

Invited Review

Set and setting: How behavioral state regulates sensory function and plasticity



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ABSTRACT

Recently developed neuroimaging and electrophysiological techniques are allowing us to answer fundamental questions about how behavioral states regulate our perception of the external environment. Studies using these techniques have yielded surprising insights into how sensory processing is affected at the earliest stages by attention and motivation, and how new sensory information received during wakefulness (e.g., during learning) continues to affect sensory brain circuits (leading to plastic changes) during subsequent sleep. This review aims to describe how brain states affect sensory response properties among neurons in primary and secondary sensory cortices, and how this relates to psychophysical detection thresholds and performance on sensory discrimination tasks. This is not intended to serve as a comprehensive overview of all brain states, or all sensory systems, but instead as an illustrative description of how three specific state variables (attention, motivation, and vigilance [i.e., sleep vs. wakefulness]) affect sensory systems in which they have been best studied.

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1. Introduction

What determines the brain's state?

“The universe is an intelligence test”.

– Timothy Leary (Wilson, 1977).

In 1964, psychologist Timothy Leary described sensory experience (in this case, channeled through the lens of psychedelic drug use) as a function of “set and setting” (Leary, Metzner, & Alpert, 1995). The term “set” refers to the internal state of the individual; “setting” refers to external stimuli. The question of how neurons and neural circuits respond to sensory stimuli has received extensive study. A relatively unexplored question is how one's “set”, or internal state, determines how these neurons and circuits process sensory information. Ultimately, how we experience the outside world can be seen as a function of both sensory input (our setting) and the state of our internal sensory processing systems (our set).

How is an organism's “set” set? The term “state” can refer to motivation, emotion, attention, consciousness, or arousal. All of these brain states can be altered by either external context (e.g., in the case of attention, by distracting stimuli) or internal factors (e.g., fatigue, hormones, and neuromodulator levels). Certain

internal factors are (relatively speaking) immutable: one obvious example is genetics (Bendesky & Bargmann, 2011; Plomin & Craig, 1997). Other internal factors can be modulated in a dynamic way over the lifespan, through behavioral, environmental, and pharmacological manipulations. This review is focused on describing neural mechanisms that affect sensory function during states of attention, motivation, and vigilance (sleep and wakefulness). These states affect both how incoming sensory information is received (i.e., how neurons respond to sensory input), and how neuronal responses are altered over time by changing sensory input (i.e., sensory plasticity).

2. Attention

Effects of attention on responses to specific, task-relevant stimuli have been described for all sensory modalities, and even across modalities (Eimer, van Velzen, & Driver, 2002). In general, attention serves to decrease sensory detection and discrimination thresholds for a subset of attended stimuli, while at the same time increasing sensory thresholds for other, non-attended stimuli. Two brain state-specific features are generally associated with attention at the early stages of sensory processing: changes in neuromodulator tone – including localized, cortical circuit-specific release of norepinephrine and acetylcholine (Lee & Dan, 2012) – and changes in network activity – including circuit-specific increases in oscillatory activity (Fontanini & Katz, 2008).

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2.1. Attention and the visual system

The effects of attention on early stages of information processing in the visual system have been studied using psychophysics, functional neuroimaging, and single-neuron recording, and have been described at the level of stimulus detection, response selectivity, and response magnitude. Numerous human studies have taken advantage of the retinotopic maps within primary and secondary visual cortices to assess local effects of attention directed to a specific retinotopic area of visual space. During various visual discrimination tasks (i.e., orientation, contrast, color, texture, or object), discrimination thresholds specifically decrease for visual stimuli presented in the attended area of visual space, and increase for those presented in a non-attended area. Similarly, BOLD fMRI signal during task performance specifically increases in the corresponding retinotopic region of visual cortex when stimuli are presented in an attended area, and decreases when they are presented in a non-attended area (Gutnisky, Hansen, Ilescu, & Dragoi, 2009; Jehee, Brady, & Tong, 2011; Pessoa, Kastner, & Ungerleider, 2003; Watanabe et al., 2011). Attention also modulates fMRI responses to visual stimuli within the lateral geniculate nucleus of the thalamus, suggesting effects on visual processing at an even earlier stage (O'Connor et al., 2002).

The underlying electrophysiological events associated with attention-mediated BOLD activity changes have been studied extensively in primate visual cortex (Fig. 1). At the earliest level of cortical processing (the primary visual cortex, V1), attention enhances firing rate responses of simple cells to visual stimuli presented within their receptive field (McAdams & Reid, 2005). Similar increases in firing have been seen in higher visual cortical areas such as V4 (i.e., at later stages of visual processing) in response to attended receptive field stimulation (Fries, Reynolds, Rorie, & Desimone, 2001b). Importantly, however, not all neuronal responses are uniformly affected by attention, but instead are altered as a function of cell type and spatial location of attention. Specifically, attention specifically enhances firing rate responses for stimuli presented within the receptive field of V1 or V4 interneurons, and specifically decreases firing rate responses for stimuli presented outside the receptive field of V1 or V4 excitatory (principal) neurons (Chen et al., 2008; Mitchell, Sundberg, & Reynolds, 2007). Both mechanisms contribute to inhibiting responses to distracting stimuli presented outside a given neuron's receptive field, leading to center-surround interactions that optimize response specificity (Reynolds, 2008; Sundberg, Mitchell, & Reynolds, 2009).

Attended stimulus presentation also increases firing synchrony with respect to ongoing gamma (30–80 Hz) oscillatory activity in corresponding retinotopic areas of V4 (Fries et al., 2001b). Gamma oscillations are specifically enhanced within V4 as a function of

attention, driven by feedforward input from attended areas in V1 (Bosman et al., 2012). This gamma-frequency oscillatory drive synchronizes V4 neuronal firing to oscillatory input from V1 areas with overlapping receptive fields (Bosman et al., 2012; Grothe, Neitzel, Mandon, & Kreiter, 2012). Because the receptive fields in V4 are much larger than those in V1 (corresponding to the combined fields of multiple V1 neurons), this selective synchronization appears to serve as a mechanism underlying selective attention (Borgers, Epstein, & Kopell, 2008). Intriguingly, inter-areal gamma synchrony may also be used at even higher levels of visual processing – recent data suggest that gamma synchrony is a correlate of visual attention during visual working memory tasks, synchronizing activity between higher visual cortical areas (e.g., area MT, which plays an important role in motion detection) and areas mediating executive control (e.g., prefrontal cortex) (Ardid, Wang, Gomez-Cabrero, & Compte, 2010).

Available data suggest that neuromodulation mediates the many of the electrophysiological changes seen in the visual system during selective attention (Fig. 1). Acetylcholine can enhance visual responses to stimuli in excitatory neurons within the lateral geniculate nucleus (Hartveit & Heggelund, 1993; Soma, Shimegi, Osaki, & Sato, 2012). Acetylcholine release from the basal forebrain appears to modulate visual responses in V1 by enhancing interneuron activity (Alitto & Dan, 2012; Disney, Aoki, & Hawken, 2007). It is also an essential mediator of visual stimulus-evoked gamma oscillations in the cortex (Rodriguez, Kallenbach, Singer, & Munk, 2004). It is likely that acetylcholine improves the precision and reliability of cortical neuronal responses to visual stimulation with regard to both spike number (i.e., response magnitude) and spike timing (Rodriguez, Kallenbach, Singer, & Munk, 2010) through this enhancement of gamma-frequency oscillations (Fries, Neuenschwander, Engel, Goebel, & Singer, 2001a). While the function of gamma oscillations within visual cortical circuits is still under investigation, it is clear that in addition to a potential role in signal selection and propagation between cortical areas (Borgers et al., 2008), these oscillations may play an important role in initiating cortical plasticity in response to changing visual input (Grossberg & Versace, 2008). *In vitro*, timing of excitatory neuronal input with respect to ongoing gamma oscillations in the visual cortex determines the sign of plastic changes between pre- and post-synaptic neurons – with excitatory potentials timed to the peak of oscillations leading to synaptic strengthening, and those timed to the trough leading to synaptic weakening (Wespatat, Tennigkeit, & Singer, 2004). Timing-dependent strengthening, but not weakening, during gamma oscillations is dependent on acetylcholine receptor activation (Wespatat et al., 2004).

Acetylcholine release is modulated as a function of both attention (Dalley et al., 2001) and visual stimulation (Fournier, Semba, &

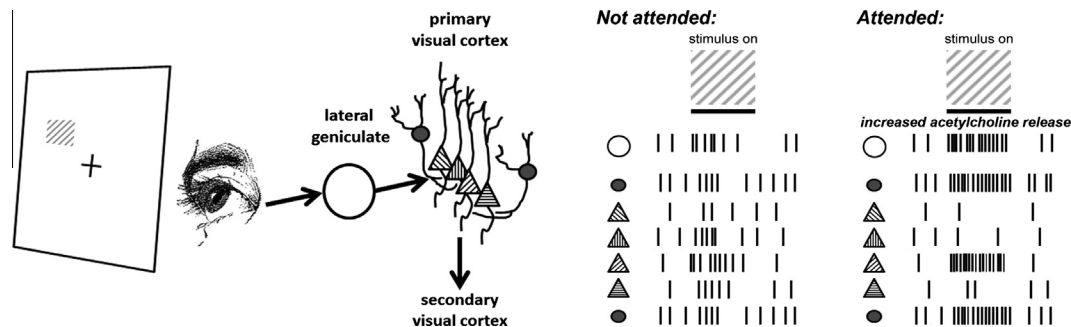


Fig. 1. Improved feature detection during spatially-selective attention. A visual stimulus presented to a specific area of the visual field evokes responses within corresponding retinotopic areas of the thalamic lateral geniculate (LGN) and primary visual cortex (V1). The stimulus is composed of an oriented grating; preferred orientations are indicated for individual V1 principal neurons (triangles), and V1 interneurons are shown as filled circles. A low-contrast grating stimulus evokes modest firing responses in the LGN and cortex, which are only slightly greater than background firing rates. Within V1, attention to the visual field area enhances stimulus-evoked interneuron activity. During stimulus presentation, LGN responses to the attended visual stimulus are enhanced. Against a background of increased inhibition in V1, incoming LGN input strongly and selectively activates only those neurons that are most selective for the stimulus orientation.

Rasmusson, 2004; Laplante, Morin, Quirion, & Vaucher, 2005), and behavioral studies have demonstrated that acetylcholine is necessary for both visual attention and cortical visual response plasticity. If the basal forebrain (which sends cholinergic projections throughout the cortex) is lesioned or transiently inhibited, performance on visually-mediated serial reaction time tasks or visual navigation tasks, which require visuospatial attention, are impaired (Dotigny, Ben Amor, Burke, & Vaucher, 2008; Muir, Robbins, & Everitt, 1992). Performance on these tasks can be rescued in basal forebrain-lesioned animals by administration of an acetylcholine receptor agonist (Muir, Everitt, & Robbins, 1995). In human subjects, naturally-occurring visual response plasticity can be induced by brief visual deprivation, resulting in reduced visual response thresholds. This type of response plasticity can be blocked pharmacologically by antagonizing cholinergic receptors (Borojerdi, Battaglia, Muellbacher, & Cohen, 2001). This acetylcholine-mediated functional plasticity may be expressed within the cortex itself (i.e., through strengthening of intracortical synapses, as described for gamma-mediated plasticity above), or through long-term potentiation (LTP) of lateral geniculate synapses within primary visual cortex, which occurs in an acetylcholine-dependent manner *in vivo* (Dringenberg, Hamze, Wilson, Speechley, & Kupo, 2007).

Since the 1960s, experimental data have shown that general arousal and motivational state (see below) regulate the effects of attention on visual responses. For example, Eason and colleagues found that while spatially selective attention augments cortical visually-evoked potentials in human subjects, the threat of shock for errors on a visual detection task augments cortical responses for attended stimuli even further, and reduces reaction times for reporting detected stimuli (Eason, Harter, & White, 1969). More recently, beneficial effects of non-spatial “alerting” stimuli on subsequent psychophysical performance during spatial visual attention tasks have been reported (Posner & Cohen, 1984); in monkeys, these “alerting” effects can be reduced by blocking norepinephrine synaptic release. The level at which norepinephrine affects the visual system during attentional tasks is unclear. Norepinephrine can have direct actions on responses of visual cortex neurons; however, these have only been described in anesthetized animals (Waterhouse, Azizi, Burne, & Woodward, 1990) or *ex vivo* in cortical slices (Kobayashi et al., 2000) – not during attentive behavior *in vivo*. Alternatively, norepinephrine may act indirectly by activating cholinergic neurons in the basal forebrain (Berridge & Waterhouse, 2003). It is worth noting that in a recent study in which the authors simultaneously measured *both* norepinephrine and acetylcholine release in the cortex during a visual attention task, attentive behavior resulted in far greater increases in the acetylcholine, while norepinephrine release seemed to be related to reward presentation, regardless of task-related attention to the stimulus (Dalley et al., 2001). Two things are clear. First, as the tonic firing rate of noradrenergic locus coeruleus neurons increases, so does the level of behavioral arousal (Carter et al., 2010). Second, sensory stimuli (of all modalities) that are behaviorally arousing increase locus coeruleus neuronal firing (Sara & Bouret, 2012). Insofar as behavioral arousal is a prerequisite for and modulator of attention, it appears likely that these functions are served by locus coeruleus release of norepinephrine.

2.2. Attention and the somatosensory system

As is true for visual processing, attention has been shown to improve psychophysical performance in somatosensory discrimination (e.g., stimulus detection, localization, and intensity or frequency discrimination) tasks in human subjects (Haegens, Handel, & Jensen, 2011; van Ede, de Lange, & Maris, 2011). And as is true for visual processing, effects of attention can be seen at the

level of BOLD fMRI responses evoked by somatosensory stimuli, within primary and secondary somatosensory cortices (Albanese, Duerden, Bohotin, Rainville, & Duncan, 2009; Chen et al., 2010; Johanson-Berg, Christensen, Woolrich, & Matthews, 2000; Schubert et al., 2008; Sterr, Shen, Zaman, Roberts, & Szameitat, 2007). These changes are specific to areas of the somatotopic cortical map corresponding to the attended part of the body (for human studies, usually the right or left hand). Primate electrophysiological studies suggest that the neural correlates of increased BOLD signal activity in somatosensory cortex with attention include modest increases in neuronal firing rate, but profound increases in neuronal firing synchrony (Steinmetz et al., 2000). Thus attended tactile stimuli activate a larger number of somatosensory cortical neurons simultaneously than non-attended stimuli. One possibility is that this attention-dependent enhancement of spike synchrony among somatosensory neurons is mediated via the same mechanisms associated with attentional modulation of visual responses, i.e., through oscillatory synchrony among neurons. Recordings from human subjects during tactile discrimination tasks have shown that performance improvements correlate with attention-dependent reduction of alpha (8–14 Hz) and beta (15–20 Hz) oscillatory activity, which is expressed in cortical areas representing the predicted site of stimulation, in anticipation of the stimulus (Haegens et al., 2011; Jones et al., 2010; van Ede et al., 2011). Outside of these anticipatory attentional effects, attended stimulation elicits even greater reductions in alpha and beta oscillations, and increased gamma oscillatory activity (Bauer, Oostenveld, Peeters, & Fries, 2006; Dockstader, Cheyne, & Tannock, 2010). Thus gamma may provide a crucial timing signal to promote synchrony of neuronal firing within and between somatosensory cortical areas as a function of attention, as it seems to do in the visual system.

Additional data have been provided by recordings from the rodent barrel cortex, the area of primary somatosensory cortex representing the facial whiskers. Rodents use their whiskers to explore the world in much the same way that humans use their hands. Thus, as is true of human hands, a relatively large proportion of the somatotopic map in the rodent somatosensory cortex is dedicated to representing the whiskers, making this area easily accessible for experimental manipulation and recording. Like tactile stimulation in human studies, attended whisker stimulation appears to decrease alpha and beta activity, and increase gamma oscillations, in the corresponding “barrels” within the barrel cortex (Hamada, Miyashita, & Tanaka, 1999; Sobolewski, Swiejkowski, Worobel, & Kublik, 2011). Intriguingly, recordings from the barrel cortex during optogenetically-induced gamma oscillations have demonstrated clearly that the timing of whisker stimulation with respect to these oscillations plays a critical role in gating cortical neurons’ response to whisker deflection (Cardin et al., 2009). Available data indicate that barrel cortex acetylcholine release is specifically modulated as a function of both tactile stimulation (Fournier et al., 2004) and attention (Alenda & Nunez, 2007). Basal forebrain stimulation decreases barrel cortex alpha and beta oscillations and increases higher-frequency oscillations in an acetylcholine-dependent manner, similar to attentional effects reported in human studies (Kuo, Rasmusson, & Dringenberg, 2009). In addition, acetylcholine release from the basal forebrain (Nunez, Dominguez, Buno, & Fernandez de Sevilla, 2012) and norepinephrine release from the locus coeruleus (Devilbiss & Waterhouse, 2004) both enhance firing rate responses of barrel cortex neurons to whisker stimulation, and may also increase the reliability of spike timing in response to stimulation (Devilbiss & Waterhouse, 2004; Lecas, 2004).

In addition to acute effects on sensory encoding, attentional mechanisms may play a role in somatotopic map plasticity. Human studies suggest that focusing on a manual sensorimotor task can lead to alterations in the functional spatial representation of the fingers and the hand within the primary somatosensory cortex

(Braun et al., 2002; Schaefer, Heinze, & Rotte, 2005). Acetylcholine release from the basal forebrain has itself been shown to promote experience-dependent plasticity in the barrel cortex. Repeated stimulation of a single whisker leads to progressive, whisker-specific response enhancement among primary somatosensory cortex neurons when the basal forebrain is stimulated *in vivo*, and this plasticity can be blocked by antagonizing acetylcholine receptors (Kuo et al., 2009).

3. Motivation and reinforcement

While neural mechanisms underlying behavioral reinforcement have been studied for decades with respect to motivation, only recently have these mechanisms been studied with respect to sensory processing and plasticity. Recent findings suggest that both rewarding and punishing behavioral feedback can affect sensory processes. Available data indicate that reward- or punishment-associated changes in release of dopamine, norepinephrine, and acetylcholine (Schultz & Dickinson, 2000) can profoundly impact how incoming sensory information is initially received, and can drive long-term plastic changes in sensory circuits.

3.1. Reinforcement and the visual system

Psychophysical studies of human subjects have demonstrated that the reward structure associated with performance of visual discrimination tasks (e.g., orientation discrimination) affects discrimination thresholds, with greater reward (not surprisingly) leading to improved performance (Baldassi & Simoncini, 2011; Weil et al., 2010). This improvement in performance is associated with increased BOLD fMRI response strength in early visual cortical areas (e.g., V1 and V4), both during post-discrimination reward presentation (Weil et al., 2010), and during presentation of visual stimuli (i.e., during discrimination task performance) when reward expectation is high (Serences, 2008). Little is known about the electrophysiological events which mediate these reward-associated activity changes. However, two recent studies have attempted to

characterize neural correlates of reward expectation in V1. The first assessed the effects of high-value vs. low-value rewards on V1 activity during a visual discrimination task in monkeys. The authors found that (as is true in human subjects) high-value rewards led to improved task performance, which was associated with both enhanced gamma oscillatory activity, and enhanced neuronal firing in V1 during stimulus presentation (Lima, Singer, & Neuenschwander, 2011) (Fig. 2). The second study, characterizing V1 response properties in mice, found that visual cues associated with pending reward availability can generate large firing rate responses (primarily increases in firing rate) in V1 neurons, which are timed with respect to both the visual cue itself, and to reward delivery (Schuler & Bear, 2006). The proportion of recorded V1 neurons which were affected by reward timing (~40%) was impressive, and of these, 50% showed a steady increase in firing from visual cue to reward presentation, while another ~30% continued to show increased firing throughout the reward delivery period (Fig. 2).

Based on presently-available data, it remains unclear whether these reward-related changes in visual cortex electrophysiology require neuromodulation (i.e., reinforcement-associated release of dopamine, norepinephrine, and acetylcholine) (Schultz & Dickinson, 2000; van Ooyen & Roelfsema, 2006). Available data suggest that dopaminergic, cholinergic, and noradrenergic neurons all respond strongly to unpredicted rewards during visual discrimination task performance, less strongly during repeated rewarded task performance, and negligibly to highly predictable rewards (Schultz & Dickinson, 2000) (Fig. 2). Activity in dopaminergic neurons is also actively suppressed during reward omission following visual discrimination task errors (Hollerman & Schultz, 1998). This suggests that neuromodulator release could act as a “salience tag” for sensory events specifically associated with new reward contingencies. In support of this idea, locus coeruleus noradrenergic neurons can respond selectively to one specific visual stimulus, and then to another, as reward contingencies change; this change in responsiveness occurs many trials in advance of behavioral changes in task performance (Aston-Jones, Rajkowski, & Kubiak, 1997; Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994). Thus

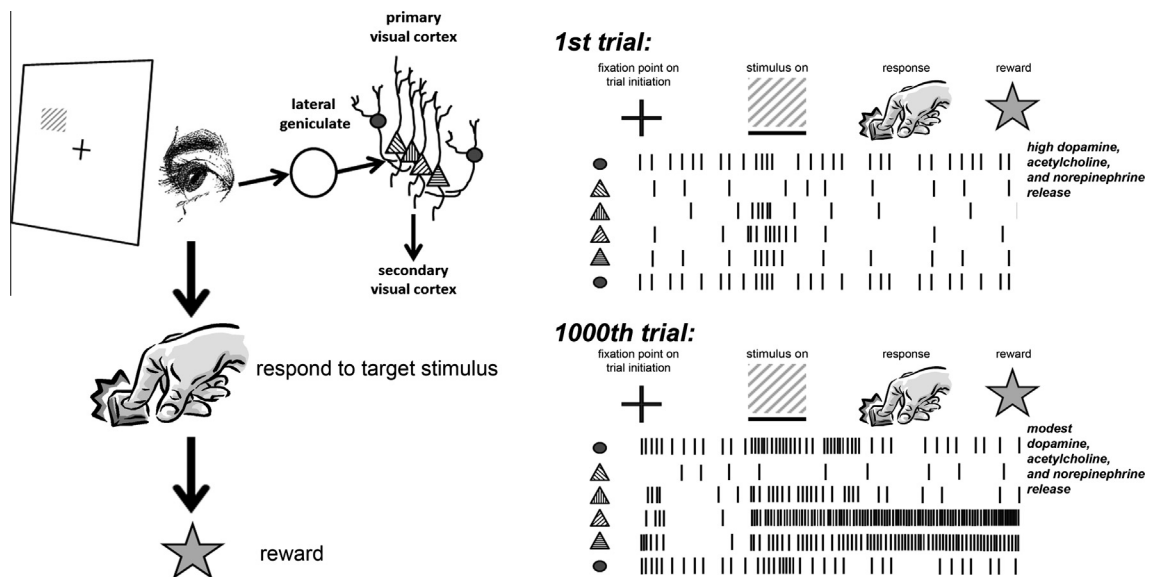


Fig. 2. Augmented stimulus- and task-associated responses following reinforcement learning. Behavioral responses to specific target visual stimulus (a grating with a 45° orientation) are rewarded after a brief interval. On the first trial (prior to reward association), V1 neurons respond normally to the grating stimulus; upon reward presentation, neuromodulators (dopamine, acetylcholine, and norepinephrine) are released at high levels. After several trials, V1 neurons show greater firing rate responses to the rewarded grating stimulus. Some may change their orientation preference in favor of the rewarded stimulus. A large proportion show prolonged firing rate increases (from the time of stimulus presentation to the time of reward presentation). Some V1 neurons develop selective responses to other stimuli associated with task performance, such as presentation of the fixation point that signals trial initiation. Over repeated trials, reward presentation evokes more modest neuromodulator release.

changes in cortical neuromodulator release (occurring rapidly as task demands change), over time, could drive adaptive circuit-level plasticity (occurring on the timescale of hours to days) that promotes visual discrimination learning.

3.2. Reinforcement and the auditory system

Relatively few studies have examined the effects of reinforcement on psychophysical measures of auditory function in human subjects. Recently, classical conditioning was used in human subjects to test the effects of pairing pleasant and noxious stimuli with a pure tone (Resnik, Sobel, & Paz, 2011), with the authors finding that pleasant stimuli decrease thresholds for auditory discrimination, while noxious stimuli increase thresholds and decrease discrimination ability. In contrast to the relative dearth of behavioral data in humans, numerous primate and rodent studies have found effects of reinforcement on auditory-driven task performance and underlying sensory response changes in the auditory system. For example, rodents will learn to press a lever in response to a pure tone cue when rewarded with water; their performance of the task is frequency-specific, and directly proportional to their level of prior water deprivation (Rutkowski & Weinberger, 2005). This improvement in task performance is associated with plasticity of the tonotopic map in the primary auditory cortex (A1), with greater cortical territory dedicated to the frequency of the cue tone. This auditory-guided behavior can be extinguished within a few training sessions if water rewards are withheld; a correlate of behavioral extinction is a contraction of A1 territory representing the frequency of the cue tone back to baseline levels (Bieszczad & Weinberger, 2012). Spectrotemporal tuning profiles of individual rat A1 neurons were also recently recorded under conditions in which target tones became associated with either reward (water) or punishment (foot shock). The authors found that association with reward and punishment led to differential changes to the tuning profile of neurons responsive to the target tone, with reward leading to a general decrease in neuronal responses to the target, and punishment leading to an increase (David, Fritz, & Shamma, 2012). While it is unclear how these cellular changes drive A1 tonotopic map remodeling and auditory-guided behavior in response to training, these data clearly demonstrate that behavioral valence (reward vs. punishment) differentially modify sensory responses at an early stage of processing. Additional recent studies carried out in primates suggest that A1 neurons encode much more detailed information about reward structure during auditory task processing than valence alone. For example, when reward size and delivery are variable, A1 neuron firing varies according to expected reward size, and according to whether or not the expected reward is received (Brosch, Selezneva, & Scheich, 2011). In well-trained monkeys carrying out a familiar rewarded auditory task, A1 neurons also can respond with great specificity to other features of task performance – including reward-associated cues in other modalities (e.g., visual cues) and actions (e.g., lever pressing and lever releasing) involved in reporting auditory discrimination (Brosch, Selezneva, & Scheich, 2005). These effects are consistent with reinforcement-related plasticity between A1 and other brain areas (e.g., other sensory cortical areas) (Harley, 2003; Schultz, 2002).

Dopamine and norepinephrine release in the rat cortex are both known to increase in response to tones that are paired with a reward. During subsequent extinction training where the same tone goes unrewarded, tone-evoked dopamine (but not norepinephrine) release ceases (Mingote, de Bruin, & Feenstra, 2004). Tone-paired stimulation of dopaminergic neurons in the ventral tegmental area is sufficient to improve discrimination of tone cues; intriguingly, this reinforcement regimen also leads to tonotopic map plasticity in A1 (Hui et al., 2009). Critically, stimulating dopaminergic

neurons just after presenting a tone is sufficient to enhance the tone's representation in A1 (Bao, Chan, & Merzenich, 2001), while stimulating them before presenting the tone shrinks the tone's representation (Bao, Chan, Zhang, & Merzenich, 2003). These data, and the recent finding that dopamine receptor antagonism within A1 leads to impairment of sound sequence discrimination learning (Kudoh & Shibuki, 2006), suggest that dopamine is a critical mediator of reinforcement-induced A1 map plasticity which accompanies auditory learning.

4. Sleep

Sensory experiences in wakefulness encode the information necessary for adaptive plastic changes in sensory circuits. However, available data suggest that many forms of sensory plasticity are only consolidated in the minutes and hours after sensory learning, and some appear to only be consolidated during sleep (Aton, Seibt, & Frank, 2009b). It is tempting to speculate that since plasticity sometimes requires sleep, this implies that either certain features of wakefulness are incompatible with plasticity mechanisms, or certain features of sleep promote these mechanisms. The features of brain function which differ between sleep and wakefulness are numerous – so numerous that a comprehensive description would be far beyond the scope of this review. However, several brain-wide changes have been characterized during sleep which may play a critical role in sensory plasticity (Fig. 3).

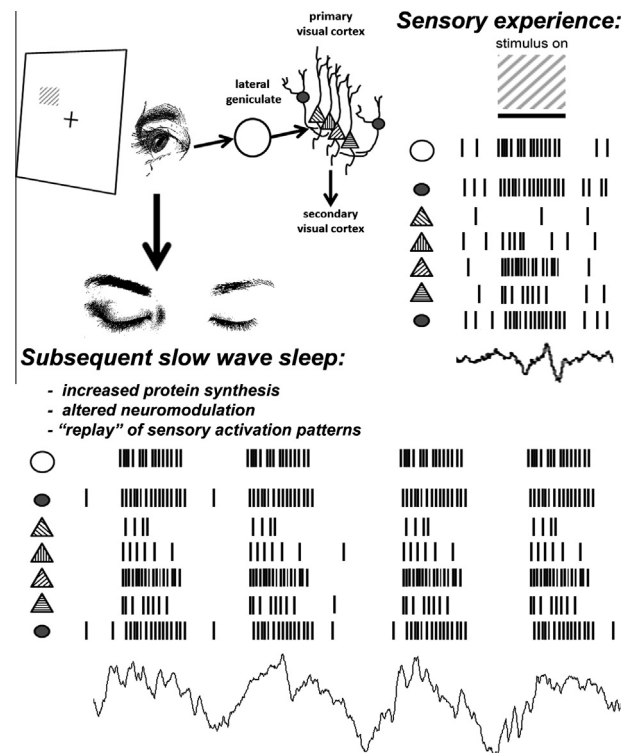


Fig. 3. Sleep-associated changes in thalamocortical circuits following sensory experience. During wakefulness, subjects are on a visual task (e.g., orientation discrimination), in which V1 neurons with a specific orientation preference (45°) are specifically activated. During subsequent sleep, numerous changes occur within LGN-V1 circuits that might be conducive to response plasticity and learning. Among these are the synchronous bursts of activity among LGN and V1 neurons that give rise to slow wave sleep oscillations, alterations in neuromodulator tone, alterations in transcription and translation, and "replay" of activity patterns associated with sensory experience. In this case, replay would consist of selective reactivation of neurons preferentially activated by oriented gratings displayed during the previous task.

One obvious state-dependent change which is likely to contribute to plasticity mechanisms is alteration of neuromodulator tone. The average firing rates of noradrenergic, cholinergic, and dopaminergic neurons are all reduced during slow wave sleep relative to wakefulness. During subsequent rapid eye movement (REM) sleep, catecholamine-producing neurons remain quiescent, while cholinergic neurons fire at their highest rates (España & Scammell, 2011). Because norepinephrine and dopamine seem to play an essential role in encoding new sensory information and *de novo* synaptic plasticity, it is possible that stabilization of cortical changes initiated by a new sensory experience requires a period of time during which catecholamine levels are reduced, to minimize further synaptic changes. In the case of norepinephrine, however, available data do not support this hypothesis. One recent study demonstrated that following training on a sensory recognition task, pharmacological manipulations which enhance norepinephrine levels during sleep lead to improved next-day task performance; manipulations that reduce norepinephrine levels impair performance (Gais, Rasch, Dahmen, Sara, & Born, 2011). Electrophysiological recordings from rats also suggest that after new learning experiences in wakefulness, firing rates in locus coeruleus neurons are enhanced during slow wave sleep, and noradrenergic neuron spike timing with respect to slow waves is altered to optimize cortical plasticity (Eschenko, Magri, Panzeri, & Sara, 2012; Eschenko & Sara, 2008). On the other hand, available data strongly support the idea that after learning, reduced cholinergic neurotransmission during sleep is critical for next-day improvements in performance (Gais & Born, 2004; Rasch, Born, & Gais, 2006).

Another obvious change which occurs specifically during slow wave sleep is the emergence of the slow waves of thalamocortical activity which give the state its name (Fig. 3). These waves are generated from bursts of neuronal activity occurring intermittently within the cortex, driven by thalamic input, and synchronized by corticothalamic feedback (Steriade, 2000; Steriade, 2005; Steriade, 2006). This dramatic change in network activity is likely to alter thalamocortical communication significantly, and is widely hypothesized to be a major contributor to sleep-dependent plasticity, through various mechanisms (Aton et al., 2009b; Sejnowski & Destexhe, 2000; Tononi & Cirelli, 2003). Recent work has used long-term recording of neuronal activity within the well-studied circuitry of mammalian sensory cortices to probe the role of sleep in neural function. Recordings from the somatosensory cortex of freely behaving rats have characterized how activity in these circuits changes as a function of prior sleep/wake history (Vyazovskiy et al., 2009). The authors found that bursts of activity among cortical neurons are more synchronized immediately after a period of extended wakefulness (vs. after a prior interval of sleep), yielding the higher-amplitude slow wave oscillations that characterize early sleep. They also found that firing rates in different classes of cortical neurons are differentially affected by sleep-wake history. While principal neurons show little change in firing after extended wakefulness, fast-spiking interneurons are exquisitely sensitive to state, and fire much more rapidly after wakefulness than after sleep (Vyazovskiy et al., 2009). Based on these findings, it is tempting to speculate that in sensory cortical circuits, the balance of excitatory and inhibitory signaling gradually decreases across wakefulness, but increases across sleep. These effects may be related to a more recent finding, which demonstrated that evoked potentials in the somatosensory cortex were enhanced after a period of slow wave sleep, through the same cellular mechanisms that mediate LTP of glutamatergic synapses (Chauvette, Seigneure, & Timofeev, 2012).

Finally, a major change in the sleeping brain is an alteration in biosynthetic pathways; this could play a critical role in regulating sensory plasticity. Both transcription and translation (Vecsey et al., 2012) are profoundly affected by sleep states. At the

transcriptional level, mRNAs that are up-regulated in the brain during sleep encode proteins involved in macromolecule biosynthesis, including those involved in protein translation, metabolism, and vesicular transport (Mackiewicz et al., 2007; Vecsey et al., 2012). While proteomic analysis of the sleeping brain, to date, has been limited (Cirelli, Pfister-Genskow, McCarthy, Woodbury, & Tononi, 2009), overall protein synthesis is higher throughout the brain during slow wave sleep than in any other state (Ramm & Smith, 1990) (Fig. 3). Thus one possibility is that sleep facilitates sensory plasticity at a very fundamental level, by promoting synthesis of structural components required to build new synapses and circuits. *In vivo* imaging of synaptic structure in sensory cortices has recently been used to study how sleep and wakefulness affect neuronal cytoarchitecture. Imaging studies of somatosensory or sensorimotor cortex in non-anesthetized juvenile mice (during a developmental period in which dendritic spine turnover, and particularly spine loss, is expected to be high) have shown that while spine formation occurs to a similar extent across intervals of wakefulness or sleep, spine loss occurs preferentially during sleep (Maret, Faraguna, Nelson, Cirelli, & Tononi, 2011; Yang & Gan, 2012). Interestingly, however, similar studies in adult mice have shown that, if anything, the opposite is true; spine loss appears to occur at a slightly higher rate across wakefulness, while spine formation occurs at a slightly higher rate across sleep (Maret et al., 2011).

4.1. Sleep and the visual system

Several examples of sleep facilitation of sensory discrimination after training have been described in human subjects, for visual texture discrimination (Gais, Plihal, Wagner, & Born, 2000; Mednick, Nakayama, & Stickgold, 2003), visual contour integration (Gervan & Kovacs, 2010), and orientation discrimination (Mata-razzo, Franko, Maquet, & Vogels, 2008) tasks. Available data suggest that improvements on these tasks are associated with plasticity at an early visual processing stage (i.e., within the primary visual cortex), and that they are specific to the features of the training stimulus (e.g., to a specific area in the retinotopic map). After post-training sleep, improved perceptual performance is associated with increased activation of the trained retinotopic area of visual cortex during subsequent task performance (Schwartz, Maquet, & Frith, 2002). Indeed, *during* post-training sleep, increased fMRI activity is seen within the trained retinotopic area of the visual cortex (Yotsumoto et al., 2009). The cellular mechanisms underlying these plastic changes are still poorly defined, but they can be blocked by ionotropic glutamate receptor antagonism (Gais, Rasch, Wagner, & Born, 2008).

Recent work using animal models to study sensory plasticity has improved our understanding of how sleep contributes to changes in these processes at the cellular level. One example is sleep-dependent consolidation of response plasticity in the cat visual cortex. Ocular dominance plasticity occurs *in vivo* following brief monocular visual experience during a critical developmental window (Hubel & Wiesel, 2004). First described 50 years ago (Wiesel & Hubel, 1963), it has since become a canonical model for studying nervous system remodeling in response to changes in sensory input. Monocular vision results in both depression of cortical responses to stimuli presented to the previously closed eye, and enhancement of cortical responses to stimuli presented to the open eye (Frenkel & Bear, 2004; Mioche & Singer, 1989). We recently demonstrated that closed eye responses are depressed across waking visual experience, while open eye responses are preferentially enhanced during subsequent sleep; the latter, sleep-dependent process is mediated by intracellular signaling pathways associated with LTP (Aton et al., 2009a). Sleep-dependent ocular dominance shifts also require activation of protein synthesis machinery, and translation of synaptic proteins required for

LTP (Seibt et al., 2012). These intracellular changes, like functional plasticity in the cortex, can be blocked by sleep deprivation in the hours after visual experience.

What happens in the visual cortex to bring about these cellular and functional changes, and why does it happen uniquely during sleep? Among the many changes occurring simultaneously in the brain during sleep are dramatic changes in thalamocortical activity patterns (Steriade, 2000) (Fig. 3). We recently carried out long-term recordings of neuronal activity in freely-behaving cats, across periods of waking visual experience and subsequent sleep, to quantify features of network activity associated with sleep-dependent cortical remodeling (Aton et al., 2013). We found that after monocular visual experience, suppression of fast-spiking interneuron activity (and disinhibition between fast-spiking interneurons and principal neurons) occurs specifically in areas of cortex representing the open eye. These changes appear to be critical for subsequent plasticity of cortical visual responses. Importantly, administration of zolpidem – a hypnotic which specifically activates GABAergic receptors at synapses between fast-spiking interneurons and principal neurons (Bacci, Rudolph, Huguenard, & Prince, 2003) – impairs ocular dominance plasticity during sleep (Seibt et al., 2008). Suppression of fast-spiking interneuron activity is present in all vigilance states (wakefulness, REM sleep, and slow wave sleep), so this change alone cannot explain why sleep is necessary for promoting ocular dominance plasticity. The most obvious feature of slow wave sleep, that makes it unique from other states, is the presence of slow waves of thalamocortical activity. We also found that following monocular visual experience, principal neurons show greater firing coherence with slow wave oscillations. The relative timing of firing between principal neurons and neighboring fast-spiking interneurons during slow wave oscillations also changes, resulting from a relative delay in firing among principal neurons (Aton et al., 2013). This interneuron-before-principal neuron firing relationship may allow fast spiking interneurons, whose overall activity is selectively reduced in open eye-biased areas of cortex, to selectively inhibit neighboring principal neurons in closed-eye biased areas of cortex during slow wave oscillations. From these data we conclude that in the case of sleep-dependent ocular dominance plasticity, waking sensory experience reconfigures cortical circuitry in a way that leads to altered spike timing, entrained by thalamocortical slow waves, in subsequent sleep. We hypothesize that such spike timing changes directly drive synaptic plasticity in the visual cortex.

4.2. Sleep and sensorimotor systems: audition and vocalization

Recent human studies have shown that central auditory processing, like many other forms of sensory processing, is adversely affected by sleep deprivation (Liberalesso et al., 2012). Auditory tone discrimination (Gaab, Paetzold, Becker, Walker, & Schlaug, 2004) and linguistic perceptual learning (Fenn, Nusbaum, & Margoliash, 2003) appear to benefit from a night of sleep following auditory task training. As is true for the visual system, little is known about the cellular or circuit-level processes that mediate these sleep-dependent phenomena. Available data from quantification of auditory evoked potentials suggest that some changes in auditory processing due to post-training sleep are associated with more precise and consistent timing of brain activity (Atienza, Cantero, & Quiroga, 2005; Atienza, Cantero, & Stickgold, 2004). However, it is unclear whether neural changes associated with improved task performance are due to synaptic plasticity in the cortex, changes in neuronal excitability, or some other process. It is also unclear what features of sleep physiology bring such changes about.

Changes in neuronal and network activity have been described in other animal model systems in which a brief interval of sleep af-

fects neuronal responses to sound and corresponding behavior. One example is in the avian song-producing sensorimotor system. Sleep has been shown to play an essential role in both song discrimination learning in adult songbirds (Brawn, Nusbaum, & Margoliash, 2010b) and in initial learning of a tutor's song in juvenile birds (Shank & Margoliash, 2009). Several sleep-dependent changes in network activity have been noted within the sensorimotor nuclei associated with song production. Specifically, during sleep (but not wakefulness), neurons in the robust nucleus of the archipallium (RA; a forebrain motor nucleus) respond selectively to the sound of the bird's own song (Dave, Yu, & Margoliash, 1998). While during wakefulness, RA neurons show a tonic pattern of activity that is not altered by auditory stimuli, during sleep they respond with bursts of firing in response to individual song syllables. The mode of firing in RA is similarly altered during sleep immediately following song tutoring, with an increased propensity to bursts of firing, rather than tonic firing (Dave et al., 1998; Shank & Margoliash, 2009). The sleep-associated, "auditory-like" song responses in RA are similar to those normally seen in wakefulness in auditory-responsive neurons which project to RA from the HVC (high vocal center) nucleus (Dave & Margoliash, 2000; Dave et al., 1998). During sleep, HVC neurons burst in a temporal pattern which mimics the pattern associated with the sound of the bird's own song (Chi, Rauske, & Margoliash, 2003). The gating of HVC auditory input to RA during wakefulness is mediated by noradrenergic and cholinergic signaling within HVC; local agonist application within HVC, or basal forebrain stimulation leads to suppression of auditory responses in RA, but not HVC (Dave et al., 1998; Rauske, Shea, & Margoliash, 2003). Because auditory feedback is essential for song learning in juveniles, and song maintenance in adults (Tschida & Mooney, 2012), one hypothesis is that the "auditory-like" input to RA during sleep drives a template-matching process, wherein premotor sequences for song production are compared with auditory representations of tutor song, or adult birds' own songs. Intriguingly, as song tutoring goes on, spontaneous sequences of activity (not driven by auditory stimuli) emerge within RA during sleep which mimic premotor activity during song production (Dave & Margoliash, 2000). It has been hypothesized that appropriately-timed replay of auditory and premotor activity sequences during sleep drives synaptic plasticity in the song system. HVC neurons undergo significant anatomical plasticity following initial exposure to a tutor's song, with the degree of *in vivo* dendritic spine remodeling predicting song learning (Roberts, Tschida, Klein, & Mooney, 2010). That this plasticity may occur during sleep is suggested by greater variability of premotor activity sequences during singing in RA immediately after a night of sleep (Rauske, Chi, Dave, & Margoliash, 2010), as well as variability in song production immediately after sleep (Shank & Margoliash, 2009).

4.3. Sleep and sensorimotor systems: learning visually-guided and sequential movements

A number of recent studies have demonstrated that for human subjects, performance of newly-learned motor tasks benefit from post-training sleep. For the most part these tasks fall into one of two categories: motor tasks guided by visual cues or visual feedback (Huber, Ghilardi, Massimini, & Tononi, 2004; Maquet, Schwartz, Passingham, & Frith, 2003; Tamaki, Matsuoka, Nitttono, & Hori, 2008), and complex motor sequence learning (guided by proprioceptive feedback) (Brawn, Fenn, Nusbaum, & Margoliash, 2010a; Debas et al., 2010; Korman et al., 2007; Kuriyama, Stickgold, & Walker, 2004). Some advances in our understanding of the underlying mechanisms have come from functional imaging studies of these sleep-dependent motor skill gains. Over a period of days, post-training sleep seems to promote a process akin to

“systems consolidation” (Aton et al., 2009b) of sensorimotor memory traces – performance improvements resulting from post-training sleep are associated with “re-mapping” of task-associated brain activity to new cortical areas. For example, sleep immediately after training leads to improvement in a sequential finger movement task several days later; this sleep-dependent change is associated with a shift in brain activation during task performance, with decreasing activation of areas involved in task acquisition (i.e., premotor and motor cortices), and increasing activation of other cortical areas (Fischer, Nitschke, Melchert, Erdmann, & Born, 2005). Certain features of brain activity during post-training sleep itself are also associated with performance improvements, including local increases in spindle (7–15 Hz) and slow wave (0.5–4 Hz) oscillations, which occur specifically in cortical areas engaged during task acquisition (Huber et al., 2004; Nishida & Walker, 2007).

As is true for other forms of sleep-dependent sensory plasticity, attempts have been made to develop animal models in order to study the underlying cellular and network mechanisms. In rodents, performance of a novel skilled reaching task improves after a post-training interval which includes sleep (Hanlon, Faraguna, Vyazovskiy, Tononi, & Cirelli, 2009). Although it is unclear whether sleep is required for improvements in performance of this task, in this model system, like motor task learning in humans, post-training sleep is characterized by increases in slow wave activity which are proportional to learning improvements.

5. Conclusions

Recent studies using an integrative neurobiology approach have yielded fundamental insights into mechanisms by which an organism’s “set”, or internal state, shapes how it experiences the external world, even at the earliest stages of sensory information processing. To date, much of our understanding of sensory system function has come from electrophysiological studies carried out in anesthetized animals. Such studies led to fundamental insights into how sensory information is encoded at the level of individual neurons. However, new recording techniques and experimental designs are allowing neuroscientists to examine how naturally-occurring behavioral states affect processes as fundamental as sensory processing and experience-dependent plasticity. These studies should improve our understanding of how state-dependent brain changes (e.g., in network activity and neuromodulator tone) affect how information about the world – one’s setting – is encoded, processed, stored for future use, and integrated with past experiences.

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