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The large-scale functional connectivity correlates of consciousness and arousal during the healthy and pathological human sleep cycle

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ABSTRACT

Advances in neuroimaging have greatly improved our understanding of human sleep from a systems neuroscience perspective. However, cognition and awareness are reduced during sleep, hindering the applicability of standard task-based paradigms. Methods recently developed to study spontaneous brain activity fluctuations have proven useful to overcome this limitation. In this review, we focus on the concept of functional connectivity (FC, i.e. statistical covariance between brain activity signals) and its application to functional magnetic resonance imaging (fMRI) data acquired during sleep. We discuss how FC analyses of endogenous brain activity during sleep have contributed towards revealing the large-scale neural networks associated with arousal and conscious awareness. We argue that the neuroimaging of deep sleep can be used to evaluate the predictions of theories of consciousness; at the same time, we highlight some apparent limitations of deep sleep as an experimental model of unconsciousness. In resting state fMRI experiments, the onset of sleep can be regarded as the object of interest but also as an undesirable confound. We discuss a series of articles contributing towards the disambiguation of wakefulness from sleep on the basis of fMRI-derived dynamic FC, and then outline a plan for the development of more general and data-driven sleep classifiers. To complement our review of studies investigating the brain systems of arousal and consciousness during healthy sleep, we then turn to pathological and abnormal sleep patterns. We review the current literature on sleep deprivation studies and sleep disorders, adopting the critical stance that lack of independent vigilance monitoring during fMRI experiments is liable for false positives related to atypical sleep propensity in clinical and sleep-deprived populations. Finally, we discuss multimodal neuroimaging as a promising future direction to achieve a better understanding of the large-scale FC of the brain during sleep and its relationship to mechanisms at the cellular level.

Introduction

The human sleep cycle consists of a regular evolution through a series of global brain states, each characterized by marked changes in behavior, cognition, and neurophysiology (Carskadon and Dement, 2005). The number of such states -or whether they consist of a continuum- remains under debate (Pardey et al., 1996; Muller et al., 2006). The current standard approach (i.e. the rules of the American Academy of Sleep Medicine [AASM]) distinguishes three stages of increasing sleep depth (N1, N2, and N3 sleep) and rapid-eye movement (REM) sleep (Iber et al., 2007). The first three stages are collectively referred to as non-REM (or NREM) sleep.

It is clear that sleep involves changes of a global nature in brain activity relative to resting wakefulness. The cellular mechanisms underlying loss of wakefulness, NREM sleep onset, and the transition between different sleep stages (including REM sleep) have been investigated in detail using animal models. Wake-promoting neurons were reported in a specific set of nuclei linking the brainstem with the cerebral cortex via relays in the thalamic intralaminar nucleus, comprising the reticular activating system (RAS) (Magoun, 1952). When their activity decreases sufficiently, NREM and REM sleep can emerge, marked by global changes in cortical rhythms as measured using scalp electroencephalography (EEG) (Carskadon and Dement, 2005; Iber et al., 2007). According to the AASM definitions (Iber et al., 2007), N1 sleep is characterized by diminished alpha power (8–12 Hz) and increased power in slower frequencies, especially in the theta band (4–8 Hz). Also present during this stage are rolling eye movements and vertex sharp waves, i.e. electronegative discharges superimposed with slower fluctuations that manifest during late drowsiness (Broughton and Hasan, 1995). N2 sleep is heralded by the onset of K-complexes and sleep spindles, transient EEG events that have been linked to suppression of cortical arousal (Roth et al., 1956) and memory-related

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processes (Diekelmann and Born, 2010), respectively. The slowing down of EEG activity continues from N1 to N2 sleep and reaches its peak during N3 sleep, also known as slow wave sleep. In this sleep stage, EEG waves are synchronized in large amplitude oscillations in the delta range (1–4 Hz). In contrast to NREM sleep, REM sleep presents desynchronized low-voltage oscillations comparable to those observed during wakefulness; however, REM sleep is also characterized by distinct simultaneous movements of both eyes and loss of muscle tone. Furthermore, the evolution from early NREM sleep towards deep NREM sleep is paralleled by diminishing arousal, increasing stimulation thresholds for awakening, and reduced cognition and conscious awareness. In contrast, an exceptional form of consciousness occurs during REM sleep in the form of vivid dreams; although it is also becoming increasingly clear that though-like and dream-like mentations are frequently reported after awakening from NREM sleep as well (Foulkes, 1962; Beckstead, 1996; Suzuki et al., 2004; Siclari et al., 2013; Siclari et al., 2017). These observations strongly suggest widespread changes in neural network activity during sleep, and that an investigation of these changes could yield important insights on the neural correlates of arousal and conscious awareness.

The development of non-invasive neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) led in recent decades to major breakthroughs in the identification of large-scale neural networks involved in different stages of the human sleep cycle. An indirect marker of decreased neural activity, diminished glucose metabolism in frontal and parietal cortices has been consistently reported during NREM sleep (Braun et al., 1997). A decline in glucose consumption during NREM sleep is also known to affect other brain areas such as the temporal cortex, amygdala, hippocampus and hypothalamus (Nofzinger et al., 2002). On the other hand, REM sleep is associated with increased brain metabolism, especially in the basal forebrain and in the limbic system (Braun et al., 1997; Nofzinger et al., 1997).

fMRI yields blood-oxygen-level dependent (BOLD) signals at a higher temporal resolution than PET, and is therefore suitable to investigate the changes in blood oxygenation (and, indirectly, in the metabolic demand of neural activity) in response to brief stimulation events during sleep. The neural correlates of auditory processing during NREM sleep provide key insights on the mechanisms suppressing cortical arousal due to stimuli being categorized as originating from innocuous sources (Portas et al., 2000; Czisch et al., 2002, 2004) - in contrast, evidence for selective awakening after potentially threatening stimuli has been reported (Velluti and Pedemonte, 1997; Lavigne et al., 2000; Kato et al., 2004). The work of Portas et al. (2000) revealed that auditory stimulation during NREM sleep increases activity in brain regions associated with perception such as the primary auditory cortex and the thalamus, but that higher-order brain regions (left parietal and bilateral prefrontal and cingulate cortices) failed to activate in a similar way, suggesting the inhibition of further processing that could be related to conscious perception of the stimuli. These results are in contrast to those found by Czisch and colleagues (Czisch et al., 2002, 2004) who established decreased activity in auditory and visual sensory areas after auditory stimulation during NREM sleep. These activity decreases were paralleled by increased delta power and frequency of K-complexes. The neural correlates of K-complexes have been examined using combined EEG-fMRI (Caporro et al., 2012; Jahnke et al., 2012), suggesting their involvement in a brief arousal with a subsequent sleep-guarding counteraction that might facilitate the periodical monitoring of the environment and, on the other hand, protect the continuity of sleep. The use of an auditory oddball paradigm revealed that deviant tones lead to a transient disengagement of motor and amygdalar responses during light NREM sleep, which was interpreted as a sleep-protective mechanism (Czisch et al., 2009). Interestingly, in this study the authors did not find changes in BOLD fMRI associated with evoked K-complexes.

In spite of these studies using event-related designs, it is clear that the standard task-based paradigm of cognitive neuroscience (Posner and Raichle, 1998) is of difficult applicability during NREM and REM sleep, since participants are sensorially disengaged from their environments, and might lack the cognitive capacity to perform even relatively simple tasks. Recently, a surge of interest in the use of fMRI to investigate the intrinsic, spontaneous activity of the human brain (as opposed to that elicited by imposed tasks or sensory stimulation) has occurred. Ever since Biswal et al. (1995) revealed significant functional connectivity (FC) between spontaneous brain activity fluctuations measured at distant brain areas, an increasing number of studies have been devoted to understand the spatial and temporal structure of the so-called resting state activity (Raichle, 2006; van Den Heuvel and Pol, 2010). It is now clear that the spatial correlation structure of these fluctuations is non-trivial (Beckmann et al., 2005) and that it spontaneously recapitulates the patterns of activity associated with different brain functions as revealed using task-based fMRI (Smith et al., 2009). Furthermore, combined EEG and fMRI studies strongly suggest that resting state activity fluctuations are of neural origin (Laufs et al., 2003; Mantini et al., 2007). Large efforts have been devoted to elucidate how different neurological and psychiatric pathologies disrupt FC of resting state activity fluctuations (Greicius, 2008; Zhang and Raichle, 2010). Importantly, resting state fMRI studies do not require the collaboration of subjects beyond remaining still in the bore of the scanner, thus facilitating the investigation of certain populations of patients. By the same principle, the study of intrinsic brain activity fluctuations and their FC allows to overcome the difficulties of querying the sleeping brain using task-based paradigms.

State-of-the-art methods based on resting state FC allow the construction of whole-brain networks ("functional connectomes") and the investigation of their topological properties, i.e. those depending on how different brain regions are connected, but not on their anatomical locations per se (Bullmore and Sporns, 2009). An arsenal of tools inherited from the mathematical study of graphs and complex networks has caused a paradigm shift in the way neuroscientists approach the analysis and interpretation of neuroimaging data (Rubinov and Sporns, 2010). In particular, the analysis of whole-brain FC networks transcends functional cartography and can yield insights on the emergence of integrated and/or segregated sub-networks of regions, and how they are related to efficient information processing in the healthy brain (Sporns, 2013). Certain contemporary theories of consciousness rely heavily upon the detection of information integration/segregation in the human brain, and are therefore synergistic with the methodological developments of graph theory applied to brain imaging data (Tononi, 2004).

The application of the methods developed for resting state fMRI to sleep neuroimaging data led to a series of breakthroughs linking global and local changes in FC with different stages of the human sleep cycle. These studies, if interpreted with caution, might contribute important insights on the neural correlates of arousal and conscious awareness. In particular, the construction of whole-brain networks from brain activity recorded during deep NREM sleep can be combined with graph theoretical tools to probe specific predictions of theories of conscious awareness (Boly et al., 2012; Spoormaker et al., 2012; Tagliazucchi et al., 2013a). The contribution of resting state fMRI towards the understanding of the neural correlates of sleep can be seen, in fact, as a two-way street: it is now clear that participants tend to fall asleep during typical resting state fMRI experiments, prompting the need to disentangle wakefulness from sleep on the basis of FC of spontaneous activity fluctuations (Tagliazucchi and Laufs, 2014). This need is especially manifest in studies comparing resting state FC of (presumably) awake healthy controls vs. sleep deprived subjects, or vs. patients suffering from sleep disorders.

The present review discusses the aforementioned points in detail, and more generally addresses our current understanding of the large-scale (i.e. whole brain, millimeter scale resolution) FC of intrinsic brain activity fluctuations during human NREM and REM sleep, as well as

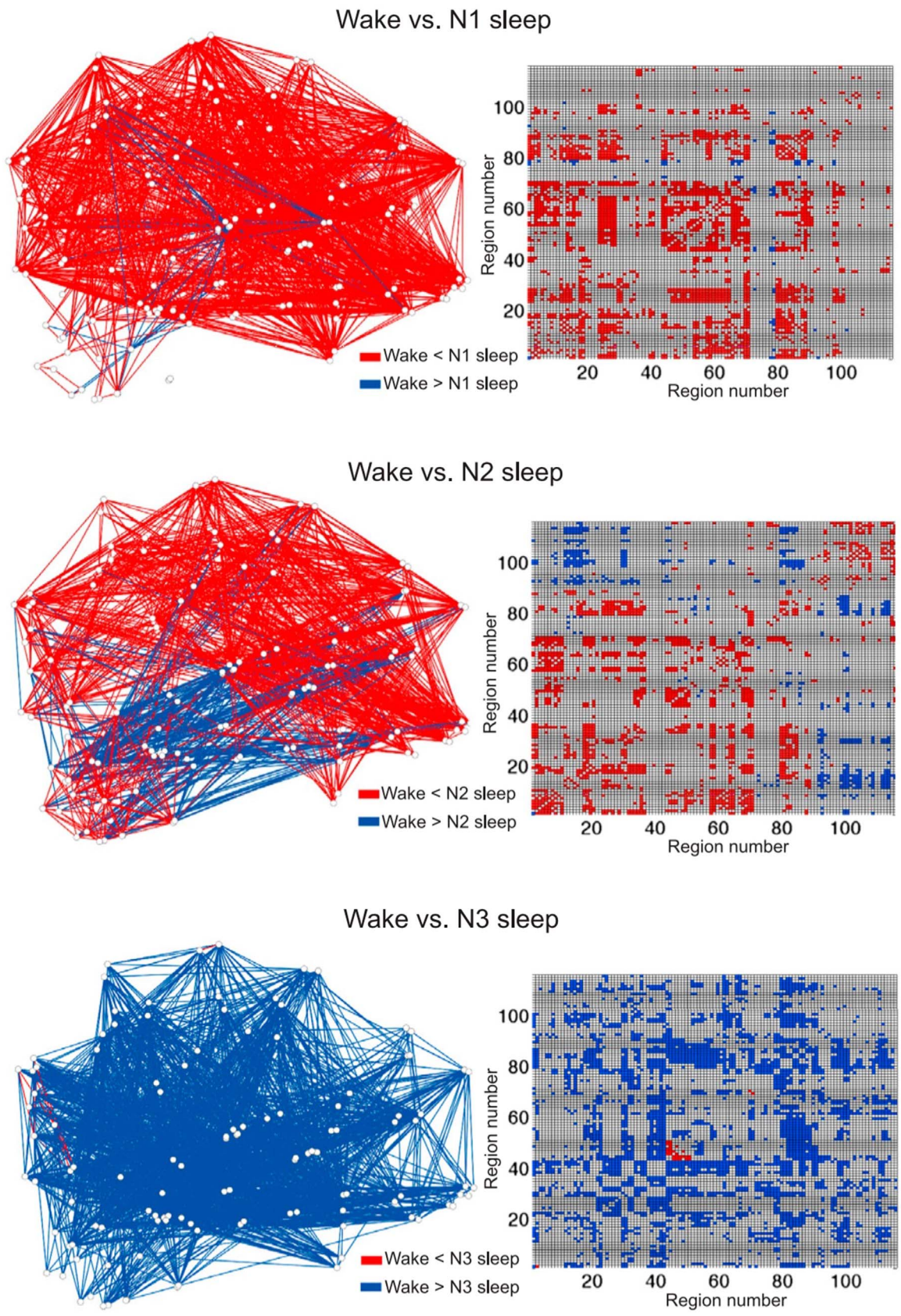


Fig. 1. Whole brain functional connectivity changes associated with NREM sleep. For each comparison of wakefulness vs. N1, N2 and N3 sleep, significantly different ($p < 0.05$, one-tailed Student's *t*-test, Bonferroni corrected) functional connections are shown as a graph (or network; with node coordinates located at the center of mass of each AAL region) and in matrix form (with rows and columns corresponding to different AAL regions and each intersection representing a functional connection). Figure adapted with permission from Tagliazucchi and Laufs (2014).

possible future directions to take this understanding further. As a complement to the study of healthy human sleep, we also review work on pathological and abnormal sleep patterns, which might yield important insights on the large-scale neural correlates of sleep, arousal and consciousness.

Exploratory analyses of functional connectivity changes during human sleep and computational modeling studies

Whole-brain neuroimaging using fMRI provides an enormous amount of spatio-temporal information on brain activity which, for the study of brain states such as sleep, might represent an "embarrassment of riches". Fully exploratory analyses have been developed to reveal widespread sleep-related changes in the "functional connectome", i.e. the set of all functional connections between selected brain areas. An example of the sleep-related changes in the set of functional connections between regions in the automated anatomic labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) is provided in Fig. 1 (adapted from Tagliazucchi and Laufs (2014)).

A drawback of exploratory analyses is their difficult interpretability. Most likely, a large proportion of the changes observed in Fig. 1 are related to very salient features of NREM sleep such as diminished arousal and conscious awareness, but other subtler changes could be related to functions such as memory replay and consolidation (Diekelmann and Born, 2010). The neurobiological significance of these FC differences must be investigated with carefully designed experiments, since the contrast of FC between different sleep stages and wakefulness might not provide sufficient information.

Computational simulation studies represent an important tool to complement the exploratory nature of whole-brain neuroimaging of sleep. Several studies have combined realistic neural dynamics and connectivity to simulate the effects of sleep onset on brain activity at different spatial and temporal scales. Hill and Tononi (2005) modeled the relationship between "microscopic" variables such as synaptic conductances and the emergence of slow oscillations during sleep, showing that corticocortical connections act to synchronize these oscillations. This work was extended to model the breakdown of effective connectivity during sleep, which revealed the existence of a "cortical gate" blocking the propagation of activity, consistent with a change in the excitation/inhibition balance of the cortex (Esser et al., 2009). More recent work constructed a model of whole-brain large-scale activity and connectivity during sleep and established the preservation of RSN after the onset of slow oscillations due to changes in cholinergic neuromodulation (Deco et al., 2014). Another large-scale model has revealed that deep sleep results in increased stability, and reduced effective connectivity and global coupling of brain dynamics (Jobst et al., 2017). These studies show that certain features of whole-brain activity and FC during sleep can be investigated using computational modeling, and that this modeling can contribute towards disentangling different mechanisms behind the alterations in the functional connectome observed during sleep (Fig. 1).

We will limit most of our discussion of the whole-brain changes presented in Fig. 1 to those associated with diminished arousal and conscious awareness. A discussion of these features of sleep can be assisted by hypotheses stemming from invasive electrophysiological experiments, the assessment of behavior across the sleep cycle, and the investigation of subjective reports upon awakening. While different methods can be employed to investigate the transition between wakefulness and sleep, such as evaluating continuous tasks or measuring reactivity to stimuli (see Goupil and Bekinschtein (2012) for an extensive review), the standard method to detect sleep stages (polysomnography) is designed as an objective evaluation of arousal based on the passive monitoring of (neuro-) physiological signals (this method is based on EEG, electrooculography and electromyography, and is briefly described in the second paragraph of the Introduction section). Thus, the majority of the results we review are derived from passive "resting state" paradigms acquired during NREM and REM sleep.

Preserved large-scale functional connectivity patterns during NREM sleep

One of the most robust findings concerning resting state fMRI fluctuations is their spatial organization into large-scale networks contained within the limits of neural systems with relatively well-understood functions. These networks, commonly termed resting state networks (RSN), can be revealed using multivariate methods such as independent component analysis (ICA) or by computing the voxel-wise FC of the cortex with activity extracted from seed regions (seed-based correlation) (Greicius et al., 2003). Both methods yield similar RSN, including visual, auditory, sensorimotor, attention, executive control, and default mode networks (DMN). This last network comprises the bilateral medial and lateral parietal cortices, the bilateral medial prefrontal cortex, and the bilateral medial and lateral temporal cortices, and increases its metabolism during baseline vs. task-performance (Raichle, 2015). It has been associated with consciousness of the environment (Fernández-Espejo et al., 2012) and of the self (Spreng and Grady, 2010; Qin and Northoff, 2011).

At a coarse spatial scale, the study of RSN provides a hypothesis-driven approach to overcome the limitations of exploratory analyses. Since deep NREM sleep is characterized by drastically diminished capacity for cognition, attention and conscious awareness, it could be speculated that higher-order cortical RSN will progressively disappear in the descent from early (N1) to deep (N3) sleep. However, the spatial extent of RSN associated with these cortical functions is preserved during early sleep (Fig. 2A) (Larson-Prior et al., 2009). Later work revealed that even during deep NREM sleep (N3) it is possible to identify all the canonical RSN that are observed during conscious wakefulness (Fig. 2B) (Tagliazucchi et al., 2013b). While these results are seemingly at odds with those shown in Fig. 1, we note that widespread changes in FC during sleep are compatible with the identification of RSN. This is because such changes might represent a global FC modulation, or they might not suffice to dissociate the spatial structure of the independent components detected using ICA. It must also be emphasized that the cited studies (Larson-Prior et al., 2009; Tagliazucchi et al., 2013b) concern the spatial extent of the RSN detected using ICA, but do not contain statistical comparisons of the independent component z-values between wakefulness and deep sleep.

The presence of these networks in resting state data recorded during deep sleep can be taken as evidence against RSN being merely a consequence of ongoing spontaneous cognition. However, this interpretation of the preservation of RSN must be confronted with empirical evidence concerning the frequency of dream reports during NREM sleep. While it is clear that conscious content is less prevalent during NREM sleep relative to REM sleep and wakefulness, and that it is associated with less rich subjective experiences, increasing evidence suggests that it is not completely abolished even during deep sleep. Siclari and colleagues (Siclari et al., 2013) established that recall of dreams with conscious content was present in 77% of awakenings from REM sleep and in 34% of awakenings from NREM sleep, and that the likelihood of reportable conscious content after awakening followed a decreasing trend with sleep depth (96% during wakefulness, 77% during N1, 42% during N2 and 23% during N3 sleep). These numbers are consistent with previous reports also showing that dream reports are shorter and less vivid after awakenings from NREM sleep (Suzuki et al., 2004). These studies suggest that the level and frequency of conscious mentation are diminished during NREM sleep, but that conscious mentation is not completely abolished, a fact that could account for the preservation of RSN spatial patterns. On the other hand, it must be noted that RSN patterns are also preserved in other brain states during which conscious content is presumably abolished, such as under anesthesia and in patients with disorders of conscious-

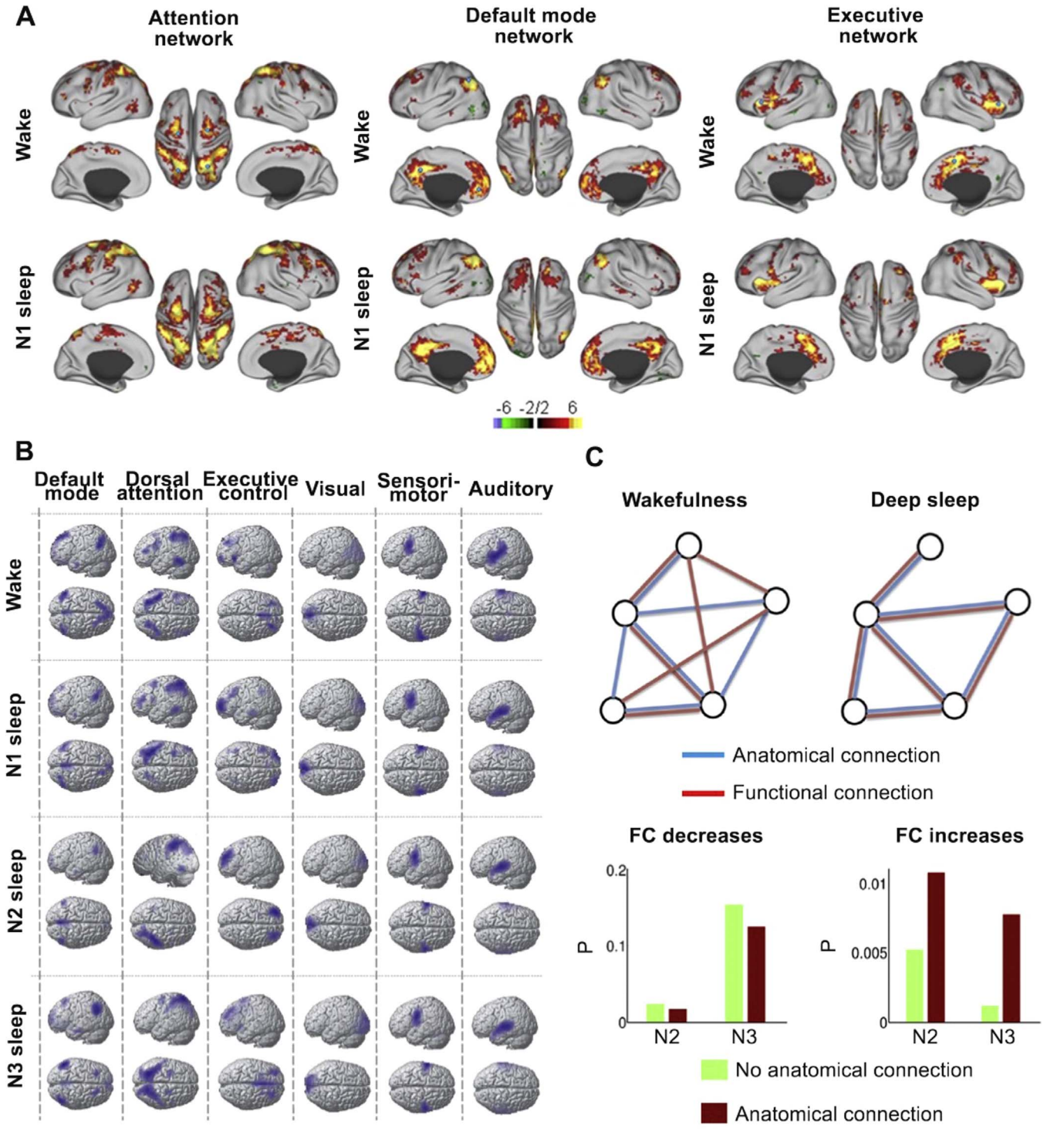
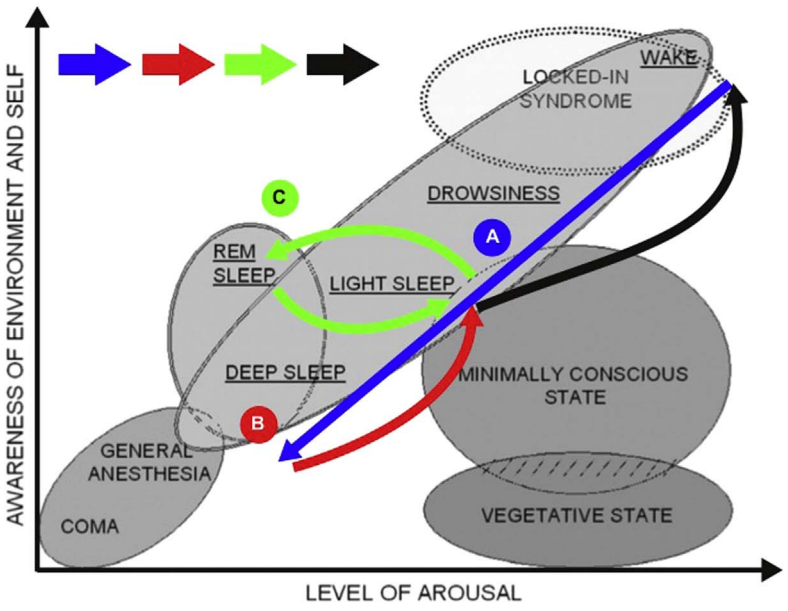


Fig. 2. Preservation of RSN topographies during NREM sleep. A) Attention, default mode, and executive RSN revealed from fMRI data acquired during N1 sleep using ICA (figure adapted from Larsion-Prior et al. (2009)). B) Default mode, dorsal attention, executive control, visual, sensorimotor and auditory RSN revealed from fMRI data acquired during N1, N2 and N3 sleep using ICA (figure adapted from Tagliazucchi et al. (2013b)) C) Upper panel: schematic showing how increased similarity between anatomical and functional connectivity networks can be expected on the basis of anatomical networks imposing an ultimate limit on the possible disintegration of RSN. Bottom panel: the probability of observing FC decreases during N2 and N3 sleep is higher between regions lacking strong anatomical connections; the opposite is observed for FC increases during sleep N2 and N3 sleep (both panels adapted from Tagliazucchi et al. (2016a). All figures reproduced with permission from the publisher.

ness (Boly et al., 2008). One important experimental condition to test the relationship between conscious mentation during sleep and RSN stability is sleep state misperception, in which patients report persistent wakefulness-like levels of consciousness during physiological NREM sleep (Bonnet and Arand, 1997b) (see the section "Functional connectivity changes associated with sleep disorders" for further discussion).

Increasing evidence suggests that FC is constrained by the underlying anatomical connectivity of the brain, i.e. axon bundles projecting over > 1 mm distances (Hagmann et al., 2008; Honey et al., 2009). In particular, the analysis of anatomical connectivity by itself allows the identification of RSN such as the DMN (van Den Heuvel et al., 2009;


AWARENESS OF ENVIRONMENT AND SELF
LEVEL OF AROUSAL
WAKE
LOCKED-IN SYNDROME
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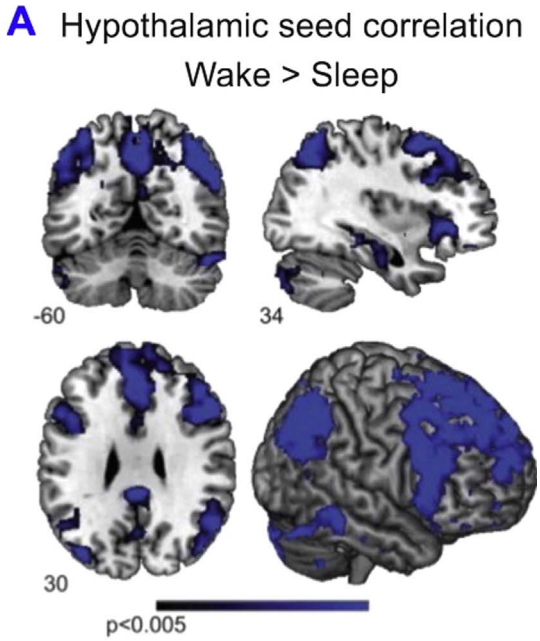
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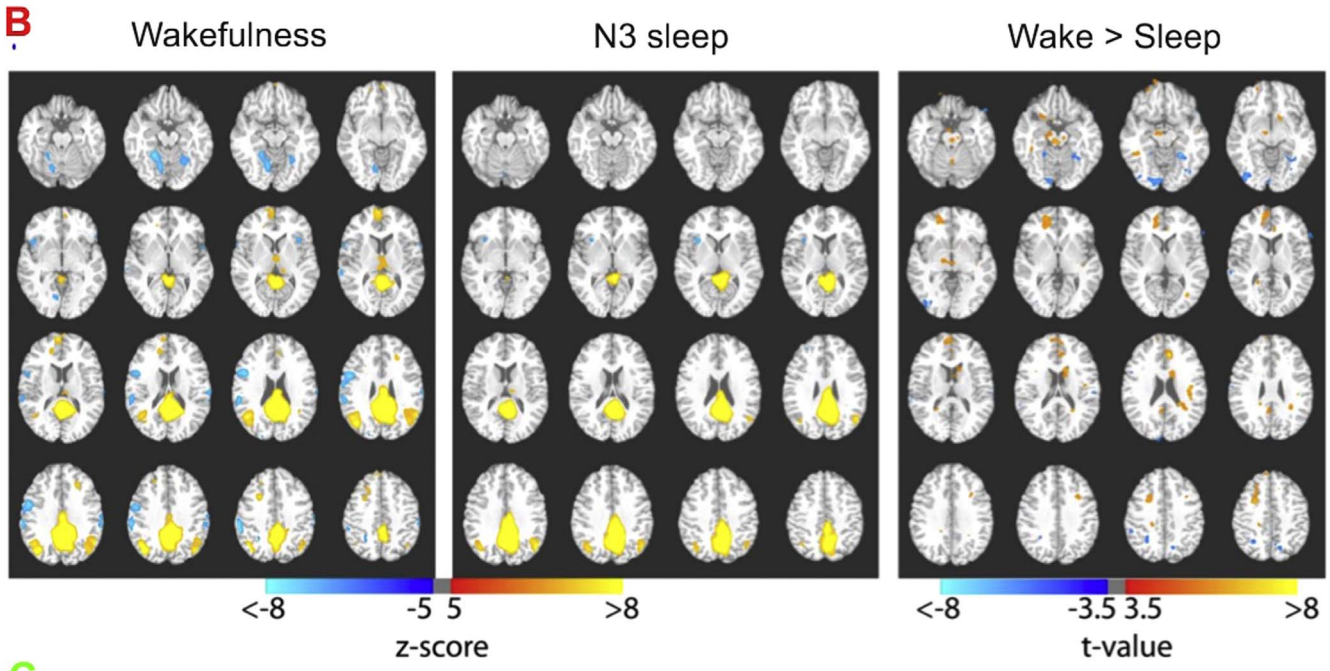
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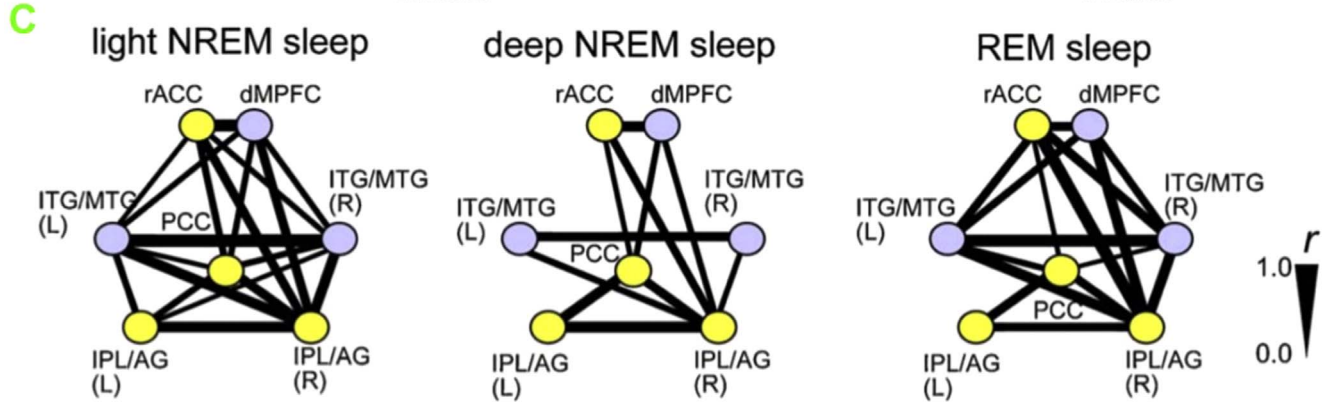
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Fig. 3. Changes in large-scale FC during sleep as a function of arousal and awareness. Left-upper panel: a diagram of brain states as a function of their level of arousal and awareness; the sequence of colored arrows (blue, red, green) indicates a typical human sleep cycle (the black arrow represents an awakening) (figure adapted from Laureys et al. (2007)). A) Reduced hypothalamic FC during early sleep as a marker of diminished arousal (Tagliazucchi and Laufs, 2014). B) FC of the posterior DMN during wakefulness, sleep, and the contrast between both conditions, revealing the uncoupling of the posterior and anterior DMN as a possible correlate of loss of conscious awareness (figure adapted from Horovitz et al. (2009)). C) FC between DMN nodes during light and deep NREM sleep, and during REM sleep. REM sleep reestablishes DMN FC, a possible correlate of conscious content during this sleep stage (figure adapted from Koike et al. (2011)). All figures reproduced with permission from the publisher.

Greicius et al., 2009). The spatial profile of RSN can be derived from the whole-brain network of anatomical connections combined with a computational model based on simple assumptions (Haimovici et al., 2013). While the sleep cycle implies considerable functional changes, anatomical connectivity is presumed to remain relatively intact throughout all its stages, thus enforcing the presence of RSN even during deep NREM sleep. Tagliazucchi and colleagues speculated that deep sleep could "prune" functional connections between brain areas not directly connected via anatomical tracts, and could even strengthen those associated with already strong anatomical connectivity (Tagliazucchi et al., 2016a). The net effect of this process would be increasing the similarity between whole-brain anatomical and functional connectivity networks during deep sleep relative to wakefulness (see Fig. 2C, upper panel). This prediction was confirmed by Tagliazucchi and colleagues, and also by independent groups using propofol anesthesia to induce unconsciousness in non-human primates (Barttfeld et al., 2015) and rodents (Ma et al., 2017). The study of structural and functional connectivity coupling during early vs. late sleep (Picchioni et al., 2008) could be useful for further evaluation of the "pruning" hypothesis. The bottom panel of Fig. 2C illustrates that diminished FC during N2 and N3 sleep tends to occur between regions lacking strong anatomical connections, while the opposite is observed for pairs of regions whose FC increases during sleep.

An alternative explanation for the preservation of RSN is the possibility that resting state FC at the scale of RSN does not directly reflect diminished consciousness, and that subtler or more localized changes are associated with this and other aspects of sleep. In the following sections we review articles investigating alterations in FC during deep sleep within the context of the levels of arousal and conscious awareness.

The human sleep cycle as a function of arousal and awareness

Human sleep can be characterized as a state defined by inhibited sensory processing, reduced muscle activity, marked changes in EEG rhythms, diminished conscious awareness (for NREM sleep), or vivid dreams and rapid eye movements (for REM sleep) (Carskadon and Dement, 2005). A well-equipped sleep laboratory can test most of these conditions by means of polysomnography, a combined assessment of EEG, electromyography to record muscle activity and electrooculography to record eye movements (Iber et al., 2007). In other words, it is possible to perform an objective assessment of the level of arousal. On the other hand, the private and subjective nature of conscious awareness precludes such an objective evaluation (Chalmers, 1995). It is generally agreed upon that the assessment of consciousness and its contents requires explicit report, either verbal or of other kind. By definition, however, sleeping subjects are unable to interact with their surroundings and thus to provide a real-time report of their conscious contents. As we discussed in a previous section and will further elaborate below, this situation led to the underestimation of the level of conscious awareness during sleep, especially during deep NREM sleep (Foulkes, 1962; Suzuki et al., 2004; Siclari et al., 2017; Windt et al., 2016).

Taking a pragmatic stance, some could argue that the distinction between loss of arousal and diminished conscious awareness is irrelevant, since both change in parallel during the human sleep cycle and perhaps more generally during other brain states as well. In other words, it could be the case that arousal and consciousness are never dissociated and therefore that the objective quantification of arousal is a reliable proxy for the level of conscious awareness. It is now clear, however, that this is not the case, as shown by the following examples of dissociated arousal and consciousness. First, as mentioned in the previous paragraph, conscious awareness can occur even during slow wave or N3 sleep, a state characterized by drastically diminished arousal (Foulkes, 1962; Suzuki et al., 2004; Siclari et al., 2013; Windt et al., 2016; Siclari et al., 2017). Conscious content during N3 sleep is typically less vivid than content during other sleep stages; an example report after awakening is provided by Siclari and colleagues: "I was seeing geometric shapes that were moving very fast." (see Siclari et al. (2017) for more examples). Second, REM sleep is a physiological brain state of reduced arousal capable of producing vivid conscious content (dreams). Third, certain pathological states collectively referred to as "disorders of consciousness" present dissociation between arousal and conscious awareness; more specifically, patients can exhibit normal levels of arousal without seemingly experiencing any conscious content (Laureys et al., 2007).

The relationship between the level of arousal and conscious awareness has been summarized by Laureys and colleagues in a two dimensional space, which is presented in the upper-left panel of Fig. 3 (Laureys et al., 2007). Within this two dimensional space, colored arrows indicate the evolution of a typical human sleep cycle. Starting from wakefulness, a gradual reduction in awareness and arousal (i.e. a displacement along the diagonal of the diagram) occurs, until subjects reach deep sleep (blue arrow). Then, levels of arousal and conscious awareness are gradually restored (red arrow) until subjects either wake up (black arrow), or enter REM sleep (green arrow), an "off-diagonal" state of diminished arousal during which conscious content is frequently manifest. After a period of REM sleep, the brain switches back to early NREM sleep (green arrow) and the cycle beings again (Carskadon and Dement, 2005). In this diagram, conscious awareness is represented in a single variable. However, a distinction is often made between "primary" and "secondary" consciousness, the first being related to perception and emotion, and the second to the development of language and the reflective self. The activation, input-output gating, and modulation (AIM) theory put forward by Hobson addresses the relationship between consciousness during sleep and wakefulness in a more sophisticated way, proposing that dreams during REM sleep represent a form of "proto-consciousness" that is required to simulate a model of the world which is of functional use during waking consciousness (Hobson, 2009). Concerning the distinction between conscious mentation during REM and NREM sleep, the differential abundant quantity and vivid quality of mental content during REM sleep versus a more sparse quantity and more thought-like quality of mental content during NREM sleep may be altered in disordered sleep. Recent findings suggest that the characteristic restless REM sleep of people suffering from insomnia is associated with thought-like rather than dream-like mental content (Wassing et al., 2016), which was hypothesized to involve phasic activity of the locus coeruleus during sleep (Vanderheyden et al., 2014), flooding the cortex with norepinephrine and bringing it into a more wake-like configuration.

The trajectory observed in Fig. 3 indicates that NREM and REM sleep are potentially useful experimental models to investigate the neural correlates of arousal and conscious awareness. However, it is also clear that for most of this trajectory the changes in both are likely correlated, so that an additional effort must be invested to disentangle them. REM sleep, as all other "off-diagonal" brain states, is particularly interesting for the disambiguation of arousal and awareness. In the following we discuss FC analyses of fMRI data acquired along the trajectory outlined in Fig. 3, and then focus on how the arousal and awareness dimensions could be disentangled. Since both dimensions

are inter-related by the very nature of the human sleep cycle, it is necessary to discuss FC changes within the larger context of previously known neurophysiological and behavioral observations, and support the search for neural correlates of conscious awareness using models that provide a theoretical account of how consciousness could emerge in the brain.

Functional connectivity changes along the arousal dimension

The physiological state of arousal is caused by the bottom-up regulation of cortical activation from the reticular activation system (RAS), consisting of several nuclei linking the brainstem to the cerebral cortex (Magoun, 1952). Several studies have reported loss of thalamic and hypothalamic FC with widespread cortical regions during early NREM sleep (Spoormaker et al., 2010; Picchioni et al., 2014; Tagliazucchi and Laufs, 2014; Hale et al., 2016); see Fig. 3B for an example extracted from Tagliazucchi and Laufs (2014). A single study reported increased hypothalamic FC with the cortex during NREM sleep (Kaufmann et al., 2006), but this contradictory finding could have resulted from confounding physiological noise (Laufs et al., 2007). We speculate that the synchronization of BOLD signals between anatomical regions containing key RAS components and the cerebral cortex might represent fluctuations in the firing rate of RAS neurons that translate into cortical excitability changes, and that this synchronization is interrupted when thalamic and hypothalamic relays block input from the upper brainstem after the onset of sleep.

Indirect and correlational observations support the idea that cortico-thalamic and cortico-hypothalamic FC decrease with the onset of sleep. A number of studies have established that cerebral blood flow and metabolism in the brainstem, thalamus, hypothalamus and regions in the RAS are in inverse relationship to behavioral and electrophysiological markers of cortical arousal (e.g. the spectral content of scalp EEG) (for a review see Paus (2000)). Results from studies of pathological conditions of hyperarousal leading to sleep disorders, such as primary insomnia disorder, are consistent with the role of these regions in regulating cortical arousal (Nofzinger et al., 2004) (see the section “Functional connectivity changes associated with sleep disorders” for further discussion). However, no fMRI studies have directly related neural firing in the aforementioned subcortical structures to changes in the BOLD signal in healthy humans, since such experiments would raise insurmountable ethical obstacles. On the other hand, animal studies show that neural firing at cortical and subcortical excitatory neurons can lead to BOLD signal increases, both locally and at distant anatomical locations to which the excited neurons project (Lee et al., 2010). Importantly, this evidence does not come from correlational studies but from causal manipulation using optogenetics to target neurons in the motor cortex and the thalamus. A more direct link exists between the activation of certain components of the RAS and relatively fast cortical oscillations associated with arousal. The classical work of Moruzzi and Magoun showed that stimulation of the reticular formation of the brainstem abolishes high-voltage low-frequency oscillations and induces low-voltage high-frequency activity (Moruzzi and Magoun, 1949). This has been shown for stimulation of the medial bulbar reticular formation, pontile and midbrain tegmentum and dorsal hypothalamus and subthalamus. Since this observation is based on direct stimulation of these structures, it also goes beyond a mere correlational association between cortical oscillations and RAS activation. Also, it has been shown that the BOLD signal at different brain structures correlates with band-limited EEG oscillations (Laufs et al., 2003; Mantini et al., 2007), and that a strong positive association exists between global fMRI BOLD fluctuations and high-frequency LFP that might reflect neurochemical input from subcortical structures regulating arousal (Schölvinck et al., 2010). It is therefore possible that spontaneous fluctuations in arousal lead to correlated changes in BOLD fMRI, and that sleep onset is associated with blocking of thalamic and hypothalamic relays, disrupting BOLD fMRI connectivity.

An invasive electrophysiological study in humans has shown that thalamic deactivation precedes cortical deactivation by minutes during sleep onset (Magnin et al., 2010). Delayed cortical vs. thalamic deactivation while falling asleep could contribute towards reduced thalamocortical FC. It has been proposed by Magnin and colleagues (Magnin et al., 2010) that a still active cortex disengaged from the environment due to thalamic deactivation could explain hypnagogic hallucinations (Ribstein, 1976). This proposal is likely an over-simplification, however, since it does not suffice to understand the differences between the quality of the hypnagogic experience and that of other conscious states (see Waters et al. (2016) for an overview of these differences).

While loss of thalamic and hypothalamic FC during N1 sleep is a robust finding, the same is generally not observed for deeper sleep stages (Spoormaker et al., 2010; Tagliazucchi and Laufs, 2014). It is likely that thalamocortical FC is reestablished after N1 sleep due to the onset of sleep spindles, electrophysiological events of thalamic origin (Schabus et al., 2007). This observation suggests that thalamocortical connectivity after N1 sleep reflects processes different to those reflected under wakefulness, e.g. memory consolidation-related processes. This hypothesis could be tested by means of a psychophysiological interaction analysis, similar to that performed by Andrade et al. (2011) linking sleep spindles to hippocampal FC.

Since the thalamus acts as a relay between peripheral sensory systems and the cortex (McCormick and Bal, 1994), loss of thalamocortical FC could also underlie the increased stimulation threshold for arousal during sleep. After thalamocortical FC is reestablished during N2 sleep, K-complexes are known to inhibit arousal by suppressing cortical activation multimodally in primary sensory areas after sensory stimulation (Jahnke et al., 2012). An effective connectivity analysis based on dynamic causal modeling established the dual nature of K-complexes: they elicit a transient episode of arousal that is afterwards limited by a disengagement of the saliency network, notably the anterior insula (Jahnke et al., 2012). In contrast, it is known that responses in the core auditory cortex are preserved regardless of whether sleep spindles are present at the time of the stimulation, suggesting that sensory disconnection in sleep is not directly mediated by spindles (Sela et al., 2016).

The investigation of thalamocortical FC during sleep could also contribute to the understanding of brain disorders related to the abnormal functioning of thalamic circuits. For instance, it has been hypothesized by Beenhakker and Huguenard that episodes such as absence seizures with generalized spike-and-wave discharges could arise due to the abnormal hypersynchronization of thalamic circuits involved in the generation of sleep spindles during N2 sleep (Beenhakker and Huguenard, 2009). A formal comparison between (inter-) ictal thalamocortical FC in patients with absence seizures and thalamocortical FC during the NREM sleep cycle could contribute towards the evaluation of the hypothesis put forward by Beenhakker and Huguenard. The relatively short nature of absence seizures might require the use of dynamic FC analyses to investigate transient changes in thalamocortical FC (Liao et al., 2014). As discussed extensively by Bagshaw and colleagues (Bagshaw et al., 2014), the fMRI correlates of generalized spike-and-wave discharges (DMN deactivation and thalamic activation) differ from those of sleep spindles (which do not involve DMN deactivation). However, thalamic involvement has been shown in EEG-fMRI studies of both spindles and K-complexes (Schabus et al., 2007; Jahnke et al., 2012). The mismatch between the cortical correlates of generalized spike-and-wave discharges and spindles could reflect different modes of neuronal firing at thalamic circuits (Bagshaw et al., 2014), possibly underlying the pathological properties of spike-and-wave discharges. Clearly, more work is required to probe the relationship between sleep and ictal events in epilepsy.

All studies mentioned in the preceding paragraphs use EEG measures as markers of arousal, but do not establish a direct link with behavioral measures. Two recent articles have investigated brain

activity and FC related to spontaneous eye-closures linked to brief episodes of diminished arousal. Chang et al. (2016) found that thalamic activation correlated with a behavioral arousal index based on eyelid closure, while cortical regions showed the opposite correlation. This result is consistent with loss of thalamocortical FC during sleep onset. Wang et al. (2016a) employed a sliding window analysis to reveal that spontaneous eyelid closure correlates with loss of FC within the DMN and the dorsal attention network, as well as with reduced anticorrelation between these two RSN. This finding is compatible with reports of increased cortico-cortical FC during early sleep (Tagliazucchi and Laufs, 2014). Also in line with previously mentioned studies, Wang and colleagues showed decoupling of the thalamus and the dorsal attention network during spontaneous eyelid closures.

Functional connectivity changes along the awareness dimension

Horovitz and colleagues first demonstrated the functional decoupling of the DMN during deep NREM sleep (see Fig. 3C) (Horovitz et al., 2009), a finding reproduced afterwards in a number of independent reports (Sämann et al., 2011; Larson-Prior et al., 2011; Spoormaker et al., 2012; Wu et al., 2012). The DMN presents substantial overlap with frontal and parietal areas whose metabolism is known to be reduced during states of reduced consciousness such as NREM sleep (Braun et al., 1997), epilepsy (Blumenfeld, 2005), anesthesia (MacDonald et al., 2015) and in disorders of consciousness (Laureys, 2005). Furthermore, transient episodes of unresponsiveness observed in epileptic patients (known as absence seizures) correlate with BOLD signal decreases in DMN regions (Blumenfeld et al., 2005; Berman et al., 2010). Cognitive neuroimaging experiments reveal that consciously perceived stimuli elicit fronto-parietal activation (including areas belonging to DMN, central executive and attentional networks), whereas subliminal stimuli result in weaker activations that are circumscribed to primary sensory areas (Sergent and Dehaene, 2004; Sergent et al., 2005). These studies suggest that the uncoupling of posterior and anterior DMN nodes during deep sleep could be indicative of loss of conscious awareness. Importantly, FC within the DMN is re-established after REM sleep onset, a result consistent with the vivid conscious experiences typical of REM sleep (see Fig. 3C) (Koike et al., 2011; Chow et al., 2013).

Studies of FC performed under anesthesia (Boveroux et al., 2010) and disorders of consciousness (Vanhaudenhuyse et al., 2010) also uncovered loss of within-DMN connectivity, adding further support to DMN integrity as a neural correlate of the conscious state. The global workspace theory, an influential account of conscious information access in the brain, posits that incoming sensory stimuli compete in a winner-takes-all fashion for the all-or-none "ignition" of a widespread set of cortical regions dubbed the "global workspace" (for a review of this theory see Baars (1997), Dehaene and Naccache (2001)). Conscious access is equated with availability to this global workspace, i.e. with the percolation of sensory information through a network of regions that "broadcast" this information for further cognitive processing. The experimental results presented here and in the preceding paragraph add support to the possible role of networks contained within the fronto-parietal cortex as constituents of the global workspace, including the prefrontal, anterior and posterior cingulate and parietal association cortices (Dehaene et al., 2006).

A key prediction of the global workspace theory is that conscious perception leads to reverberant and self-sustained activity; in other words, once a stimulus is consciously perceived, the elicited activity must present non-trivial temporal correlations in global workspace regions (Dehaene and Changeux, 2003). If deep sleep diminishes the capacity for conscious information access, as suggested by our everyday experience, then loss of temporal correlations of brain activity fluctuations is expected in DMN, executive and attentional networks. The autocorrelation of a signal can be understood as the FC of the signal with itself displaced a number of time steps into the past; long-range autocorrelation implies that such FC decays very slowly, persisting for minutes or even hours. Tagliazucchi and colleagues showed that, while DMN and attentional networks present long-range temporal correlations during wakefulness, these are drastically diminished or lost during deep NREM sleep (N3 sleep) (Tagliazucchi et al., 2013b). This result has been replicated for humans and non-human primates under general anesthesia (Barttfeld et al., 2015; Tagliazucchi et al., 2016b).

The global workspace theory does not directly address the phenomenology of consciousness, i.e. the familiar features that characterize how it "feels like" to be conscious. A theory of consciousness based on phenomenology has been put forward by Tononi (2004). The earliest versions of this theory are based on two facts rooted in the phenomenology of consciousness. First, consciousness is highly differentiated, meaning that the number of different possible conscious experiences is extremely large. Second, consciousness is highly integrated, since at every moment in time we experience ourselves and the world as a unitary, indecomposable scene. It follows from these two observations that consciousness must be associated with a balance between integration and segregation. A highly integrated system will behave as a whole and thus will not exhibit a sufficiently large repertoire of states, leading to reduced differentiation. On the other hand, a system in which each constituent behaves independently of the others will present a maximal number of potential states, leading to very high differentiation, but will lack integration between its constituents.

Whole-brain FC can be represented as network composed of nodes, i.e. regions from which the BOLD time series are extracted, and links between them, representing sufficiently high FC between the BOLD time series of a pair of regions (an overview of network methods in neuroscience can be found in Bullmore and Sporns (2009) and van Den Heuvel and Pol (2010)). This mathematical representation abstracts the relationship between brain regions, in the same way other networks abstract social relationship (e.g. Facebook "friendship networks") or scientific collaboration (co-authorship network). The presence of integration and segregation can be evaluated using algorithms that seek to partition the network into modules, defined as sub-sets of nodes presenting dense connections among them (i.e. modules are highly integrated) but relatively weak connections with other modules (i.e. different modules are segregated) (Sporns, 2013). An example showing three modules circled in red, blue and orange is presented in Fig. 4A. It is clear that some networks are more modular than others; for instance, if we keep adding links between the modules of Fig. 4A, the network will start to lose segregation until all modules coalesce into one. The network modularity (Q) represents a quantitative measure of how well a network can be split into modules (Newman and Girvan, 2004). An illustration showing two networks with the same number of nodes and the same modules, but different between-module connectivity, is shown in Fig. 4B. Clearly, as the number of between-module links is increased, Q is reduced.

The detection of modules and their associated Q in whole-brain FC networks during deep NREM sleep can be used to evaluate the predictions of the theory put forward by Tononi (2004). This investigation was pursued by Tagliazucchi and colleagues, who applied an algorithm to decompose whole brain networks derived from wake, N1, N2 and N3 sleep fMRI data into modules associated with coarse anatomical brain regions (Fig. 4C). From this decomposition into modules it was possible to compute Q as a function of the NREM sleep stage and to show that wakefulness and early sleep presented very similar values. However, increased Q relative to wakefulness was observed for deeper (N2 and N3) NREM sleep stages. This can be interpreted as FC networks becoming more segregated during deep sleep. The simultaneous recording of EEG and the computation of dynamic FC using sliding windows allowed the authors to show an inverse correlation between FC and delta (< 4 Hz) oscillations during N3 sleep, and that most of the affected functional connections represented between-module links in the network (see Fig. 4D).

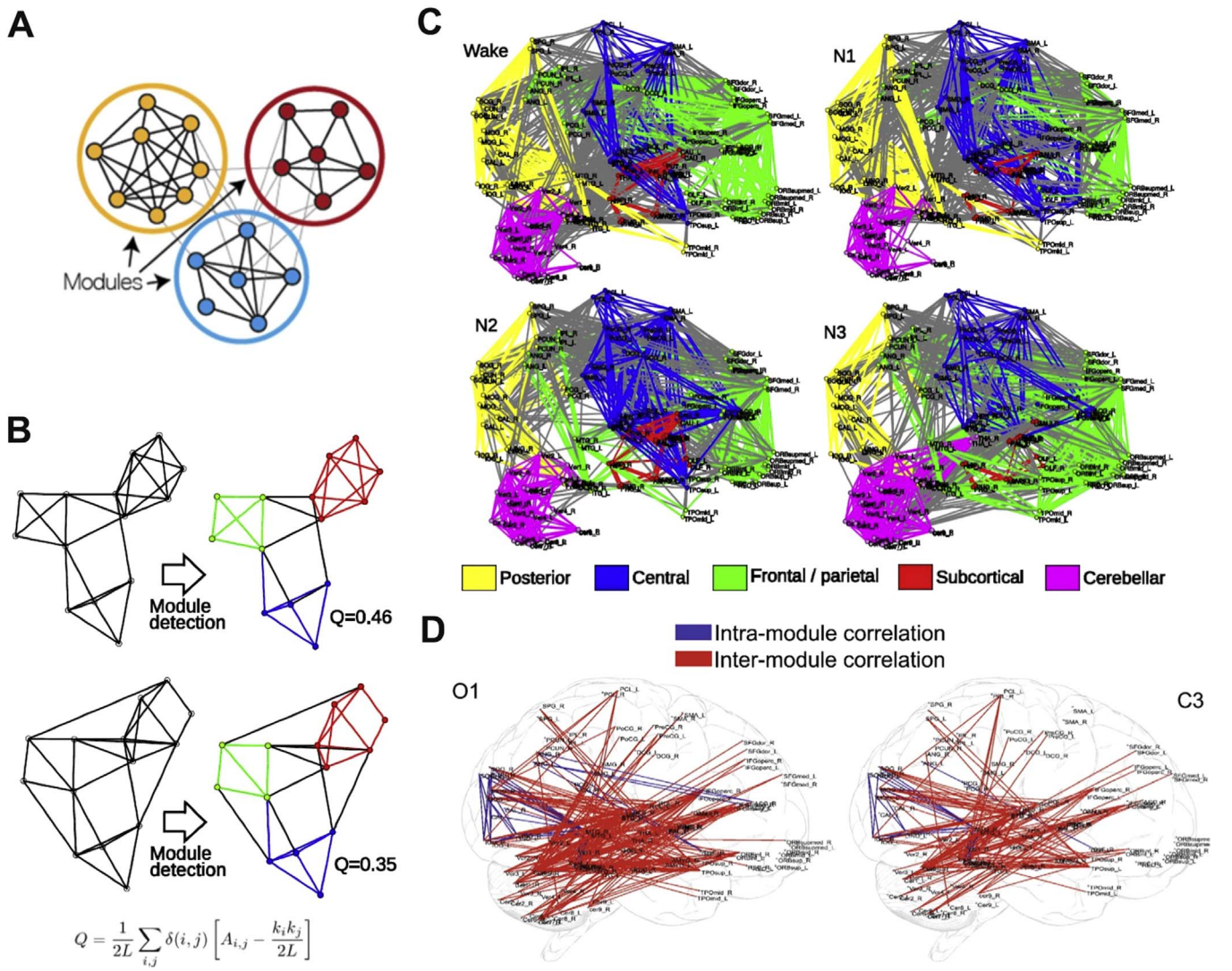

Fig. 4. FC network integration/segregation as a signature of consciousness during deep sleep. A) Illustration of the concept of modules in a binary network (figure adapted from Deco et al. (2015)). B) Schematic showing how the modularity (Q) changes depending on the level of within- and between-module connectivity (figure adapted from Tagliazucchi et al. (2013a)). C) Result of applying a modularity maximization algorithm to whole-brain FC networks computed from fMRI data acquired during wake, N1, N2 and N3 sleep (figure adapted from Tagliazucchi et al. (2013a)). D) Functional connections showing an inverse relationship with delta (< 4 Hz) power (measured in two different scalp electrodes, O1 and C3) during N3 sleep. The functional connections that lose strength during periods of high delta power are predominantly between-module connections (shown in red) (figure adapted from Tagliazucchi et al. (2013b)). All figures reproduced with permission from the publisher.

Increased functional segregation during deep sleep has been independently reported by other research groups (Boly et al., 2012; Spoormaker et al., 2012), and similar alterations in segregation/integration have been shown for other unconscious brain states, such as under propofol anesthesia (Monti et al., 2013).

An apparent paradox emerges from the synchronized nature of slow waves during N3 sleep, and the loss of functional integration measured with fMRI during the same sleep stage. It is important to remember, however, that fMRI only indirectly measures neural activity and that in this context it is important to discuss how the different frequency bands that dominate wakefulness and NREM sleep are reflected in the BOLD signal. Evidence from multimodal studies suggests that fMRI is particularly sensitive to relatively fast (gamma range) oscillations (He et al., 2008; Schölvinck et al., 2010). In terms of RSN, BOLD fluctuations in frontal nodes of the DMN (bilateral medial prefrontal cortex) correlate most strongly with gamma oscillations (Mantini et al., 2007). It has been reported that dynamic changes in FC correlate negatively with alpha and beta power fluctuations, and positively with gamma power fluctuations (Tagliazucchi et al., 2012b). Taken together, these results suggest that loss of fMRI FC measured during deep NREM sleep could indicate loss of power and coherence in the gamma range (Schartner et al., 2016).

In principle, deep NREM sleep appears to be a suitable experimental model to investigate the neural correlates of consciousness. However, two important limitations are manifest. First, as shown in Fig. 3, the descent into sleep is characterized by simultaneous loss of arousal and diminished conscious awareness. It is therefore difficult to disambiguate the changes associated with each, although this limitation can be mitigated by performing hypothesis-driven analyses based on theoretical predictions. Second, and most importantly, consciousness is not completely abolished even during deep sleep. For instance, Tagliazucchi et al. (2013c) showed that experiences of visual imagery and inner speech (both reported after awakening) correlated with BOLD signal amplitude in primary visual and Broca's area, respectively, during N2 sleep. A much more exhaustive experiment based on the paradigm of serial awakening revealed that subjects report the presence of conscious content prior to awakening in approximately 70% of the cases, showing that a third of what we usually consider a state of unconsciousness presents, in fact, reportable conscious content (Siclari et al., 2013; Siclari et al., 2017).

The presence of conscious content during deep NREM sleep might be perceived as a limitation in terms of finding the neural correlates of consciousness, but in fact it should be considered as an opportunity. The use of the serial awakening paradigm allows to contrast brain activity associated with conscious content vs. brain activity measured during unconsciousness, both recorded within the same brain state. This would be impossible, for instance, during wakefulness, since subjects would report the presence of conscious content in all trials. Siclari and colleagues employed this experimental technique to show that the presence of conscious content during deep sleep is associated with increased activity at a posterior "hotspot" that is only a subcomponent of the DMN (Siclari et al., 2017). Whether lack of report upon awakening reflects lack of prior conscious content or the inability to recall such content remains an open question. This and other recent investigations suggest that brain activity in the anterior part of the fronto-parietal network might be a neural correlate of the reporting of the conscious experience, but not of such experience itself (Tsuchiya et al., 2015). Future work using fMRI must employ the serial awakening paradigm during NREM sleep to investigate FC and integration/segregation changes between epochs of sleep associated with and without reports of consciousness.

Given that other pathological and physiological brain states result in diminished conscious awareness, e.g. anesthesia (Alkire et al., 2008), epilepsy (Blumenfeld, 2012), disorders of consciousness (Owen, 2008), an interesting question is whether the neural correlates of deep sleep (i.e. the set of changes in fMRI activity and FC measured during N3 sleep relative to wakefulness) are predictive of the changes observed in other unconscious brain states. In other words: does the pattern of measured FC changes during unconsciousness depend on the mechanisms used for its induction? A formal analysis of this problem could isolate the "core features" common to many unconscious brain states, and hence contribute towards identifying the consciousness-supporting system of the brain, independently of other confounding factors specific to the different brain states under investigation.

Assessing the prevalence of sleep in resting state fMRI

The work reviewed in the previous sections establishes major changes in BOLD fMRI connectivity and dynamics during sleep onset, NREM sleep and REM sleep. This raises the important concern that FC changes observed during sleep are possible confounds during resting state fMRI studies. Understanding the large-scale FC changes associated with sleep is therefore not only relevant in the context of the neurobiology of sleep itself, but also crucial to establish resting state fMRI as a reliable tool to investigate and diagnose brain pathology.

Most commonly, participants of resting state fMRI studies close their eyes and remain still in the bore of the MRI scanner, while attempting to avoid falling asleep. However, incursions in the earliest stages of sleep already result in marked FC changes related to diminished arousal (e.g. loss of thalamocortical connectivity) (Spoormaker et al., 2010; Picchioni et al., 2014; Hale et al., 2016), and descent into deep sleep is known to globally impair cortico-cortical FC (Horovitz et al., 2009; Spoormaker et al., 2010; Larson-Prior et al., 2011; Tagliazucchi and Laufs, 2014). Intrusion of sleep in resting state fMRI studies is especially problematic when comparing a group of healthy controls vs. a clinical population presenting an abnormal level of sleep propensity, either due to the nature of the disorder itself, e.g. insomnia, or due to the influence of medication, e.g. neuroleptic drugs. Not controlling for the level of wakefulness in resting state experiments could result in false positives wrongly reporting FC changes related to sleep as a "biomarker" for the disease, as well as in false negatives, i.e. the influence of sleep could obscure FC changes due to the disease itself.

Sleep confounds are also possible when populations of different ages are compared. An extreme example is the investigation of newborns and infants, and more generally of populations of subjects that need to be sleeping or sedated for successful resting state fMRI acquisition (Redcay et al., 2007). The full-term sleeping infant brain presents five RSN comprising sensory cortices, parietal and temporal areas, and the prefrontal cortex (Fransson et al., 2007). While these RSN show some similarities with that of young adults, some notable differences can be observed; however, a comparison with older subjects under the same experimental conditions (including same levels of sleep) is necessary to establish the developmental nature of these differences. EEG-fMRI studies of sleep in mature and elderly populations are currently lacking. Such studies should be performed due to their intrinsic neuroscientific value, but also to train classifiers to detect sleep from fMRI data specific to different age groups (see below for a discussion of fMRI-based sleep staging).

Self-assessment of sleep levels during resting state experiments is difficult. Subjects are often unable to report a state of sleep when awakened from N1 and N2 sleep (Ogilvie and Wilkinson, 1984), with around 25% of awakenings from N2 sleep being self-assessed as wakefulness (Hori et al., 1994). The threshold for subjective sleep is determined as 2–4 min after N2 sleep onset (Bonnet and Moore, 1982), a point at which strong FC changes related to diminished arousal are invariably present. It then becomes necessary to rely on objective markers of sleep, such as simultaneous EEG recordings. Since combined EEG-fMRI poses certain technical challenges, an easier alternative is to leverage the FC changes observed during sleep to perform sleep-staging based on fMRI data only. Machine learning classifiers based on fMRI-derived FC have been successful in detecting wakefulness and all NREM sleep stages with relatively high accuracy (Tagliazucchi et al., 2012a; Altmann et al., 2016) (for an overview of machine learning methods applied to neuroimaging see Pereira et al. (2009)). The analysis of a large database of subjects scanned using simultaneous EEG and fMRI revealed that, under conditions of a typical resting state experiment, approximately 50% of the subjects left wakefulness after 10 min (Tagliazucchi and Laufs, 2014). Training a support vector machine classifier on this data and applying it to a large ($n > 1000$) collaborative database revealed similar patterns of sleep in resting state experiments supposedly conducted during wakefulness (Tagliazucchi and Laufs, 2014).

The use of supervised learning as an approach to detect FC changes associated with NREM sleep presents some limitations. Since such classifiers might generalize poorly across data acquired with different scanners and sequences (Huf et al., 2014), the optimal solution would be to train a model on data acquired at each individual scanner. However, this solution would require the use of combined EEG and fMRI at least for some period of time. A plausible alternative is the use of unsupervised learning methods, in particular, the clustering of dynamic FC time series could provide approximate hypnograms without need of a training set (Calhoun et al., 2014). The feasibility of this solution is supported by the work of Allen and colleagues, showing that certain dynamic FC states (obtained via a clustering procedure) are manifest with increasing or decreasing probabilities over time (Allen et al., 2012), as would be expected for clusters related to sleep or wakefulness FC patterns, respectively. Fig. 5 illustrates a possible procedure: whole-brain FC is first computed over short windows of time, then submitted to a clustering algorithm, e.g. k-means, and finally put in correspondence with the hypnogram derived from EEG data for validation purposes. A good correspondence between EEG-derived hypnograms and the temporal evolution of fMRI-derived clusters would add support to the feasibility of an unsupervised learning approach towards sleep staging based on fMRI FC.

Functional connectivity of the sleep-deprived brain

Different forms of intrinsic and experimentally induced sleep disruption result in a widespread derangement of physiology, ranging from subcellular levels to complex affective behavior (Van Someren et al., 2015). Sleep deprivation studies are of key importance to

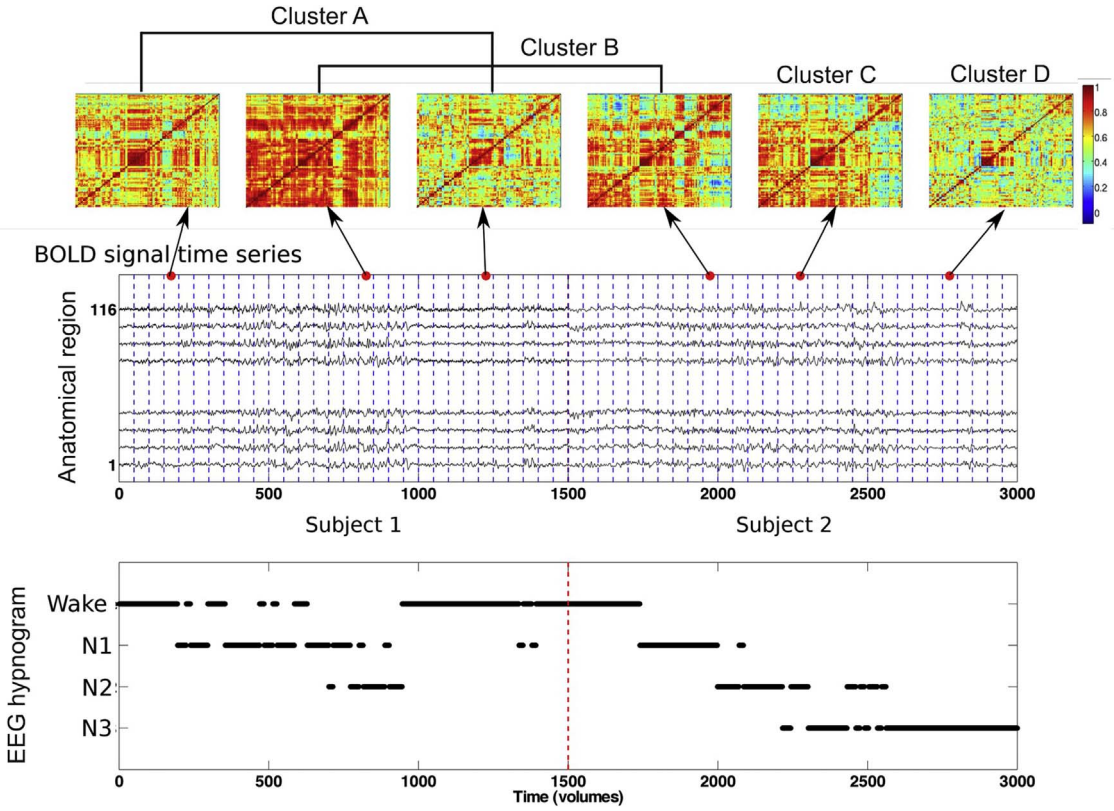

Fig. 5. A possible pipeline for the unsupervised, data-driven sleep staging of resting state fMRI recordings. After extracting the BOLD signal from each anatomical region in a given brain atlas, dynamic FC can be computed using sliding temporal windows. A clustering algorithm can then be applied to the dynamic FC matrices to reveal a sequence of discrete "dynamic FC states" explored by the brain. These states can be put in correspondence with the EEG-derived hypnogram to evaluate the extent of their overlap with wakefulness and the stages of NREM sleep.

elucidate the homeostatic aspects of sleep regulation. However, by the very nature of this experimental paradigm, they are also highly susceptible to sleep-related confounds. This section pursues the dual goal of reviewing relevant literature on the topic of sleep deprivation and its relationship to large-scale FC, and of highlighting the possibility of false positives related to the intrusion of sleep during resting state studies, both in the published literature and in future studies.

In light of the high propensity for sleep during resting state fMRI (Tagliazucchi and Laufs, 2014), some published findings could be re-interpreted as possibly caused by different proportions of sleep between the contrasted conditions. This is especially worrisome for resting state fMRI experiments conducted on sleep deprived subjects. While some researchers took sensible precautions to avoid loss of vigilance during resting state experiments involving sleep deprived subjects (e.g. monitoring eyelid closure, instructing subjects to fixate on a cross) others have proceeded with the traditional "eyes closed, avoid falling asleep" paradigm. This is very problematic, since it can be safely assumed that the amount of NREM sleep misclassified as wakefulness is generally increased after sleep deprivation. Of note, studies of sleep deprived subjects combining resting state fMRI with the gold standard for sleep staging (simultaneous EEG recordings) are lacking.

Most studies to date report diminished FC after sleep deprivation, especially within DMN and the dorsal attention network (Sämann et al., 2010; De Havas et al., 2012; Shao et al., 2013; Verweij et al., 2014; Dai et al., 2015; Zhu et al., 2016). Exceptions are reports of increased interhemispheric (Zhu et al., 2016) and dorsolateral prefrontal cortex FC (Bosch et al., 2013). These results are consistent with episodes of NREM sleep occurring more frequently in the sleep deprived condition than during baseline. BOLD signal dynamics after sleep deprivation can also be interpreted this way, since increased sleep pressure has been shown to reduce the temporal autocorrelations and low-frequency content of BOLD signals in DMN areas (Sämann et al., 2010), results analogous to those observed during deep NREM sleep (Tagliazucchi et al., 2013b).

It is important to note, however, that we can only speculate about some of these results being a consequence of sleep confounds. For instance, sleep deprivation could lead to changes in whole-brain FC similar to those observed during NREM sleep, but without a transition from wakefulness to sleep. A recent study by Kaufmann and colleagues applied a machine learning classifier based on whole-brain FC to fMRI data obtained before and after sleep deprivation (Kaufmann et al., 2016). The classifier detected higher levels of NREM sleep after sleep deprivation, but the core results of the paper remained after removing epochs labeled as NREM sleep from the analyses.

Cognitive neuroimaging experiments reveal changes in the BOLD activity patterns associated with the performance of different tasks as a consequence of sleep deprivation. For instance, the DMN fails to de-activate during episodes of rest in sleep deprived subjects (Gujar et al., 2010), and the activation patterns elicited by a working memory task after sleep deprivation present increased resemblance to those observed in elderly subjects (Chee and Choo, 2004). It is important to note that task-based paradigms are not exempt from confounds related to loss of vigilance, as discussed by Czisch et al. (2012).

It is interesting to speculate on the neural mechanisms underlying reports of decreased FC after sleep deprivation (other than sleep confounds). It has been proposed that human sleep is necessary for the rescaling of synaptic weights (Tononi and Cirelli, 2006). According to this proposal, sustained wakefulness increases synaptic weights, which are then downscaled to baseline levels during sleep. Rescaling is important to reduce the overall energetic consumption and excitability of the human cortex. Huber and colleagues have used TMS and EEG to show that cortical excitability increases with time awake (Huber et al., 2013). Meisel et al. (2013) have also revealed signatures of increased cortical excitability after sleep deprivation, which resulted in a drift

from critical dynamics towards the super-critical state. The normalizing role of sleep is also suggested by the recent work of Khalsa et al. (2016), who established that the cumulative amount of sleep over a period of several days is predictive of FC patterns during wakefulness. Studies directly linking cortical excitability levels with resting state FC are lacking. However, we can hypothesize that increased excitability leads to decreased FC based on two observations: 1) fast EEG rhythms such as gamma (30–60 Hz) are indicative of both decreased excitation/inhibition ratio (Pinotsis and Friston, 2014; Gao et al., 2016) and increased resting state FC (Tagliazucchi et al., 2012b), and 2) decreased resting state FC has been repeatedly reported for epilepsy patients, a brain disorder characterized by increased levels of neural excitability (Waites et al., 2006; Bettus et al., 2009; Luo et al., 2012; Lee et al., 2014).

Functional connectivity changes associated with insomnia

The study of patients suffering from sleep disorders is of clinical and neuroscientific relevance, and complements neuroimaging studies of the healthy human sleep cycle. However, the use of resting state fMRI to investigate patients with sleep disorders shares the risk of sleep confounds with sleep deprivation studies. We will here focus on insomnia disorder, the most prevalent of all sleep disorders, with increasingly recognized neurobiological substrates including risk genes (Hammerschlag et al., 2017). Insomnia moreover seems the sleep disorder with most relevance to the study of consciousness, given its characteristic ongoing thoughts during the night (Wassing et al., 2016) that may result in severe sleep state misperception.

Only few studies investigated whether vulnerable sleep and insomnia are associated with alterations in the structural connectivity that forms the backbone of FC (Piantoni et al., 2013; Spiegelhalder et al., 2014; Zhao et al., 2015). The study of insomnia is further complicated by the large heterogeneity in the population suffering from this disorder (Benjamins et al., 2016). While perhaps useful from a clinical perspective, coarse-level distinctions such as primary vs. secondary insomnia, or sleep-onset vs. sleep-maintenance insomnia, are most likely insufficient to understand the mechanistic bases of the disease. The creation of an online sleep registry to recruit patients of very specific insomnia sub-types could be fundamental to restrict experiments to more homogeneous, data-driven subpopulations (Benjamins et al., 2016). These two factors (sleep confounds and sample heterogeneity) are likely behind the lack of consistency in neuroimaging studies of insomnia (Chee, 2013).

Current research on the causes of primary insomnia is informed by the hypothesis that this sleep disorder is a consequence of hyperarousal, i.e. that elevated arousal produces sleep difficulties and other symptoms such as abnormal hormone secretion, increased heart rate and overall higher metabolic levels (see Bonnet and Arand (1997a), Nofzinger et al. (2004), Bonnet and Arand (2010), Riemann et al. (2010) for a detailed overview of this hypothesis). The hyperarousal hypothesis of insomnia has received support from metabolic imaging studies showing increased energetic demands in the RAS and neighboring areas of patients with insomnia disorder vs. good sleepers (Nofzinger et al., 2004) (but see also Kay et al. (2016) for conflicting results). The intrusion of high-frequency EEG rhythms both during wakefulness (Colombo et al., 2016a) and sleep (Perlis et al., 2001) of patients suffering from insomnia further supports this theory, with sleep complaints being correlated with the temporal persistence of specific EEG rhythms (Colombo et al., 2016b). The use of perturbative techniques has revealed that insomniacs present increased cortical excitability (van der Werf et al., 2010). Increased excitability has been hypothesized to involve suboptimal excitatory input from the orbitofrontal cortex to the head of the caudate nucleus, which has an important role in suppressing or setting limits on cortical excitability (Altena et al., 2010; Stoffers et al., 2012, 2014). Finally, cognitive neuroimaging studies suggested less activation during the performance of attention demanding tasks in people suffering from primary insomnia (Altena et al., 2008; Drummond et al., 2013), which may be explained by higher baseline activity in the patients, a possible consequence of higher levels of background excitability (Chee, 2013). Besides a subcortical origin of hyperarousal, preliminary evidence exists of lower levels of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in patients suffering from primary insomnia (Winkelman et al., 2008) – but see Morgan et al. (2012) for a report of increased levels of occipital GABA in insomnia patients vs. good sleepers.

In spite of this converging evidence supporting the hyperarousal theory of insomnia, resting state fMRI studies often provide conflicting results and generally fail to directly address the theory, e.g. by investigating the FC of RAS components. Primary insomnia has been related to increased FC between the prefrontal and parietal cortices (Li et al., 2014). This finding is consistent with a lower proportion of sleep in people suffering from insomnia vs. controls during the resting state fMRI assessment, possibly due to increased daytime sleep latencies in the patients, despite poor nocturnal sleep (Bonnet, 2006). Enhanced DMN synchronization measured with EEG has been shown in insomniacs during the wake-sleep transition (Corsi-Cabrera et al., 2012). Conversely, a different report showed decreased FC of the parietal cortex with other DMN regions (Nie et al., 2015). It is important to remark that both studies were performed with subjects having their eyes closed and receiving the explicit instruction to relax during the scanning session. More specific seed-based analyses have tested the interaction between insomnia and emotional disturbances by investigating the FC profile of the amygdala (Huang et al., 2012). A very relevant study has been performed by Chen and colleagues (Chen et al., 2014), showing increased insular co-activation with the salience network in insomniacs. This study is important because 1) it shows increased insular co-activation with regions directly involved in arousal regulation and 2) data were acquired using simultaneous EEG-fMRI, thus eliminating the possibility of sleep confounds. Related to this study, increased co-activation of the salience network with insular processing has also been proposed to underlie the enhanced interoceptive heartbeat evoked potential recently found in insomnia (Wei et al., 2016). Finally, a number of articles investigate local or “regional” functional homogeneity changes in patients with insomnia, but these studies are difficult to interpret without a prior hypothesis of what regional homogeneity could mean in terms of the hyperarousal hypothesis (Dai et al., 2014; Li et al., 2016; Wang et al., 2016b).

The hyperarousal hypothesis of insomnia can be visualized as an abnormal path in the awareness vs. arousal diagram presented in Fig. 3. The path followed by the sleep cycle of a patient with insomnia disorder would be displaced towards the right, indicating an overall higher level of arousal. Conversely, sleep state misperception, a disorder characterized by the subjective underestimation of the amount of sleep experienced during the night (Bonnet and Arand, 1997b), could be related to a positive displacement in the awareness direction. Thus, while a wide spectrum of insomnia sub-types could be categorized as disorders of arousal, sleep state misperception could be classified as a disorder of conscious awareness. If the amount of conscious content experienced by sleep state misperception patients during the night is higher than for good sleepers, then combined EEG-fMRI experiments could be used to investigate the prevalence of signatures of consciousness during their sleep; for instance, changes in integration/segregation network measures (Boly et al., 2012; Spoormaker et al., 2012; Tagliazucchi et al., 2013a), or in the long-range temporal correlation of DMN and attentional network activity fluctuations (Barttfeld et al., 2015; Tagliazucchi et al., 2013b). This is a promising future area of research, not only for the understanding of sleep state misperception itself, but also for the identification of the neural correlates of consciousness during sleep.

Limitations of resting state fMRI and their interaction with sleep

Resting state fMRI is an indirect measure of brain activity and as such it is prone to a number of confounds and artefacts. Even relatively small (< 1 mm) head displacements can induce artificial correlations between distant anatomical regions and thus introduce spurious "functional connectivity" (Power et al., 2014, 2015). The regression of head motion estimates and their first derivatives (Friston et al., 1996), together with the removal of epochs of high relative displacement ("scrubbing") (Power et al., 2014) are useful techniques to alleviate head motion artefacts, but residual effects are known to remain. The current literature does not include reports of overall levels of head displacement during different sleep stages, but it can be speculated that wakefulness and transitional (N1, N2) sleep stages are associated with more movement than the deeper and relatively more stable N3 sleep. Given this possibility, future studies must investigate differences in head movement between sleep stages, and test whether the effect size of the results correlates with the amount of head movement on an individual subject basis.

BOLD signals are also prone to contamination due to artefacts of respiratory and cardiac origin (Birn, 2012). This represents a serious concern for neuroimaging studies of sleep, since these variables correlate with levels of arousal and are expected to change during the sleep cycle (Iber et al., 2007). The registration, modeling, and regression of physiological brain signals from fMRI data can be useful to overcome this potential issue. As an example of the impact of physiological noise on FC during NREM sleep, it has been shown that differences in FC between sleep and wakefulness can be obscured by such noise due to the presence of false negatives, i.e. failing to reject the null-hypothesis in the face of sufficient evidence - see the supplementary information of Tagliazucchi and Laufs (2014) for an example of differences in FC with and without the application of RETROICOR (Glover et al., 2000) to clean physiological noise from the data.

Conclusions and future directions

We started this review by discussing the preservation of large-scale coordinated patterns of spontaneous activity (RSN) across NREM sleep, and how this preservation could be linked to FC being upheld by the backbone of anatomical connections. These early studies suggested a more focused and hypothesis-driven approach. The human sleep cycle can be mapped as a trajectory in a two dimensional diagram of brain states sorted by their level of arousal and conscious awareness. Thus, it is natural to classify (as a first approximation) neuroimaging studies as addressing the arousal and/or the conscious awareness dimension of sleep. These studies yield important insights on the neurophysiology of sleep itself, but more generally on the neural correlates of arousal and conscious awareness. It is expected that some of these insights can be translated to the study of other brain states; for instance, is the analysis of integrated/segregated network structures as a signature of consciousness during sleep (Boly et al., 2012; Spoormaker et al., 2012; Tagliazucchi et al., 2013a) also useful for the quantification of residual consciousness in non-responsive brain-injured patients? (Laureys et al., 2007).

The study of large-scale FC during sleep should be seen as a research goal in itself, but also as a necessary tool to avoid sleep confounds during resting state fMRI experiments (Tagliazucchi and Laufs, 2014). We have discussed both supervised and unsupervised learning approaches to this problem, and highlighted the need of combining fMRI with some objective measure of wakefulness. This need is particularly manifest in studies of sleep deprived subjects and patients suffering from insomnia disorder. Much of the resting state fMRI literature on these topics is compatible with the presence of sleep confounds during experiments. Taking adequate precautions is especially important for the study of insomnia: the combination of sleep-related confounds with the heterogeneity intrinsic to the disorder might underlie the relative lack of consistency present in the resting state fMRI literature (Chee, 2013).

The present review is restricted to articles addressing the macroscopic, large-scale changes in FC related to sleep and associated conditions. Even within this narrow scope it was not possible to cover other interesting areas of research, such as studies on the role of sleep in memory consolidation. For instance, recent large-scale FC analyses have been employed to reveal the dynamics of the human cortical-hippocampal dialogue during NREM sleep (Mitra et al., 2016), and the reactivation of specific long-range functional connections associated with visuomotor learning during sleep (Piantoni et al., 2015). Also, it was not possible to present a detailed discussion of perturbative approaches to investigate effective connectivity during sleep (Massimini et al., 2005), and their important theoretical relevance as signatures of conscious awareness (Tononi, 2004).

As it is frequently the case with fMRI studies of brain function, the interpretation of FC in terms of mechanisms at the cellular level can be difficult. To deepen our understanding of the neurobiological meaning of FC changes during sleep, it is imperative to move towards the multimodal combination of electrophysiological (EEG), metabolic (PET), behavioral and cognitive neuroscience techniques, e.g. analysis of reported conscious content in serial awakening paradigms. The use of animal models can be of great value due to the possibility of combining fMRI with invasive electrophysiological measurements as well as with pharmacological manipulations to induce and control sleep. Our recommendation also applies to future studies of sleep deprivation and sleep disorders. The requirement of objective and independent vigilance monitoring during resting state experiments establishes that the information provided by fMRI recordings alone is generally insufficient, prompting the need of moving towards EEG-fMRI or other paradigms allowing the independent assessment of vigilance. Tools to improve the quality of the EEG signals under the challenging condition of simultaneous MRI continue to be developed (e.g. van der Meer et al., 2016). Since EEG-fMRI can still be challenging to set up as well as costly, the combination of supervised/unsupervised fMRI-based sleep-staging and eye-tracking devices could be useful to monitor and restrict the intrusion of sleep in resting state experiments. However, combined EEG-fMRI is likely to remain the gold standard in fMRI studies of sleep, encouraging the development of better multimodal fusion techniques to complement the indirect nature of fMRI recordings. More generally, we believe that sleep neuroimaging could be instrumental in pushing resting state fMRI towards a multimodal imaging approach, a much required methodological update in the field.

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