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CHAPTER 1

Slow brain oscillations of sleep, resting state, and vigilance

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Abstract: The most important quest of cognitive neuroscience may be to unravel the mechanisms by which the brain selects, links, consolidates, and integrates new information into its neuronal network, while preventing saturation to occur. During the past decade, neuroscientists working within several disciplines have observed an important involvement of the specific types of brain oscillations that occur during sleep—the cortical slow oscillations; during the resting state — the fMRI resting state networks including the default-mode network (DMN); and during task performance — the performance modulations that link as well to modulations in electroencephalography or magnetoencephalography frequency content.

Understanding the role of these slow oscillations thus appears to be essential for our fundamental understanding of brain function. Brain activity is characterized by oscillations occurring in spike frequency, field potentials or blood oxygen level-dependent functional magnetic resonance imaging signals. Environmental stimuli, reaching the brain through our senses, activate or inactivate neuronal populations and modulate ongoing activity. The effect they sort is to a large extent determined by the momentary state of the slow endogenous oscillations of the brain. In the absence of sensory input, as is the case during rest or sleep, brain activity does not cease. Rather, its oscillations continue and change with respect to their dominant frequencies and coupling topography. This chapter briefly introduces the topics that will be addressed in this dedicated volume of *Progress in Brain Research* on slow oscillations and sets the stage for excellent papers discussing their molecular, cellular, network physiological and

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cognitive performance aspects. Getting to know about slow oscillations is essential for our understanding of plasticity, memory, brain structure from synapse to DMN, cognition, consciousness, and ultimately for our understanding of the mechanisms and functions of sleep and vigilance.

Keywords: slow waves; traveling waves; slow oscillation; infraslow oscillation; sleep; resting state networks; default mode network; vigilance; cognition; learning and memory; behavioral performance; consciousness; electroencephalography; magnetoencephalography; functional magnetic resonance imaging; blood oxygen level-dependent signal; brain imaging; replay; synaptic scaling.

Introduction

The brain is most often studied in paradigms that evaluate its response on stimuli. In the absence of stimuli, the brain by no means silences but rather shows prominent spontaneous fluctuations in activity. These fluctuations dramatically influence the neural network responses on input and thus information processing. The typical periodicity is due to the rhythmic discharge of large numbers of neurons that synchronize with frequencies ranging from 1 to over a 100 Hz, the frequencies that are usually observed in neurophysiological recordings of field potentials. This chapter focuses on even slower oscillations - or fluctuations; the slow oscillations (0.5–1 Hz) of sleep and the infraslow oscillations (ISOs; 0.01–0.1 Hz) that have been found in time series of behavioral performance, of neuronal firing rates, of electroencephalography (EEG), of magnetoencephalography (MEG), and of functional magnetic resonance imaging (fMRI) blood oxygen level-dependent (BOLD) signal. These oscillations have been the topic of the 2010 Summer School of Brain Research in Amsterdam, the Netherlands, of which this dedicated volume of *Progress in Brain Research* accounts. This introductory chapter provides a bird's eye view on the relevance of slow oscillations and sets the stage for excellent papers discussing their molecular, cellular, network physiological and cognitive performance aspects.

Slow oscillations of sleep: When, where, who, and why?

As reviewed in this volume by Riedner et al. (2011), soon after Hans Berger showed the feasibility to record electrical activity from the human brain, its profound changes with sleep started to draw attention. The most striking electroencephalographic characteristic of deep non-rapid eye movement (NREM) sleep is the 0.5–1.0 Hz slow oscillation of very high amplitude ($>140\ \mu V$). It has been argued that the equally characteristic 1–4 Hz delta waves of sleep, with amplitudes between 75 and 140 μV, are, in fact, realizations of slow oscillations with less-marked network synchronization (Esser et al., 2007; Vyazovskiy et al., 2009).

The signal originates in synchronization of membrane potential fluctuations of massive numbers of neurons, both excitatory and inhibitory, in the cerebral cortex. During the hyperpolarized phase, mostly called "down-state," neurons remain silent for a few hundred milliseconds, while during the depolarized phase, mostly called "up-state," neuronal spike activity takes place, often including burst firing (Steriade et al., 1993). The alternation of up- and down-states is an intrinsic property of cerebral cortex and maybe even of neuronal networks *per se*, because it can be demonstrated in cortical slabs and slices and even in neuronal networks

grown in a dish from dispersed cells under specific conditions (Borg-Graham, 2001; Sanchez-Vives and McCormick, 2000; Timofeev, 2011; Timofeev et al., 2000).

In the intact brain, up-states are associated with such complex and widespread neuronal network activity throughout the brain that they have been proposed to resemble small fragments of wakefulness (Destexhe et al., 2007). As discussed later, the resemblance with wakefulness may go as far as including phasic activation, during up-states, of brainstem nuclei that have long been thought to be virtually silent in NREM sleep.

When?

Slow (0.5–1 Hz) cortical oscillations occur during sleep (but see Petersen et al., 2003). The strength by which the brain expresses slow oscillations at sleep onset, increases with the duration of prior wakefulness. The consensus model for this phenomenon is that there exists a homeostatic "process S" that refers to a gradual buildup of slow-wave sleep pressure during wakefulness. The buildup is usually described to follow the time course of a saturating exponential. The homeostatic regulation of sleep pressure, proposed in the early eighties of the past century (Akerstedt and Gilberg, 1981; Borbely et al., 1981; Daan et al., 1984), has become a major cornerstone in the quest to understand the mechanisms and functions of sleep. Although it has been proposed that the seemingly inevitable buildup of sleep pressure can effectively be attenuated by means of repeated sleep restriction (Kim et al., 2007), more recent work indicates that this procedure of chronic sleep restriction cannot beat or reset the homeostatic process but rather results in brief intrusions of slow-wave pressure dissipation into wakefulness (Akerstedt et al., 2009; Leemburg et al., 2010; Van Someren, 2010). Thus, slow-wave activity occurs preferably during sleep, but if the sleep period is too restricted, it is as if the brain finds a way out by leaking it into the wake state.

Once the organism falls asleep, the hypothesized underlying slow-wave sleep pressure dissipates, once more according to a saturating exponential. Electrophysiological findings presented by Vyazovskiy et al. (2011) in this volume indicate that, during the course of sleep, the amplitude and slope of slow oscillations gradually decrease. The decline in amplitude results in the typical reduction of low-frequency power spectral density with increasing duration of sleep. The decline in slope results in the less often recognized shift toward a lower frequency. Vyazovskiy et al. argue that the slope of slow oscillations, like the slope of triggered cortical responses, is an indicator of synaptic efficacy. The steep slope of slow oscillations of early sleep indicates saturation of the synaptic pool. After a period of sleep, the slope of the later slow oscillations becomes less steep, indicating that downscaling has occurred. This process restores the dynamic range and independence of the synapse, that would become too synchronized with others if downscaling would not occur (Tononi and Cirelli, 2006).

It should be noted that slow oscillations are not exclusively found to occur spontaneously in a sleeping (or anesthetized) brain unresponsive to external input. Riedner et al. (2011) review in this volume how slow oscillations can also be triggered by external stimuli delivered during sleep. Moreover, slow oscillations resembling those that occur during sleep have also been found to occur during quiet wakefulness in the somatosensory cortex of mice (Petersen et al., 2003). Quite contrary to the enhanced neuronal response to input during the up-state while asleep, whisker deflections evoked fewer action potentials during the up-state while awake.

Where?

Although up-state-related neuronal firing may start in any cortical layer, it is most likely to be ignited in layer V where the large pyramidal cells have the most numerous synaptic inputs and

largest projection fields (Chauvette et al., 2010; Oberlaender et al., 2011). Slow oscillations are also not expressed equally strong over the spatial map of the cerebral cortical surface. There is a clear anterior-to-posterior gradient in slow-wave power, indicating that the more frontal cortical areas express slow oscillations most profoundly (Werth et al., 1996). Already more than 60 years ago, researchers tried to estimate the underlying sources of this unequal distribution over the scalp, as reviewed by Riedner et al. (2011) in this volume. Only recently, it became feasible to record the human sleep EEG with a very high density of electrodes, a requirement for reliable estimates of the cortical sources underlying the scalp signals. These methods have shown that, in humans, slow oscillations originate relatively often in the insula and anterior cingulate gyrus and often occur as waves traveling along the anterior-to-posterior cingulate cortex (Massimini et al., 2004; Murphy et al., 2009). Also in cats, activity was found to spread preferentially in the anterior-to-posterior direction (Volgushev et al., 2006, 2011). Endogenous electric fields generated by slow oscillations may be involved in their propagation (Frohlich and McCormick, 2010). Modeling distributed cortical sources from high-density sleep EEG, Murphy et al. (2009) found a particularly strong expression of slow oscillations in the inferior frontal gyrus, anterior cingulate, posterior cingulate, and precuneus. These findings seem robust, since the areas largely overlap with those found in studies that simultaneously obtained EEG and fMRI BOLD signal in sleeping humans. As discussed by Mascetti et al. (2011) in this volume, these multimodal studies also showed that slow delta waves were most significantly associated with activation in the inferior frontal, medial prefrontal, precuneus, and posterior cingulate cortical areas and, unexpectedly, with transient activations in the pontine tegmentum (Dang-Vu et al., 2008). Interestingly, the cortical areas that are most activated during slow sleep oscillations overlap to a great extent with the areas that form the default-mode network (DMN) measured with fMRI during resting state wakefulness (Riedner et al., 2011). The ongoing background activity in this and other resting state networks (RSNs) is by no means trivial; it consumes most of the energy the brain requires (Raichle, 2006, 2010).

The overlap of the topography of slow oscillations and the topography of the DMN may be more than coincidence and energy consumption may be involved. Recent work has shown that the local cortical expression of slow oscillations reflects the activation history of the cortical area during prior wakefulness. Indeed, manipulation studies show that—on top of the more general spatial differences in the expression of slow oscillations discussed above—local induction of synaptic plasticity during wakefulness induces a locally increased expression of slow-wave activity during subsequent sleep (Huber et al., 2004, 2006, 2007a). Slow-wave activity even varies between cortical columns, depending on their prior cellular activity. To cite Mölle and Born (2011): "the more information is encoded during wakefulness, the higher the subsequent amplitude of slow sleep oscillations is".

The biological and biochemical processes underlying this echoing of prior local cortical activity in the spatial distribution of subsequent slow-wave power may provide important clues on the function and regulation of sleep. Brain-derived nerve growth factor (BDNF; Huber et al., 2007b) and the cytokines such as tumor necrosis factor alpha (TNF) and interleukin-1 beta (IL1; Krueger et al., 2011) may be mediators of this link at the molecular level. As discussed in this volume by Krueger et al. (2011), neuronal and glial activity increases extracellular ATP which in turn indirectly enhances the release of these cytokines via activation of purine receptors. Krueger et al. (2011) propose a role for TNF and IL1 in synaptic scaling, which is one of the leading hypotheses on the function of slow oscillations during sleep (Tononi and Cirelli, 2006).

Who?

On top of the within-subject variance in slow-wave activity related to the duration of wakefulness and consequent homeostatic buildup of sleep pressure, and on top of the anterior-to-posterior gradient and prior local cortical plasticity, there are considerable between-subject differences. As reviewed by Landolt (2011) in this volume, these individual differences are remarkably stable, heritable traits. Several genes are involved in these differences, as indicated by the sensitivity of the sleep EEG for polymorphisms in the clock gene *PER3*, in the *ADA* gene coding for the adenosine deaminase enzyme, in the adenosine A2A receptor (*ADORA2A*) gene, in the gene encoding BDNF, in the gene encoding catechol-*O*-methyltransferase (COMT), and in the prion protein (PRNP) gene. The polymorphisms in these genes differentially affect the typical oscillations in the sleep EEG; slow-wave activity is most prominently affected by *PER3*, *ADA*, and *BDNF*.

Age is another important modulator of slow-wave activity. As discussed by Ringli and Huber (2011) in this volume, the amplitude of slow waves increases during childhood to peak shortly before the onset of puberty. This peak is followed by a steep decline of more than 60% between the age of 11 and 16 years. After about 17 years of age, a much milder decline occurs. Interestingly, this time course of the amplitude of slow waves parallels the time course of the changes in synaptic density in the cerebral cortex. Age does not only affect the average amplitude of slow waves but also markedly affects its topography. Slow-wave activity in infancy is characterized by a posterior dominance, slowly changing toward the anterior-to-posterior gradient typical of adults. The anterior-to-posterior gradient is not yet maximal during adolescence (Kurth et al., 2010). This changing topography of slow-wave activity dominance parallels cortical brain maturation; synaptic density of the visual cortex starts to decrease already during the first year of life, about 3–4 years before it starts to decrease in the frontal cortex. Ringli and Huber (2011) suggest that there may be more than a parallel. From the perspective of the synaptic scaling hypothesis (Tononi and Cirelli, 2006), slow-wave activity may be actively involved in downscaling of synaptic strength, initially occurring predominantly occipitally and only later occurring also more frontally.

Why?

What could the functional implications of slow oscillations be? The functions most often attributed to slow oscillations of sleep concern learning and memory. Destexhe et al. (2007) proposed the cortical up-states to represent brief fragments of a wake-like state where effective communication between different neuronal systems can take place. This idea is supported by the fact that, nested within the up-state, high-frequency oscillations occur that are implicated in network communication and systems consolidation of memory traces, as discussed by Mölle and Born (2011) in this volume. They propose that, during the up-states of slow oscillations, newly encoded memory representations are reactivated and can be redistributed, enabling a shift from temporary hippocampus-dependent storage to long-term hippocampus-independent neocortical storage. As discussed in this volume by Volgushev et al. (2011), this process may be facilitated by slow oscillations. The transitions between down- to up-states are accompanied by a very strong long-range correlation of membrane potentials. Thus, the slow oscillation imposes concurrent membrane potential changes to occur between very distant neurons. Subsequently, within an up-state, complex activity patterns are possible, similar to the dynamical formation of neuronal ensembles during wakefulness, thus allowing for information processing.

Slow cortical oscillations are associated with rhythmic discharges in corticofugal pathways that synchronize activity in subcortical structures including the basal ganglia, thalamus, and

subthalamic nucleus (e.g., Lacey et al., 2007; Magill et al., 2001). For example, simultaneous field potential derivations in the cortex and striatum demonstrated striatal slow waves to follow cortical ones with a maximal crosscorrelation of near one at a delay of ~11 ms (Mallet et al., 2005). Mölle and Born (2011) discuss in this volume that also the up-state-dependent grouping of thalamus-generated 10–15 Hz spindles and hippocampus-generated sharp-wave ripples appear crucial to the redistribution of memory representations and the strengthening of the synaptic connections that underlie them. The nesting of oscillations occurs over multiple spatiotemporal levels: hippocampal sharp-wave ripple events—possibly associated with memory information—are nested in the troughs of the thalamic spindles which in turn occur at the depolarizing up-state of cortical slow oscillations; moreover, subcortical activation and neocortical fast oscillations occur during the up-state (Mölle and Born, 2011).

It is indeed well conceivable that this precisely timed and looped complex network activity, that is moreover dependent on prior activations, is beneficial to memory consolidation. The memory-enhancing capacity of cortical slow oscillations is further indirectly supported by experimental studies that applied exogenous electric fields using transcranial direct current stimulation to induce slow oscillations (Marshall et al., 2004, 2006), and a study that suppressed their expression—without affecting sleep duration—using closed-loop mild acoustic stimulation (Van Der Werf et al., 2009). These and even less-invasive tools to directly and subtly modulate slow oscillations in humans become increasingly available (e.g., Raymann et al., 2008). In this volume, Van Der Werf et al. (2011) extend their initial findings on the effect of selective slow oscillation disruption. They show selectivity of the effects of this disruption on subsequent performance; in addition to its detrimental effects on hippocampal activation and memory encoding, the procedure increased the number of lapses on a sustained vigilance task. However, it affected neither the reaction times nor the performance on an implicit memory task. The results suggest that the involvement of slow oscillations in memory processes surfaces most strongly in tasks that require a dialog between hippocampus and neocortex.

Schwindel and McNaughton (2011) review in this volume how specific patterns of reactivation during sleep could support memory consolidation in the hippocampal–neocortical network. The trace reactivation theory of memory consolidation states that the coordinated patterns of activation of cortical modules elicited during encoding can subsequently be reactivated. This reactivation supports strengthening and adaptation of horizontal connections between the modules. The hippocampus is initially essential to index—that is, provide "pointers" to—the coordinated patterns of activation of cortical modules. Such gradual strengthening of the horizontal corticocortical connections could ultimately release memory traces from hippocampal involvement. Sleep provides an optimal window for this process, because the brain is functionally disconnected from environmental input that could interfere with appropriate network adaptation. Schwindel and McNaughton not only provide an excellent review of 20 years of support for memory trace reactivation in the hippocampo–neocortical circuits during slow-wave sleep but also review essential developments in the statistical analyses of multichannel recordings to test the validity of the hypothesis. Detailed analyses of the timing of hippocampal and cortical events suggest that reactivation of recent memory traces might be led by the hippocampus, while reactivation of more established memory traces could, in certain cases, be led by the medial prefrontal cortex. Schwindel and McNaughton point out that a major challenge remains to demonstrate more convincingly that memory trace reactivation indeed facilitates subsequent memory performance.

Another leading hypothesis on the role of slow oscillations that can exist in parallel to the memory trace reactivation hypothesis is that they support synaptic scaling. In brief, the alternating pattern of up- and down-states is conductive to a general

downscaling of synaptic strength. This is necessary to preserve cost-efficiency in a network driven to saturation by a wake-induced net increase in synaptic weights (Tononi and Cirelli, 2006). Substantial support, from the molecular to the systems level, has accumulated over the past decade. In an overview of synaptic modulation in relation to sleep and wake states in this volume, Timofeev (2011) questions whether a wake-related monotonic increase in synaptic weights would occur and suggests a modification of the downscaling hypothesis. He proposes that the wake state produces a steady state of synaptic plasticity, consisting mostly from depression of synapses, from which the brain can recover during the down-state of sleep slow oscillations. Another critical role for the down-state is put forward by Schei and Rector (2011) in this volume. They suppose that there is a physiological limit to the vascular dilation that is required to deliver oxygen and glucose in brain tissue with wake-related prolonged neuronal activity. They argue that the hyperpolarized down-state that repeatedly occurs during slow-wave sleep is metabolically less demanding and thus allows for a restoration of vascular compliance.

Frank (2011) reviews in this volume how he and his team have elegantly exploited the ocular dominance plasticity model of Hubel and Wiesel (1970) to elucidate cellular mechanisms involved in the role of sleep in synaptic plasticity. Although originally applied to study critical periods of the developing occipital cortex, it has become evident that many of the underlying cellular mechanisms apply as well to plasticity in the hippocampus and non-sensory cortex during adulthood. The studies of Frank and colleagues, as well as those of McNaughton and colleagues summarized in this volume (Schwindel and McNaughton, 2011), indicate that synaptic changes in wakefulness are consolidated during sleep through cortical reactivation and signaling cascades that involve activation of the NMDA receptor and the kinases activated by it. The ontogenetic model Frank and colleagues used, strongly supports an active role of sleep in memory consolidation processes, rather than a permissive role merely related to a lack of interference: only sleep augments ocular dominance plasticity, while anesthesia or cortical inactivation do not (Jha et al., 2005). Frank moreover suggests that REM sleep may be more involved when endogenous neuronal activity is critical to support the development of a rudimentary neural circuitry, while slow-wave sleep is most essential in synaptic processes that support learning from experience.

Under the hood

The focus with respect to the alternating up-state and down-state is usually on the cerebral cortex and the related hippocampal and thalamic activity. Recently, it has become increasingly clear that also other brain structures "under the hood," previously thought to be silent during sleep, in fact show activity in synchrony with the alternating up- and down-states. Their activity may even promote up-states to occur, or alter network activity within the up-state. In an early study, Nunez (1996) found putative cholinergic basal forebrain neurons to fire in synchrony with slow oscillations. He proposed that they might enhance the activity of cortical neurons during slow-wave sleep by means of synchronized release of acetylcholine in the cortex.

Mena-Segovia and Bolam (2011) review in this volume their work on the association of activity in the pedunculopontine nucleus (PPN) with slow oscillations during sleep. The PPN contains cholinergic, GABAergic, and glutamatergic neurons that project mainly to the intralaminar thalamic nuclei. Of the cholinergic neurons, about 80% fires sparsely ($\sim$1 Hz) and mostly during the up-state. Local PPN activation using carbachol left slow cortical oscillations intact but enhanced the power of nested gamma oscillations during the up-state. Another 20% of the PPN cholinergic neurons fires fast ($\sim$30 Hz) and mostly during the down-state. A third class, of putative glutamatergic neurons, fires preferentially during the cortical transition from up- to down-state.

The group of Sara (Eschenko and Sara, 2008; Sara, 2009, 2010) previously showed an association of slow oscillations and activity of noradrenergic neurons in the locus coeruleus (LC) activation. They presented exciting new work (Eschenko et al., 2011) at the 2010 Summer School of Brain Research in Amsterdam, the Netherlands, of which this dedicated volume of *Progress in Brain Research* accounts. Unit activity of the noradrenergic neurons of the LC was recorded simultaneously with cortical EEG in unrestrained rats. Activity of LC neurons turned out to precede cortical up-states by ~100 ms. This suggests a possible noradrenergic contribution to the generation of cortical up-states or to the coordinated activity of neuronal assemblies that occurs during up-states. Such timed noradrenergic release is highly relevant for off-line information processing, synaptic plasticity, and memory consolidation.

With respect to dopaminergic innervation of the cortex during slow-wave sleep, only a small minority of neurons in the substantia nigra synchronize their firing rate to cortical slow oscillations (Brown et al., 2009).

Even slower: The when, where, who, and why of ISOs

During the past decade, neuroscience has developed a specific interest in even slower fluctuations of brain activity, occurring in the 0.01–0.1 Hz frequency range. These ISOs were known from animal studies long ago (Aladjalova, 1957) but have received massive interest only since their presence was shown in the fMRI BOLD signal in subjects at rest. The fluctuations are strongly coupled within functionally connected distributed anatomical networks called RSNs. RSNs have also been demonstrated using high-density full-band electroencephalography (fbEEG; Vanhatalo et al., 2005), as reviewed by Palva and Palva (2011) in this volume. Still, by far the most studies concern ISOs in the BOLD signal that occur with correlated time courses in distributed networks of voxels (Biswal et al., 1995). After some initial doubts as to the neuronal origin of the fluctuations, Beckmann et al. (2005) showed that RSN fluctuations can indeed be discriminated from low-frequency nonneural noise introduced by the cardiac cycle and respiration. The neural and nonneural contributions to the slow fluctuating BOLD signals are discussed in detail by Duyn (2011) in this volume.

When?

RSN fluctuations occur both during tasks and during rest (Duyn, 2011; Smith et al., 2009). Thus, as pointed out in a review of Duyn (2011) in this volume, the term "resting state networks" may not really be appropriate. The alternative "intrinsic functional connectivity networks" (ICNs) would be more appropriate (Seeley et al., 2009). One network received particular interest because its coupled fluctuations are suppressed during most tasks and become more pronounced during rest. It has therefore been called the default mode network (DMN) (Raichle et al., 2001). DMN activation has been related to self-referential processing, such as thinking about oneself and one's memories, and mind wandering (Mason et al., 2007). It seems to deactivate on most tasks with the possible exception of some explicit memory tasks, where activation has been reported (Smith et al., 2009).

While initially regarded as simple stationary oscillations, two recent studies show that this is not the case. Chang and Glover (2010) showed that coherence between RSN fluctuations varies over time. Niazy et al. (2011) show in this volume that the infraslow fluctuations in BOLD signal contain rich, complex patterns of interactions at different frequencies both within and between different RSNs. They also show data that argue against the generally accepted idea that the power of RSN fluctuations shows a specific ($1/f$) monotonic decrease with increasing frequency. The spectrum shows more variability and peaks may occur at somewhat higher frequencies

(0.02–0.05 Hz) than the traditional 0.015 Hz. It may thus be of value to examine whether specific conditions or patient groups differ with respect to the more complex and time-varying frequency interactions within and between RSNs.

Interestingly, the amplitude of BOLD signal RSN fluctuations predicts whether subjects are likely to fall asleep during a resting state scanning period (Fukunaga et al., 2006). Activity in the DMN continues to increase in the earliest phase of sleep (Picchioni et al., 2008). Larson-Prior et al. (2011) examine in this volume what happens to the DMN during the transition from wake to initial sleep and from initial sleep to more consolidated sleep. During the early transitional stage from wake to superficial sleep, subtle shifts in the network architecture occur that are compatible with a decrease in attention to external stimuli and an increase in self-referential processing. At the subsequent entry into slow-wave sleep, containing either isolated K-complexes or sequential slow waves, connectivity between anterior and posterior portions of the DMN decreases (Horovitz et al., 2009).

Where?

Independent component analysis (ICA) can be used to simultaneously extract the spatial representations of multiple RSNs. These RSNs comprise distributed yet functionally related cortical areas. The number of RSNs extracted depends on the methods applied, but often a number of $\sim$10 is reported. For example, Damoiseaux et al. (2006) found, consistently over subjects, 10 patterns with potential functional relevance, consisting of regions known to be involved in motor function, visual processing, executive functioning, auditory processing, memory, and the so-called DMN. Although the focus of RSN research is often on distributed cortical areas, they can involve subcortical areas including basal ganglia, thalamus, amygdala, and hippocampus (Robinson et al., 2009).

Subtle changes in spatial coupling *within* RSNs is a topic of increasing interest, especially in relation to conscious experience. As mentioned above, upon entering slow-wave sleep with its typical low level of conscious awareness, connectivity between anterior and posterior portions of the DMN decreases (Horovitz et al., 2009). Demertzi et al. (2011) show in this volume that hypnosis lowers involvement of the posterior midline and parahippocampal structures in DMN activity fluctuations, while it increases involvement of the lateral parietal and middle frontal areas. Hypnosis moreover attenuated connectivity in the "extrinsic" frontoparietal RSN involved in the perception of external stimuli. As discussed by Bruno et al. (2011) in this volume, functional connectivity within this network is of importance for determining the level of consciousness in patients with minimally conscious states. The decrease in connectivity with lower conscious awareness seems compatible with the findings of Massimini et al. (2005), who reported a shift toward a more local response of the cortex upon stimulation with transcranial magnetic stimulation during slow-wave sleep.

Who?

RSNs are well reproducible over different subjects (Damoiseaux et al., 2006) and also stable over time within subjects (Fukunaga et al., 2006), possibly more so in the DMN than in task-positive networks (Shehzad et al., 2009). RSN connectivity is affected by aging, as well as by neurological and neurodegenerative diseases (cf. Niazy et al., 2011).

Why?

ISOs modulate the excitability of widely distributed neuronal networks. It is therefore not surprising that behavioral performance covaries with the fluctuations (Makeig and Inlow, 1993;

Monto et al., 2008), as reviewed by Palva and Palva (2011) in this volume. They posit that the fluctuations constitute the neurophysiological foundation for trial-to-trial behavioral variability in performance tasks. Just as is the case for the slow sleep oscillations, there is nested expression of faster electrophysiological oscillations within electrophysiologically assessed ISOs (Vanhatalo et al., 2004) and ISOs assessed using BOLD fMRI. In several RSNs, BOLD fluctuations correlate with fluctuations in EEG alpha activity.

As reviewed by Duyn (2011) in this volume, another parallel between possible functions of slow sleep oscillations and infraslow RSN fluctuations is their proposed role in synaptic downscaling and memory consolidation. Interestingly, several studies noted an increased power of ISOs in RSNs following their activation in learning tasks (cf. Duyn, 2011; Waites et al., 2005), just like slow sleep oscillations increase their amplitude specifically over cortical areas that have been activated during prior wakefulness (Huber et al., 2004, 2006, 2007a).

Under the hood

As reviewed by Hughes et al. (2011) in this volume, animal studies show ISOs in local field potentials or neuronal activity in the hippocampus, basal ganglia, LC, dorsal raphe, olivary pretectal nucleus, and most notably in the thalamus. They persist even in acute thalamic slices *in vitro*, suggestive of a fundamental trait of neuronal networks. Hughes and colleagues suggest that the synchronous fluctuation of membrane currents in the thalamus is due to a nonneuronal process, likely involving astrocytes.

Conclusion

This chapter aimed to provide a bird's eye view of ongoing research on slow sleep oscillations (0.5–1 Hz) and ISOs (0.01–0.1 Hz), as an introduction to the excellent papers in this volume of *Progress in Brain Research*. The papers reflect presentations during 2010 Summer School of Brain Research in Amsterdam, the Netherlands, on the molecular, cellular, network physiological, and cognitive performance aspects of slow oscillations. Concertedly the papers in this volume provide ample inspiration to investigate these aspects in a multidisciplinary way. It is clear that the slow oscillations provide a rich view on the brain. They echo its past activation, provide a dynamic image of its current state, determine its response to pending input, and predict its future information processing capacities. They appear to be crucially involved in multiple dimensions of brain function, including synaptic plasticity, learning and memory, behavioral performance, and consciousness. Slow oscillations thus encompass all major interests of neuroscience.

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