisms of release in a given monoaminergic nucleus will enable

neuroscientists to tackle important questions concerning the function of monoamines in health and disease.

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