ANNUAL REVIEWS

Annual Review of Vision Science

How Sleep Shapes Thalamocortical Circuit Function in the Visual System

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Annu. Rev. Vis. Sci. 2019. 5:16.1–16.21

The *Annual Review of Vision Science* is online at vision.annualreviews.org

https://doi.org/10.1146/annurev-vision-091718-014715

Keywords

rapid eye movement sleep, REM, non-REM sleep, NREM, lateral geniculate nucleus, LGN, thalamic reticular nucleus, TRN, primary visual cortex, V1, oscillation

Abstract

Recent data have shown that sleep plays a beneficial role for cognitive functions such as declarative memory consolidation and perceptual learning. In this article, we review recent findings on the role of sleep in promoting adaptive visual response changes in the lateral geniculate nucleus and primary visual cortex following novel visual experiences. We discuss these findings in the context of what is currently known about how sleep affects the activity and function of thalamocortical circuits and current hypotheses regarding how sleep facilitates synaptic plasticity.

INTRODUCTION

Sleep is a highly conserved and homeostatically regulated behavior, which is seen in nearly every animal species studied. One of the hallmarks of sleep is decreased responsiveness to sensory stimuli, leading to an increase in arousal threshold. It should come as no surprise that altered activity in the brain's sensory processing circuits coincides with transitions from wake to sleep and vice versa. The thalamocortical network connects thalamic sensory nuclei and cortical regions that process sensory information. Early hypotheses about neural activity during sleep suggested that sleep was simply a state of prolonged cortical inhibition (Pavlov 2010), allowing for disengagement from the world around us and relief from fatigue. However, over the past few decades, electrophysiological data have demonstrated that thalamocortical circuitry displays unique ~~neural~~ activity patterns in sleep states. This activity serves to reduce sensory input to the cortex but may also play a unique role in shaping the circuit's sensory functions during subsequent wake. This review examines sleep-associated changes in neural activity within the visual thalamocortical network, focusing on recent work carried out in cats and rodent species. An understanding of these changes will provide insight into (*a*) how sleeping animals temporarily disengage from sensory input from their environment and (*b*) how sleep promotes adaptive changes to visual system function initiated by changing visual experience during prior wake.

THE STRUCTURE AND FUNCTION OF VISUAL THALAMOCORTICAL CIRCUITS

Early processing of visual stimuli by the thalamocortical network can be considered as occurring within a circuit of three major components: the relay thalamic nucleus, the thalamic reticular nucleus, and the cortex, which are mutually interconnected (**Figure 1*a***).

The Thalamus: Lateral Geniculate Nucleus and Thalamic Reticular Nucleus

Form vision is mediated by retinal ganglion cells projecting to the lateral geniculate nucleus (LGN) of the thalamus. This nucleus plays an important role in relaying information to the

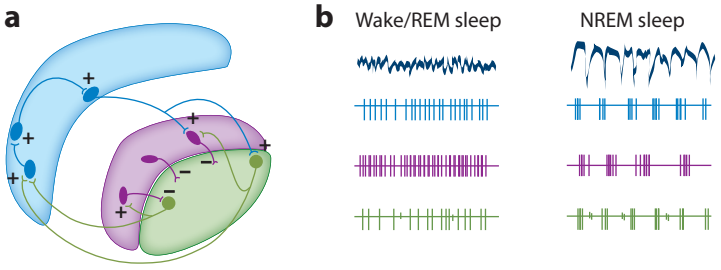

Figure 1

Structure and state-dependent activity of the thalamocortical circuit. (*a*) The thalamocortical circuit is comprised of the thalamus proper (*green*; lateral geniculate nucleus in the visual system), the thalamic reticular nucleus (*purple*), and the cortex (*blue*; primary visual cortex in the visual system). Reciprocal connections among these regions process sensory information and also provide a mechanism for synchronization of activity during non–rapid eye movement (NREM) sleep. (+) signifies excitatory connections, while (−) denotes inhibitory connections. (*b*, *left*) During both wake and rapid eye movement (REM) sleep, activity in the thalamocortical circuit is desynchronized, leading to a lower-amplitude, faster electroencephalogram (EEG). Neurons in the thalamocortical circuit fire tonically. (*right*) During NREM sleep, neurons in the thalamocortical circuit fire in bursts, which synchronize across the circuit, leading to a high-amplitude, slow EEG.

cortex for visual perception. Quantitative analysis of LGN receptive fields in the mouse confirmed the presence of classic center-surround organization (Grubb & Thompson 2003). As is the case in most mammals, it was believed that the mouse LGN lacked visual response properties such as direction or orientation selectivity, and that these were generated at the level of the visual cortex (Hubel & Wiesel 1962, Wiesel & Hubel 1963). However, recent work demonstrates that the mouse LGN contains a significant proportion of cells that are orientation and/or direction selective, in contrast to the more traditionally studied cat LGN (Marshel et al. 2012, Niell 2013, Piscopo et al. 2013, Scholl et al. 2013, Zhao et al. 2013). Interestingly, many of these cells are found in a region of the LGN onto which direction-selective retinal ganglion cells synapse, providing a potential mechanism for the emergence of both direction and orientation selectivity (Piscopo et al. 2013). Orientation selectivity in the LGN seems to be a direct result of retinogeniculate input, as opposed to cortical feedback, since inhibition of corticothalamic (CT) activity does not affect orientation selectivity in the LGN (Scholl et al. 2013).

In addition to relay thalamic nuclei, the thalamus also contains a cluster of GABAergic neurons called the thalamic reticular nucleus (TRN). TRN neurons form reciprocal connections with excitatory relay neurons in many thalamic nuclei. These connections act to modulate relay neurons' activity during wake and sleep alike. Because of these inhibitory connections with many sensory nuclei, the TRN is hypothesized to play an important role in controlling selection of sensory modalities. Francis Crick famously put forward the searchlight hypothesis of reticular thalamic function, which postulated that the TRN modulates thalamocortical circuits to select for specific sensory modalities over others (Crick 1984). More recently, Wimmer et al. (2015) tested this proposed function of the TRN using optogenetic and electrophysiological approaches in mice performing a divided attention task. They demonstrated that, by specifically manipulating the visual portion of the TRN, they could select for or against attendance to a visual stimulus over an auditory stimulus. This bidirectional modulation suggests that the visual TRN is controlling LGN gain via feedforward inhibition, enabling the animal to select among multiple sensory inputs for a specific behavioral task (Wimmer et al. 2015). Thus, the TRN plays a vital role in gating sensory information propagation from thalamocortical relay nuclei to the sensory cortex.

Primary Visual Cortex

LGN thalamocortical relay neurons send excitatory projections to neurons of the primary visual cortex (V1), primarily in layer 4 (Antonini et al. 1999, Dräger 1974). Rodents generally have much lower visual acuity than predator species, and this is reflected in the responses of neurons in the rodent V1 (Van Hooser 2007). Despite this, and cytoarchitectural differences in the V1 (e.g., lack of orientation or ocular dominance columns), mouse V1 neurons do have similar basic response properties (e.g., orientation selectivity and eye preference) as V1 neurons in other mammals (Huberman & Niell 2011, Niell 2015). Orientation tuning among V1 neurons appears to be a function of both excitatory thalamic input, as the LGN has orientation tuning (Sun et al. 2016), and inhibitory interneuron-mediated refinement (Huberman & Niell 2011). For example, parvalbumin-expressing interneurons show little orientation selectivity and therefore could be important for gain control (Cardin et al. 2007, Huberman & Niell 2011). However, somatostatin-expressing interneurons are relatively orientation tuned and could serve to gate excitatory inputs (Huberman & Niell 2011, Ma et al. 2010). Recent work has shown that mouse V1 response properties vary as a function of the animal's behavior. Locomotion, for example, appears to enhance visual responses in V1 neurons without altering their response selectivity or spontaneous activity (Niell & Stryker 2010). Further studies demonstrated that this enhancement of activity is caused by a disinhibitory circuit effect. This mechanism is mediated through the actions of vasoactive

intestinal peptide (VIP) –expressing interneurons, which in turn inhibit somatostatin-expressing interneurons. Thus, when VIP interneurons are activated by locomotion, pyramidal neurons in the V1 targeted by somatostatin-expressing interneurons are disinhibited (Fu et al. 2014). Optogenetic manipulation of the VIP interneuron population demonstrated that this disinhibitory circuit is both necessary and sufficient for locomotion-induced enhancement of visual responsiveness (Fu et al. 2014, 2015; Stryker & Zahs 1983).

Corticothalamic Projections

V1 layer 6 neurons consist of corticocortical and CT projections, which appear to play unique roles in sensory processing within the V1. Recent work by the Scanziani lab has shown that layer 6 CT projections are particularly important for gain control of visual input (Olsen et al. 2012). This population of neurons projects both to the thalamus (as the name implies) and intracortically. The intracortical projections modulate visual activity indirectly through connections onto parvalbumin-expressing interneurons in layer 6, which send axons to other layers of the cortex (Bortone et al. 2014). CT neurons are also uniquely positioned to influence thalamocortical activity in response to visual stimuli. For example, CT feedback can refine the borders of receptive fields, leading to sharper visual responses in the LGN (Briggs & Usrey 2008).

THE THALAMOCORTICAL CIRCUIT DURING SLEEP

Thalamocortical circuit dynamics are dramatically different between sleep and wake. Mammalian sleep consists of two very distinct states, rapid eye movement (REM) sleep and non-REM (NREM) sleep. These states can be identified and differentiated by thalamocortical electroencephalogram (EEG) features, as well as differences in neuronal firing patterns. REM, the phase of sleep associated with vivid dreaming, features low-amplitude, desynchronized EEG activity in thalamocortical circuits (similar to wake) and pronounced theta (4–10 Hz) rhythms generated in the hippocampus. Like wake, REM is characterized by relatively tonic firing patterns among thalamic and cortical neurons (**Figure 1*b***). NREM, in contrast, is characterized by high-amplitude, slow, synchronous EEG activity, which appears due to the transition to burst-pause firing patterns among cortical, thalamocortical, and TRN neurons during NREM sleep (**Figure 1*b***). NREM sleep shows features of homeostatic regulation, which are present at the EEG level, with higher-amplitude and more coherent oscillations present across the cortex after a period of sleep deprivation (Berger & Oswald 1962, Borbély et al. 1981).

Nearly a century of study has refined our understanding of the circuitry involved in promoting transitions between sleep and wake states, based in large part on regulation of thalamocortical circuit function. Early studies by Bremer (1935) demonstrated that disrupting ascending neuromodulatory pathways from the brainstem to the forebrain resulted in deficits in arousal. More recent work has shown that release of norepinephrine, acetylcholine, dopamine, and serotonin in the thalamus and cortex promotes arousal, while reduction in levels of these neuromodulators contribute to the initiation of NREM sleep (Brown et al. 2012, Eban-Rothschild et al. 2017, Saper & Fuller 2017, Weber & Dan 2016). These neuromodulators act through IP3/DAG and cAMP messenger systems to reduce potassium leak currents, leading to a relative depolarization of neuronal membrane potential (Hirsch et al. 1983). At the transition to NREM, neuromodulator release in the thalamus decreases, leading to hyperpolarization in both thalamic reticular and relay thalamic neurons. This hyperpolarized membrane potential leads to selective deinactivation of low-threshold T-type calcium channels (McCormick & Bal 1997), which are responsible for generating the bursting activity characteristic of the thalamus in NREM sleep.

Both wake and REM show elevated levels of acetylcholine relative to NREM sleep. During either arousal from NREM sleep or transitions to REM sleep, increases in acetylcholine (acting on nicotinic receptors) cause TRN neurons to undergo rapid depolarization, followed by a slow muscarinic receptor-mediated hyperpolarization; this process terminates inhibition of thalamocortical relay neurons by the TRN (Pinault & Deschênes 1992, McCormick & Bal 1997). Thalamocortical neurons are also depolarized by increases in acetylcholine and, with the lack of inhibition from TRN neurons, are unable to generate the oscillations associated with NREM sleep, marking the transition to either REM or wake (Curro Dossi et al. 1991). Thus, acetylcholine release in the thalamus is believed to modulate the transition to cortically active states (either REM or wake) (Watson et al. 2010). One difference between wake and REM transitions is that during transitions to wake, many additional neuromodulators, such as serotonin, dopamine, and norepinephrine, are also released in thalamocortical circuits. In contrast, serotonin-, dopamine-, and norepinephrine-producing neuronal nuclei are virtually silent during REM sleep, and stimulation of these regions appears to suppress REM and promote wake (Steriade & McCarley 2005). Thus, NREM, REM, and wake are distinct from one another with regard to their neuromodulator release profiles.

THALAMOCORTICAL OSCILLATIONS DURING NON–RAPID EYE MOVEMENT SLEEP

During NREM sleep, thalamocortical networks generate unique circuit-level oscillations, brought about through synchronous burst firing. In humans, NREM sleep is often subdivided into stages, based on characteristic prominent oscillatory features of the EEG. For example, stage 2 NREM sleep is characterized by the presence of sleep spindles (discrete occurrences of waxing and waning 7–15 Hz oscillatory activity), while subsequent stage 3 NREM sleep is marked by the appearance of delta (1–4 Hz) and slow (<1 Hz) oscillations. These thalamocortical oscillations not only are markers of NREM sleep, but are also thought to play an important role in maintaining the continuity of sleep (Steriade 2006).

Sleep spindles are discrete, 7–15 Hz EEG events, each lasting approximately 0.5–3 seconds (Lüthi 2014), with a characteristic waxing and waning envelope (**Figure 2*a***). The neurobiological mechanisms of spindle generation have been extensively reviewed previously (Clawson et al. 2016, Lüthi 2014). Briefly, during the transition from wake to NREM sleep, neuromodulatory input to the thalamus is reduced, causing a gradual drop in thalamic neurons' membrane potential. As the membrane potential falls to a range between −60 and −65 mV, spindling behavior begins to emerge in the thalamic network (Nun et al. 1992, Steriade et al. 1991a). At this hyperpolarized level, glutamatergic input to the TRN is able to activate low-threshold T-type calcium (Cav3.2, Cav3.3) channels in TRN neurons, generating a transient calcium spike. Subsequent bursting of TRN neurons leads to generation of inhibitory postsynaptic potentials (IPSPs) in thalamocortical neurons and membrane hyperpolarization, which activates low-threshold calcium (Cav3.1) channels. Calcium influx through these channels initiates bursting in thalamocortical relay neurons, which generates volleys of excitatory postsynaptic potentials (EPSPs) in cortical and TRN neurons (Brown et al. 2012, Talley et al. 1999), which initiate the next cycle of burst firing. Spiking of cortical neurons and subsequent CT feedback synchronize the firing of TRN neurons in successive cycles of bursting—a feature that appears to underlie the waxing phase of the spindle envelope (for a review, see Clawson et al. 2016). Recordings from decorticated cats (Contreras et al. 1996a) demonstrated that CT input to the thalamus is essential for coordinating spindle oscillations, and more recent optogenetic studies in mice (Durkin et al. 2017) demonstrated that activity in CT neurons is sufficient to generate these oscillations in the thalamus. Both TRN and thalamocortical relay neurons receive excitatory CT input. However the amplitude EPSPs

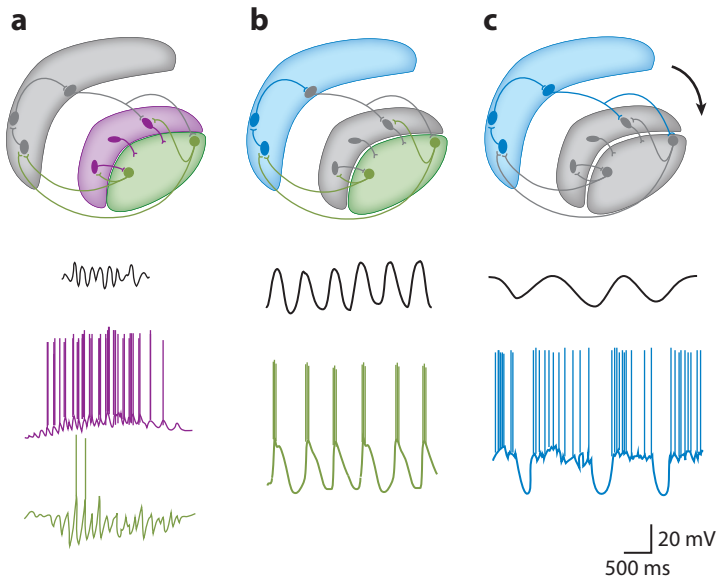

Figure 2

Generation of non–rapid eye movement oscillations within the thalamocortical circuit. (*a*) Sleep spindles (7–15 Hz) are generated by the interaction between the thalamic reticular nucleus (*purple*) and thalamus proper (*green*). Sample intracellular recordings adapted with permission from Steriade & Deschênes (1988) and Steriade (2003). (*b*) Delta is generated in both the cortex (*blue*) and thalamus proper. The better-understood clock-like delta of the thalamus is shown as an intracellular trace adapted with permission from Amzica & Steriade (1998) and Timofeev & Steriade (1996). (*c*) The slow oscillation is generated in the cortex (*blue*) and, through layer 6 corticothalamic input to thalamus, synchronizes the other thalamocortical oscillations (*arrow*). Intracellular activity of the cortical slow oscillation adapted with permission from Timofeev & Chauvette (2011).

produced by CT input are larger in the TRN than in relay neurons due to the greater abundance of postsynaptic glutamate receptors in the TRN compared with relay nuclei (Golshani et al. 2001, Jones 2002, Steriade 2006). During spindles, inhibition of thalamocortical neurons by IPSPs from TRN bursts tends to overwhelm excitatory input from CT neurons. This inhibitory input allows for the continuation of hyperpolarization-induced activation of T-type calcium channels during subsequent spindle volleys. Ultimately, spindles wane and terminate, due in part to the gradual desynchronization of thalamocortical relay, TRN, and CT activity (Bonjean et al. 2011, Lüthi 2014).

Spindle generation is blocked outside of NREM sleep due to increased neuromodulator levels. During wake, norepinephrine and serotonin block potassium leak conductance in TRN neurons, preventing the activation of low-threshold T-type calcium channels (McCormick & Wang 1991). High acetylcholine release, which occurs during both REM and wake, can lead to spindle blockade through a number of mechanisms (Steriade 2004). Acetylcholine from the peribrachial region hyperpolarizes TRN neurons while simultaneously increasing conductance, preventing burst firing to set off the spindle initiation (Hu et al. 1989). Acetylcholine can also act on thalamocortical relay neurons, depolarizing them through both fast nicotinic and slow muscarinic activity (McCormick 1992). This depolarization blocks the low-threshold calcium spikes required for spindle activity in thalamocortical neurons (Steriade 2004).

Delta (1–4 Hz) oscillations are generated by mechanisms intrinsic to both the thalamus and cortex during NREM sleep. The best described of these is the clock-like mechanism for generating delta rhythms intrinsic to thalamocortical relay neurons (**Figure 2*b***). Rhythms in membrane potential are generated via reciprocal interactions between a hyperpolarization-activated cation current (I_h) and a transient low-threshold calcium current (I_t) (McCormick & Pape 1990). As thalamocortical relay neurons hyperpolarize beyond the range where spindling occurs in thalamocortical circuits (between −65 and −90 mV) (Nun et al. 1992, Steriade et al. 1991a), I_h is activated, moving the membrane potential closer to depolarization, activating I_t and generating a low-threshold spike (Steriade 2003). This mechanism appears to be intrinsic to thalamic relay neurons, as delta rhythms are generated within structures such as the LGN independent of input from the cortex (Timofeev & Steriade 1996). However, both lesion studies in cats and optogenetic studies in mice indicate that delta oscillations in the thalamus can be synchronized in vivo by input from the cortex (Durkin et al. 2017, Timofeev & Steriade 1996). Delta oscillations also appear to be generated via a separate mechanism in the cortex, independent of thalamic input (Villablanca & Salinas-Zeballos 1972). While the precise mechanism underlying generation of delta within the cortex is less understood, it appears to emerge initially among cortical pyramidal neurons within cortical layers 2/3 and 5 (Ball et al. 1977, Petsche et al. 1984, Steriade et al. 1993a).

The slow oscillation (<1 Hz) was first described in the context of intracellular recordings of cortical neurons (Steriade et al. 1993b). The slow oscillation consists of up states (slow depolarizations with superimposed action potentials) and down states (long hyperpolarizations) occurring at a frequency less than 1 Hz (**Figure 2*c***). The up state of the slow oscillation is a prolonged depolarization caused by NMDA receptor- and non-NMDA receptor-mediated EPSPs and a persistent sodium current; during up states, fast IPSPs from local GABAergic cortical cells are also present (Brown et al. 2012, Steriade et al. 1993b). Subsequent down state hyperpolarization appears to be initiated by a combination of short-term synaptic depression of active synaptic connections (due to depletion of calcium), slow inactivation of sodium current, and activation of potassium current (gated by calcium and sodium) (Massimini & Amzica 2001). This hyperpolarized state is due to disfacilitation, not inhibition, as GABAergic neurons fire in the same up/down phase as pyramidal neurons (Contreras et al. 1996b, Timofeev et al. 2001).

The slow oscillation plays a key role in the thalamocortical network during NREM sleep because of its unique role in synchronizing the other NREM oscillations (Steriade et al. 1993a). Via periodic activation of CT neurons, the slow oscillation causes synchronous, rhythmic activation of neurons in the thalamus. This mechanism promotes coherent spindle and delta rhythms across the extent of the thalamus during NREM sleep (Contreras et al. 1996a, Timofeev & Steriade 1996). CT input can initiate delta oscillations in thalamocortical neurons and can also reset the phase of the ongoing delta oscillations to synchronize periodic activity across the thalamocortical network (Lytton et al. 1996). CT feedback to the thalamus synchronizes sleep spindles, but also plays important roles in initiating and terminating them (Fuentealba & Steriade 2005, Fuentealba et al. 2005). Thus, available data suggest that the coordination of these rhythms depends on the reciprocal loops between the cortex and thalamus.

How might the aforementioned NREM oscillations affect thalamocortical circuit function? The synchronous bursting pattern of neurons in the circuit during NREM sleep is distinct from the relatively tonic firing pattern of thalamic and cortical neurons seen during wake or REM sleep. This change in activity pattern appears to be crucial for filtering out incoming sensory input, leading to a higher arousal threshold during sleep. The relatively hyperpolarized membrane potential (combined with inhibition mediated by GABAergic TRN neurons) is critical for making thalamic relay neurons refractory to incoming visually driven excitatory input during sleep. In support of this idea, recent work has demonstrated that subnetworks of TRN neurons may be

specialized for state-dependent filtering of sensory input at the level of the thalamus. While TRN neurons projecting to limbic structures show activity that coincides with arousal, TRN neurons projecting to sensory thalamic nuclei (such as those projecting to LGN) are more likely to be active during NREM sleep, with firing synchronized by NREM oscillations, and are more likely to participate in spindle generation (Halassa et al. 2014). The activity of this population of sensory-projecting TRN neurons is suppressed by aroused attention during wake (Halassa et al. 2014). This suggests that sensory-projecting TRN neurons and the NREM oscillations that they generate are important for blocking incoming sensory input, allowing for the maintenance of sleep. However, it is worth noting that sensory gating during NREM is not monolithic, but rather varies as a function of NREM stage and oscillatory phase. Recently, Schabus et al. (2012) demonstrated that, if a sensory stimulus coincides with a spindle or the down state of the slow oscillation, then it is unlikely to elicit a response in the cortex; however, cortical responses can be elicited during the depolarizing up state of the slow oscillation.

IMPACT OF NON–RAPID EYE MOVEMENT SLEEP OSCILLATIONS ON THALAMOCORTICAL PROCESSING

Numerous studies have linked NREM oscillations to the cognitive benefits of sleep (Clawson et al. 2016, Diekelmann & Born 2010, Maquet 2001, Puentes-Mestril & Aton 2017, Stickgold 2005, Walker & Stickgold 2006). There is a wealth of correlational data from human subjects suggesting a link between specific NREM oscillations and sleep-associated improvements on specific sensory and motor tasks (for a review, see Puentes-Mestril et al. 2019). These data suggest that the density and amplitude of NREM oscillations can increase in specific cortical regions after modality-specific training (for a review, see Aton 2013). For example, auditory stimulation in wake leads to increased power of sleep spindles during subsequent NREM sleep over temporal (auditory) cortical areas and increased spindle-frequency coherence between these areas and other cortical regions (Cantero et al. 2002). Similarly, following sensorimotor learning, slow wave (delta and slow oscillatory) activity increases during NREM in motor and proprioceptive cortical regions (Huber et al. 2004). Because such changes in NREM oscillations are linked to improved task performance, it raises the question of how they contribute to the function of thalamocortical circuits.

More recently, experimental manipulation of NREM oscillations (through administration of hypnotic drugs, transcranial stimulation, auditory stimulation, or optogenetics) have aimed to demonstrate a causal role of specific rhythms in cognitive processes. For example, boosting slow oscillations through transcranial magnetic stimulation in human subjects increases retention of hippocampus-dependent declarative memory (Marshall et al. 2006). Optogenetically driven, synchronized rhythms generated simultaneously in the secondary motor area and primary sensory cortices (mimicking synchronized delta activity during NREM) were sufficient to promote perceptual memory retention in mice. Using this same paradigm, optogenetic disruption of cortical activity during NREM sleep blocked memory retention (Miyamoto et al. 2016). Such manipulations have been used to demonstrate a crucial role of specific phase relationships between NREM oscillations (e.g., between spindles and slow waves) for cognitive performance enhancement. For example, administration of the hypnotic drug zolpidem increases the temporal coupling of NREM slow oscillations and spindles, which predicts across-sleep improvements in verbal memory (Niknazar et al. 2015). Auditory closed-loop stimulation has also been used as a noninvasive strategy to alter the temporal coupling between NREM oscillations following learning. Using this technique, increasing the phase coupling between spindles and slow waves (by stimulating in phase with slow oscillation up states) following training on a declarative memory

task improves memory consolidation (Ngo et al. 2013). Together, these data suggest that both thalamocortical oscillations themselves and the temporal relationships among these oscillations during NREM sleep are essential for at least some of the cognitive benefits of sleep.

THALAMOCORTICAL ACTIVITY IN RAPID EYE MOVEMENT SLEEP

During both wake and REM sleep, input from the brainstem nuclei causes depolarization of thalamocortical and cortical neurons. During REM, brainstem mesopontine nuclei release acetylcholine in thalamic structures, while nucleus basalis projections release acetylcholine in the cortex (Rasmusson et al. 1996, Steriade 2003). In thalamocortical relay neurons, cholinergic input from the pons causes prolonged depolarization, with an increase in input resistance, leading to increased responsiveness of thalamocortical relay neurons during wake and REM (Curro Dossi et al. 1991, Glenn & Steriade 1982). Depolarization of thalamocortical relays and cortical neurons inhibit slower oscillatory activities associated with NREM sleep and promote faster oscillations, including beta (20–30 Hz) and gamma (30–60 Hz) (Llinas et al. 1991, Nunez et al. 1992, Steriade et al. 1991b). These fast oscillations can be generated in thalamocortical systems by activation of the mesopontine cholinergic nuclei and require muscarinic receptor activation (Steriade et al. 1991b). Both intracortical and CT connections appear to be required to synchronize these fast oscillations across thalamocortical networks during REM and wake states (Nunez et al. 1992).

Ponto-geniculo-occipital (PGO) waves are discrete propagating waves, characteristically appearing during REM sleep in cats, rats, and primates (Gott et al. 2017). These waves are caused by bursts of action potentials initiating in the pontine region, which propagate through the LGN to the occipital cortex in species with highly developed visual systems (Benington & Frank 2003). PGO waves emerge in synchrony with saccadic eye movements occurring during REM sleep; thus, one possibility is that they reflect a corollary discharge from eye movements (Gott et al. 2017). Another is that they have additional functions in thalamocortical circuits mediating visual perception, for example, in facilitating visual imagery during the vivid dreams associated with REM sleep in humans.

The function of PGO waves with regard to cognition is largely unstudied. However, in rodents, similar events, referred to simply as P waves (it is unclear whether they propagate through thalamocortical visual circuits in the same manner), have been implicated in promoting hippocampus- and amygdala-dependent memory consolidation. (Gott et al. 2017). P waves appear to facilitate synaptic plasticity in these structures during REM sleep—a process that is augmented by prior learning (Datta 2000, Datta & O'Malley 2013, Datta et al. 2008).

SLEEP-DEPENDENT THALAMOCORTICAL ACTIVITY PATTERNS AND VISUAL SYSTEM PLASTICITY

In recent years, sleep has been shown to play a role in promoting synaptic plasticity in various brain structures (Aton 2013, Puentes-Mestril & Aton 2017, Puentes-Mestril et al. 2019). Sleep-dependent plasticity has been shown to have a role in promoting adaptive visual response changes in thalamocortical circuits following novel visual experiences.

Ocular dominance plasticity (ODP) is one of the best-studied examples of in vivo brain circuit plasticity initiated by changes in sensory input. ODP occurs in the V1 during a period of early postnatal development, in which V1 neurons are highly sensitive to the relative strength of inputs representing the two eyes. If, during this timeframe, one of the two eyes is occluded [a process known as monocular deprivation (MD)], then the relative weights of these synaptic inputs and their morphology can be dramatically altered (Hubel and Wiesel 1970). MD first initiates

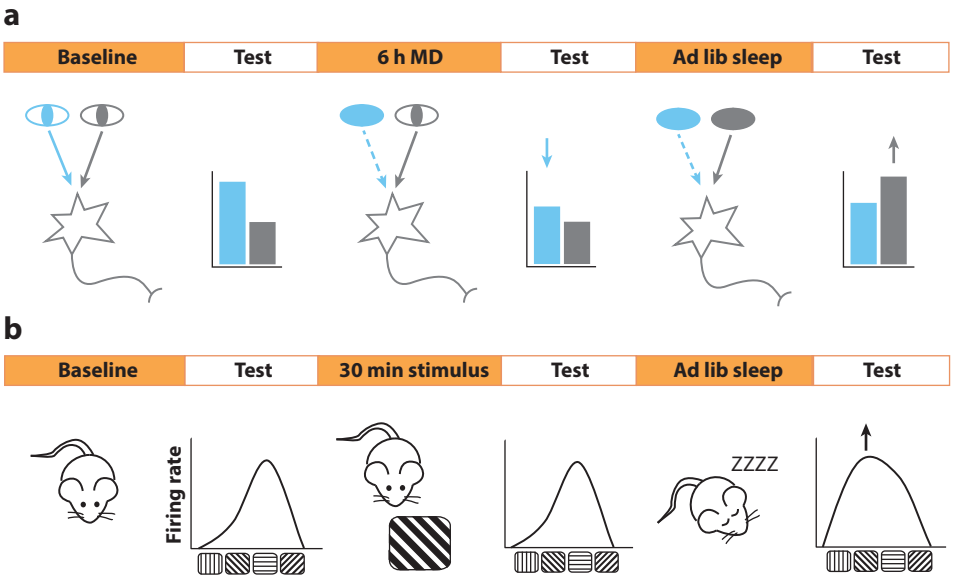

Figure 3

Ocular dominance plasticity (ODP) and orientation-specific response potentiation (OSRP) are sleep-dependent forms of visual system plasticity. (*a*) In cats, ODP is initiated following 6 h of monocular deprivation and manifests as a decrease in thalamocortical input to the primary visual cortex (V1) from the deprived eye (*blue*) and an increase in thalamocortical input to the V1 from the open eye (*gray*; see *arrows*). Sleep is required for this enhancement of input for the open eye. These changes in neuronal activity at baseline, after 6 h of monocular deprivation, and after 6 h of ad lib sleep periods are schematized below. Under test periods, relative firing rate responses to stimulation of each eye are provided. Panel adapted with permission from Aton et al. (2013) and Frank (2017). (*b*) OSRP is initiated by prolonged (i.e., 30 min) exposure to a grating stimulus and manifests as an enhancement in response (e.g., firing rate) to the presented orientation (*arrow*). This enhancement is not seen immediately following stimulus presentation, but instead requires sleep for consolidation, as sleep deprivation prevents OSRP.

a reduction in V1 neurons' firing responses to stimulation of the deprived eye; this change is followed by an increase in firing responses to stimulation of the spared eye (**Figure 3*a***) (Crair et al. 1997, Freeman & Olson 1979, Frenkel & Bear 2004, Olson & Freeman 1980). ODP induced in a developing cat visual system by just a few hours of monocular visual experience is significantly enhanced by a period of subsequent sleep (Frank et al. 2001). While brief monocular experience alone causes a relatively modest ocular dominance shift in the V1 (and initial depression of deprived-eye responses), subsequent sleep increases the overall shift by increasing the magnitude of firing rate responses to spared-eye stimulation (Aton et al. 2009). This selective potentiation of responses during sleep is mediated by increased cortical firing and activation of intracellular pathways involved in the long-term potentiation (LTP) of glutamatergic synapses (Aton et al. 2009) and on the transcription and translation of genes and proteins required for synaptic plasticity (Dumoulin et al. 2013, Seibt et al. 2012). REM sleep appears essential for activation of some of these intracellular pathways, as post-MD REM deprivation disrupts their activity (Bridi et al. 2015). However, there is also evidence that firing patterns associated with NREM oscillations (including delta and sleep spindles) could play a role in sleep-dependent augmentation of spared-eye responses in the V1. For example, coherence of V1 neurons' firing with spindle-frequency oscillations is predictive of their nondeprived eye response enhancements across a period of post-MD sleep (Aton et al. 2013).

In the rodent visual system, work has primarily focused on sleep-dependent changes in monocular (as opposed to binocular) V1 following MD. Loss of visual input to monocular V1 caused by MD leads to an immediate decrease in firing, followed by a gradual recovery to baseline firing rates over the next two days. This recovery process relies on homeostatic scaling, rather than Hebbian plasticity mechanisms (Hengen et al. 2013). Recent data suggest that this homeostatic upscaling occurs specifically during wake, and that sleep may actually inhibit this process (Hengen et al. 2016). Taken together, these data suggest that sleep-associated activity in the visual system may play a role in regulating both Hebbian and homeostatic plasticity mechanisms to modulate visual responses to changing inputs (Frank 2017, Mrsic-Flogel et al. 2007).

Orientation-specific response potentiation (OSRP) is another form of experience-dependent plasticity that occurs in the adult mouse visual system in response to presentation of a flickering grating of a single orientation over several minutes (Aton et al. 2014, Frenkel et al. 2006). OSRP is characterized by an increase in the amplitude of V1 visually evoked potential (VEP) responses (Cooke & Bear 2010, Frenkel et al. 2006) or in V1 neurons' firing rate responses (Aton et al. 2014, Durkin & Aton 2016) to stimuli of the same orientation (**Figure 3*b***). OSRP appears to be initiated at thalamocortical synapses, relies on NMDA receptor activation and AMPA receptor trafficking (Frenkel et al. 2006), and occludes thalamocortical LTP (induced by theta burst stimulation) in vivo (Cooke & Bear 2010). Taken together, a parsimonious interpretation of available data is that visual experience induces potentiation of thalamocortical synapses, which leads to stimulus-specific response changes in the V1.

Early studies on OSRP indicated that V1 response changes were not detectable immediately following stimulus presentation, but rather required a period of several hours to be consolidated (Frenkel et al. 2006). Work from our lab has shown that changes in V1 neurons' firing rate responses are not seen after presentation of oriented gratings for as long as 1 h but can be detected after as little as 6 h of subsequent sleep (Aton et al. 2014). The mechanism driving consolidation of OSRP is not simply time dependent, as sleep deprivation of similar duration (in the absence of additional visual input) disrupts OSRP (**Figure 3*b***) (Aton et al. 2014, Durkin & Aton 2016, Durkin et al. 2017). Based on prior data indicating that changes in the strength of thalamocortical synapses mediate OSRP, we hypothesized that changes in V1 responses are preceded by changes in the LGN. By recording simultaneously in both the LGN and V1 of freely behaving mice, we found that stimulus presentation during wake is sufficient to induce changes in the firing rate responses of LGN neurons. With continued exposure to the grating used to induce OSRP, LGN neurons gradually increase their firing (Durkin et al. 2017). Within 30 min of stimulus exposure, LGN neurons have selectively shifted their firing responses to favor the orientation of the presented stimulus, while simultaneously recorded V1 neurons show no such changes (Durkin et al. 2017). Together, these data suggest that visual experience initiates firing rate response changes in that LGN, and that LGN–V1 communication during subsequent sleep is essential for later response changes in the V1.

Subsequent work in our lab has demonstrated that coherent NREM oscillations are crucial for transfer of stimulus-specific information from the LGN to the V1. Based on prior work indicating that CT feedback was essential for synchronizing delta and spindle activities across the thalamus (Contreras et al. 1996a, Timofeev & Steriade 1996), we used optogenetics to disrupt CT feedback from the V1 to the LGN, specifically during bouts of NREM sleep, in the hours following oriented grating presentation. We found that, when activity in CT neurons was transiently suppressed during poststimulus NREM sleep, coherent firing between the LGN and V1 was disrupted, delta and spindle oscillations in the circuit were dampened, and OSRP consolidation in the V1 was blocked (Durkin et al. 2017). Because OSRP was not disrupted when CT feedback from the V1 to the LGN was inhibited during bouts of REM sleep or wake, this suggests that coherent

thalamocortical oscillations unique to NREM sleep may play an essential role in consolidating OSRP.

SLEEP'S BROADER EFFECTS ON PRIMARY VISUAL CORTEX NEURONAL FIRING RATES AND RESPONSE PROPERTIES

Recent work has begun to assess the heterogeneous effects of sleep and wake across populations of neurons that have a wide spectrum of baseline firing rates and other properties. For example, Watson et al. (2016) recently demonstrated that sleep-associated changes in firing rates of frontal cortical neurons varied depending on the neurons' baseline firing rates, with higher firing neurons showing net decreases in firing rate and more sparsely firing neurons showing a net increases. A related study recently showed similarly heterogeneous effects of sleep on the firing rates of hippocampal neurons, with the extent of change dependent on baseline firing rates (Miyawaki & Diba 2016). Thus, it appears as though sleep may support redistribution of neuronal firing rates in these systems.

Our lab was interested in assessing whether similar firing rate changes are mediated by sleep in V1 neurons, and whether firing rate changes in highly active and sparsely firing V1 neurons are maintained in the context of sleep-dependent plasticity. To do this, we examined how highly active and sparsely firing V1 neurons' firing rates change across bouts of sleep and wake, either following induction of OSRP or under control conditions (Clawson et al. 2018). Under both OSRP and control conditions, the baseline neuron firing rate was negatively correlated with changes in firing across the sleep period. Thus, low-firing neurons were more likely to increase their firing and vice versa. Critically, these firing rate changes were completely eliminated in mice that were sleep deprived, suggesting a causal role for sleep in firing rate redistribution (Clawson et al. 2018). In the context of OSRP consolidation, there was also a significant relationship between V1 neurons' baseline firing rates and the degree to which they shifted their orientation preferences across a period of poststimulus sleep. More sparsely firing neurons, which were at baseline more orientation selective, showed the largest increase in firing rates, and the largest shift in their orientation preference, across poststimulus sleep. High-firing neurons, which were minimally orientation tuned at baseline, showed firing decreases across poststimulus sleep (Clawson et al. 2018). These data suggest that, in the V1, sleep plays different roles in regulating the firing of different neuronal populations—augmenting the activity of sparsely firing neurons that carry very specific visual information and simultaneously reducing the firing of neurons with high activity but lower information content. We speculate that this circuit-level redistribution of firing rates could play a critical role in improving the signal-to-noise ratio with regard to visual information processing in the cortex. This sleep-dependent process may be particularly important under conditions where adaptive response changes are initiated by new visual experiences in prior wake.

THALAMOCORTICAL CIRCUIT ACTIVITY AND SYNAPTIC PLASTICITY

Work carried out in the visual system to date suggests that sleep promotes response changes in visual system neurons by promoting changes in the strength of specific synapses. Why might sleep selectively promote these changes? Multiple hypotheses have been put forward to explain how sleep contributes to brain plasticity and cognitive function (Benington & Frank 2003, Puentes-Mestril & Aton 2017, Puentes-Mestril et al. 2019, Tononi & Cirelli 2003). In this section, we examine some of the major hypotheses regarding the role of sleep-dependent thalamocortical activity in promoting synaptic plasticity.

Slow Wave Activity and Synaptic Downscaling

Why has sleep (and sleep-specific neural activity) proved so crucial for cognition and brain plasticity? Arguably the most prominent hypothesis in the sleep field, the synaptic homeostasis hypothesis, posits that, due to the multitude of learning experiences occurring during wake, net synaptic strength is increased, and that sleep plays a critical role in offsetting this net potentiation through global synaptic downscaling (Tononi & Cirelli 2003, 2006). As originally described, the mechanism for synaptic homeostasis is a non-Hebbian form of plasticity, in that it does not selectively alter synapses based on inputs, but rather does so globally to combat oversaturation of synapses (Frank 2012, Tononi & Cirelli 2003). Thus, increases in network activity should cause downscaling of synapses, or vice versa, to maintain neuronal activity within a specific range (Turrigiano 1999). Synaptic downscaling would potentially also enhance the signal-to-noise ratio by reducing synapse strength equally across synapses, so that important synapses would be stronger relative to less important synapses (Tononi & Cirelli 2003). Because there are some data available to suggest that firing rates among cortical neurons decrease across NREM sleep (Vyazovskiy et al. 2009), and because some features of NREM sleep [e.g., the coherence of neuronal firing during slow wave activity (i.e., delta and slow oscillations) and the amplitude of slow waves themselves] also decrease across the rest phase, proponents of the hypothesis have linked downscaling to slow wave oscillations during NREM. This aspect of the hypothesis is particularly elegant because it relates a potential homeostatic feature of synapse regulation to the homeostatic regulation of sleep itself.

Since its proposal, a wealth of biochemical, electrophysiological, and anatomical evidence has emerged in support of the synaptic homeostasis hypothesis. Biochemical analysis of immediate early genes and phosphoproteins involved in synaptic potentiation appear to be elevated during both wake and sleep deprivation relative to sleep (Vyazovskiy et al. 2008). Electrophysiological recordings of cortical neurons show increased firing across sleep deprivation and decreased firing across sleep (Vyazovskiy et al. 2009). More recent work assessing dendritic spine structure has shown a modest but still significant decline in spine size after a period of sleep relative to after a similar period of sleep deprivation (de Vivo et al. 2017). Despite this, there are several caveats related to the synaptic homeostasis hypothesis (Puentes-Mestril & Aton 2017). First, most of the data in support of the hypothesis come from juvenile animals at a developmental stage (around the time of weaning) when synapse elimination is naturally at its peak, and from the somatosensory and motor cortices, which are necessarily highly active during experimental sleep deprivation. Second, there are no data linking sleep-dependent synaptic downscaling to any sleep-dependent cognitive process (e.g., to memory consolidation or functional plasticity in the sensory cortex). Third, and most importantly, a definitive mechanism for the hypothesis is lacking. One appealing possibility is that the cortical slow oscillation and delta oscillations are mediators of downscaling (Puentes-Mestril & Aton 2017). Because lower-frequency stimulation has been hypothesized to drive synaptic depression, the synchronized slow activity of these oscillations could be regulating downscaling of synapses through slow, sustained calcium activity. However, to date, there are no experiments linking slow wave activity in thalamocortical circuits to synaptic downscaling.

Sleep Facilitation of Synapse-Specific Potentiation

Recent data have suggested that synaptic potentiation can occur during sleep under certain conditions (e.g., following learning) (Puentes-Mestril & Aton 2017, Puentes-Mestril et al. 2019). Biochemical analyses of cortical tissue have shown that, following behavioral manipulations leading to synaptic remodeling (e.g., MD to induce ODP), cellular pathways involved in mediating synaptic potentiation are activated in a sleep-dependent manner (Aton et al. 2013, Bridi et al. 2015,

Seibt et al. 2012). Following training on a novel motor task, spine formation occurs preferentially during sleep among neurons in the motor cortex (Yang et al. 2014). Finally, our lab's work on OSRP has demonstrated that visual cortical neurons require sleep to consolidate this LTP-like form of plasticity (Aton et al. 2014). V1 neurons selectively increase their firing rates across bouts of sleep following induction of OSRP (Durkin & Aton 2016).

Given the hypothesis that NREM oscillations drive synaptic downscaling, one would assume that slow wave activity of NREM could not support synaptic strengthening. However, work by Chauvette et al. (2012) challenges this assumption by pointing to the up state of the cortical slow oscillation. Although the slow oscillation up and down states cycle at approximately 1 Hz, the up state features high-frequency spike trains, with increases in calcium levels at the transition from down to up state (Chauvette et al. 2012, Timofeev & Chauvette 2017). This alternation between depolarized and hyperpolarized membrane potential could support LTP. In cats, stimulation of the ascending somatosensory pathway elicited evoked potentials in the somatosensory cortex, which were potentiated across a bout of NREM sleep (Chauvette et al. 2012). Furthermore, this potentiation relied upon calcium influx and required activation of both AMPA and NMDA receptors, indicating a LTP-like mechanism. Recent data also suggest a role for sleep spindles in synaptic potentiation. Presynaptic bursts of thalamic (TRN and relay neuron) activity at ~10 Hz have been used to model the effects of sleep spindles on a thalamocortical circuit (Golomb et al. 1996). This frequency of stimulation overlaps with theta burst stimulation, which is commonly used to elicit LTP at thalamocortical synapses in the visual system and other sensory systems (Cooke and Bear 2010, Soutar et al. 2016). Rosanova & Ulrich (2005) recorded patterns of cortical activity associated with a NREM spindle in vivo and then repeated this pattern as an in vitro stimulus to mimic grouping of spindles by the slow oscillation. When this grouped spindle stimulation pattern was applied to cortical pyramidal cells in vitro, it elicited both short-term and long-term synaptic potentiation (Rosanova & Ulrich 2005). Consistent with a role of spindles in synaptic potentiation, rhythmic spike bursts in thalamocortical relay neurons during spindles depolarize dendrites, but not cell bodies, of cortical neurons, leading to large calcium influx (Seibt et al. 2017). Spindle-locked calcium activity appears to be limited to the dendritic arbors and does not appear to correlate with neuronal firing (Seibt et al. 2017). This indicates that calcium influx during spindles might provide an optimal scenario for non-Hebbian forms of synaptic plasticity.

Taken together, these data suggest not only that synaptic potentiation occurs during sleep in thalamocortical circuits, but also that there are multiple mechanisms by which NREM oscillations could support such potentiation. These mechanisms may come into play selectively following learning experiences during wake.

Plasticity Based on Neuronal Resonance with Sleep Oscillations

Recently, we proposed a novel hypothesis that may be useful for explaining the diverse experimental results that indicate a role for sleep in either synaptic strengthening or, conversely, synaptic weakening. Central to this hypothesis is the idea that firing of thalamic and cortical neurons is ordered during sleep oscillations in such a way that synapses between neurons can be either strengthened or weakened via spike timing–dependent plasticity (for a review, see Puentes-Mestril et al. 2019). This hypothesis, supported by computational models (Roach et al. 2018), is based on the idea that experience-dependent plasticity during wake can lead to increased excitability in specific subsets of neurons. Resonance of neuronal activity with subsequent sleep-associated oscillations in the thalamocortical circuit leads to these neurons' firing occurring at an earlier phase in each up state. In other words, neurons that receive increased excitatory drive due to plasticity

during wake experience fire before neighboring neurons. This leads to plasticity being propagated throughout the circuit (with both synaptic strengthening and weakening occurring depending on the relative phase of firing for pairs of neurons). This hypothetical mechanism for sleep-dependent plasticity, based on resonance-based ordering of spike timing, leads to specific predictions regarding how neuronal firing rates would change across a period of sleep based on their initial firing rates (Puentes-Mestril et al. 2019, Roach et al. 2018). Specifically, this hypothesis predicts that excitatory synapses onto more highly active neurons will undergo depression in the context of sleep-associated network oscillations, while excitatory synapses onto sparsely firing neurons will be potentiated. These predictions are actually supported by the experimental data described by our lab and others, which demonstrate heterogeneous effects of sleep on neuronal firing rates, with increases or decreases across sleep depending on the neurons' baseline activity level (Clawson et al. 2018). Thus, while it is highly speculative, this simple resonance-based mechanism could explain a number of diverse sleep-related effects on the nervous system.

CONCLUSION

In addition to its other benefits for cognitive function, sleep plays an essential role in promoting changes in visual system function following novel visual experience. These changes include alterations in the response properties of neurons in the V1, which occur within just a few hours of experience in a sleep-dependent manner. Like other thalamocortical circuits, the LGN and V1 undergo dramatic changes in neuronal and network activity as animals transition from wake to NREM sleep and from NREM to REM sleep. Thus, it is tempting to speculate that during sleep, these changes in network dynamics promote the synaptic plasticity that underlies V1 response changes that emerge following a period of postexperience sleep. Indeed, recent work suggests that disruption of NREM-associated thalamocortical oscillations interferes with sleep-dependent brain plasticity, while augmentation of these oscillations (through invasive or noninvasive means) promotes it. Future work is needed to understand exactly how these oscillations promote intracellular processes that could lead to synapse-specific strengthening or weakening, and whether similar mechanisms underlie thalamocortical plasticity in other systems of the brain (e.g., the somatosensory and auditory systems).

SUMMARY POINTS

1. The visual thalamocortical circuit is composed of the LGN, TRN, and V1, with each area contributing to the processing of visual input via selective responses to parameters such as direction and orientation.
2. During transitions from wake to sleep, decreased neuromodulator levels hyperpolarize thalamocortical neurons, allowing for both the generation of NREM oscillations and disengagement from the sensory environment.
3. Coherent NREM oscillations in thalamocortical circuits are coordinated by reciprocal communication between the thalamus and cortex.
4. NREM oscillations (delta, spindle, and slow) have been correlated with perceptual learning and declarative memory consolidation.
5. Sleep is required for consolidating multiple forms of plasticity affecting LGN and V1 neuron visual response properties.

6. The precise mechanisms linking sleep-specific thalamocortical activity and plasticity are unclear, but NREM oscillations have been linked to both synaptic strengthening and weakening.

FUTURE ISSUES

1. It is unclear how certain facets of sleeping brain physiology (such as changes in neuromodulator release) affect visual response properties, neuronal and network activity, and plasticity in the LGN and V1.
2. While NREM and REM sleep oscillations are hypothesized to support brain plasticity, the mechanistic role by which these oscillations contribute to changes in synaptic strength is unknown.
3. Sleep leads to heterogeneous firing rate changes in V1 neurons, with differential effects on highly active and sparsely firing neuronal populations. How these changes affect visual system function and visual perception is unknown.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was supported by a Graduate Research Fellowship to J.M.D. from the National Science Foundation and research grants to S.J.A. from the National Institutes of Health (R01 NS104776), the Human Frontier Science Program (RGY0063), and Research to Prevent Blindness.

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