Functional connectivity and the sleep-deprived brain

7

Michael W.L. Chee[a,*], Juan Zhou[b]

[a]*Centre for Cognitive Neuroscience, Neuroscience and Behavioral Disorders Program, Duke-NUS Medical School, Singapore, Singapore*
[b]*Centre for Cognitive Neuroscience, Duke-NUS Medical School, Singapore, Singapore*
Corresponding author: Tel.: (+65) 6516 4916; Fax: (+65) 6221 8625, e-mail address: michael.chee@duke-nus.edu.sg

Abstract

Resting state functional connectivity (rsFC) evaluated by detecting temporal co-variation of BOLD signals across multiple brain regions undergoes three major changes following sleep deprivation that indicate the occurrence of sleep intrusions; a loss of integration within networks like the default mode network as well as between networks like the salience and dorsal attention systems; a loss of segregation between networks, for example, between the dorsal attention and default mode networks; and an increase in global signal. Changes in vigilance affect rsFC and these likely occur in many scans involving persons with neuropsychiatric conditions. Ensuring "healthy" or "control" participants do not fall asleep in the scanner is increasingly acknowledged as a being important for proper inference in fMRI studies. Dynamic functional connectivity analyses evaluating the relative proportion of time spent in "low" or "high" arousal states during the well-rested state can predict propensity for vigilance decline when sleep deprived.

Keywords

1 Resting state functional connectivity (rsFC) and its measurement

Our brains contain large scale neural networks displaying spontaneous, slow (0.01–0.1 Hz) temporal covariation in fluctuations of blood-oxygenation-level-dependent (BOLD) signal in spatially non-contiguous regions (Biswal et al., 1995, 2010; Smith et al., 2009; Wig et al., 2011). Such "resting state functional connectivity" can be uncovered without explicit task performance while a person lies still in a MR scanner for several minutes, looking at a fixation point.

Intriguingly, the spatial pattern of functionally clustered brain regions so defined, corresponds to patterns of BOLD signal change elicited when specific cognitive tasks are performed (Smith et al., 2009). Functionally connected brain regions uncovered in this manner are often, though not invariably, structurally connected. For example, functional connectivity patterns in the visual cortex are consistent with the topographical hierarchy of polysynaptic anatomical pathways in anesthetized monkeys (Vincent et al., 2007). Further, multi-region intrinsic connectivity networks (Menon, 2011; Sporns and Betzel, 2016) detected using rsfMRI have homologues across species (Vincent et al., 2007).

The attractiveness of rsFC lies in its ability to characterize effects of a condition of interest (e.g., sleep deprivation) on multiple functional brain networks concurrently, without having to design elaborate cognitive tasks. Even with thoughtful task design and successful implementation, it would take far more time to interrogate multiple functional networks than a typical 10 min "resting state" study. This apparent freedom to "effortlessly" obtain highly informative data on brain function has driven intensive research on functional connectivity.

With years of experience now available, it is apparent that multiple factors must be considered for the proper conduct and interpretation of a resting state study. Adequate control of motion and accounting for physiological artifacts are important. Mental activity prior (Lewis et al., 2009) or during (Kucyi and Davis, 2014) the MRI evaluation and state (alert, sleepy) (Tagliazucchi and van Someren, 2017; Thompson et al., 2013) can also affect functional connectivity. Certainly, in fatigued participants, performing a study with eyes closed is an invitation for sleep to occur (Tagliazucchi and Laufs, 2014) and for connectivity findings to be unwittingly distorted. There are many ways to prepare (pre-process) data prior to analysis and a slew of techniques to analyze data and to infer from it. We next briefly describe four main approaches of deriving brain functional connectivity from rsfMRI data (Fig. 1A).

2 An overview of resting state fMRI analysis techniques

Seed-based analysis refers to the delineation of connectivity networks by calculating the temporal synchrony of BOLD signals of a seed region relative to the time series of all other voxels of the brain (Biswal et al., 1995). There are several temporal synchronization indices (Pedersen et al., 2018) but the Pearson's correlation coefficient is most commonly used. Every voxel in the resulting connectivity map depicts regions with significantly correlated signal with the seed region. For example, by seeding at the posterior cingulate cortex, reduced FC within the default mode network (DMN) was found following sleep deprivation (De Havas et al., 2012). Because the resulting network is seed-dependent, it is crucial to define seeds with reference to a functional localizer or previous literature, as from a meta-analysis of task-based fMRI studies.

Independent component analysis (*ICA*) is a data driven method whereby BOLD signals from all brain voxels are simultaneously decomposed into multiple networks
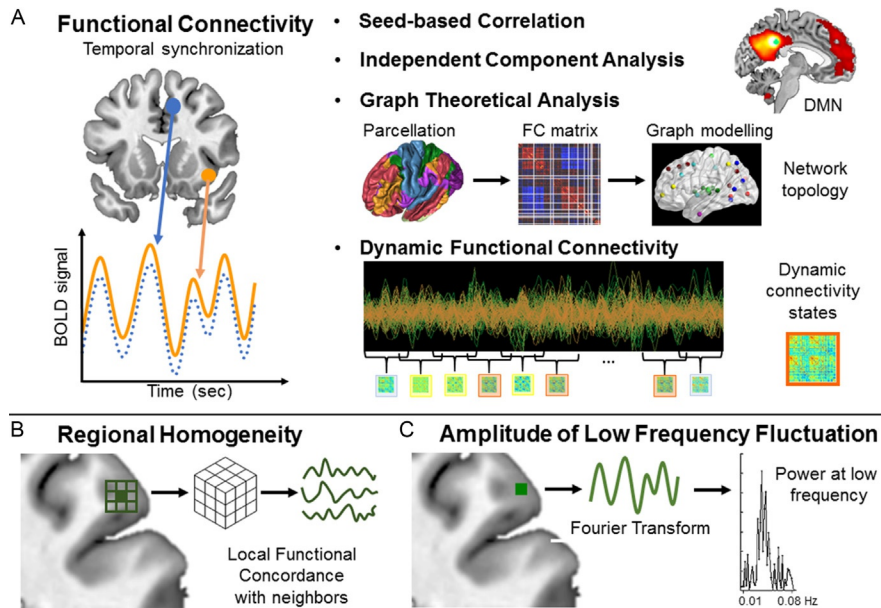
FIG. 1

Resting state fMRI-based functional connectivity derivation and analytical methods. (A) The most common definition of functional connectivity (FC) is the temporal synchrony of the slow oscillations of the blood-oxygen-level-dependent (BOLD) signals between two brain regions of interest (ROIs), quantified by measures such as Pearson's correlation coefficient. There are four main methods of deriving intrinsic connectivity networks (ICNs; hot color). (1) Seed-based correlations reveal networks by seeding at representative ROIs within each network (green dot). (2) Independent component analysis (ICA) simultaneously extract multiple independent component networks by decomposing the four-dimensional fMRI data. (3) The multiple-seed based brain parcellation approach measure FC between all possible ROI pairs, which are subsequently depicted in a single FC matrix. Intra- and internetwork FC can be measured. Moreover, graph theoretical analysis can be applied to the FC matrix to characterize brain functional network topology. (4) Rather than assuming static FC over the whole fMRI time course, dynamic functional connectivity is evaluated from multiple shorter epochs (e.g., 20–40s instead of 8min), resulting in multiple FC matrices across time. These matrices can be clustered according to their spatial similarities (denoted by different colors) to give a more discrete view of time-varying FC dynamics. Each cluster centroid represents a "dynamic connectivity state." (B) Regional homogeneity (Reho) measures local FC defined as temporal coherence or synchronization of the BOLD time series within a set of nearest neighbors of a given voxel. (C) Amplitude of low frequency fluctuation (ALFF) measures the regional amplitude of BOLD fluctuations by taking the square root of power spectrum averaged across low-frequency range.

with associated time courses that are spatially "independent" from one another (Erhardt et al., 2011; McKeown et al., 2003). Using the ICA approach, reduced FC within the DMN was detected in healthy young adults after partial sleep deprivation (Samann et al., 2010).

Although seed-based and ICA-based approaches can be used to study internetwork FC, a more systematic approach for characterizing both intra- and internetwork FC is the *multiple-seed-based FC matrix* approach which measures FC between multiple brain regions (many-to-many) based on predefined brain functional *parcellation*. The functional connectivity between all region of interest (ROI) pairs covering the whole brain is computed and arranged into an adjacency matrix before applying network-based statistics (Arslan et al., 2018; Wig et al., 2014). Using this approach, Yeo and colleagues found reduced FC within the DMN and attentional networks as well as decreased anti-correlations between the DMN and attentional networks following sleep deprivation (Yeo et al., 2015).

Given the high dimensional nature of FC data within individual matrices, *graph theoretical methods* are sometimes applied to characterize brain network topology. A brain graph comprises nodes (defined by brain ROIs) connected by edges (strength equals to functional connectivity). Nodes can be clustered into modules or communities featured with stronger within-module connectivity and weaker between-module connectivity. To capture topological properties, graph theoretical measures such as degree centrality, efficiency, and modularity can be calculated at nodal, network, and whole-brain levels (Fornito et al., 2013; Sporns, 2013). Modularity measures functional segregation, i.e., the degree to which brain functional graph can be partitioned into delineated subgroups (Newman, 2004; Rubinov and Sporns, 2010). Sleep deprivation has been reported to reduce network modularity in limbic, default-mode, salience and executive modules (Ben Simon et al., 2017).

Beyond these static functional connectivity methods that brain FC patterns remain constant over the duration of the rsfMRI scan (e.g., 6–12 min), recent advances in *dynamic, time-varying functional connectivity* (synchrony over tens of seconds) may provide a more detailed characterization of functional network organization. For example, a seed-, ICA-, or multiple-seed parcellation can be combined with the sliding window approach, followed by a clustering algorithm (Allen et al., 2014) to identify representative "dynamic connectivity states." Other approaches include Hidden Markov Models (Rabiner, 1989; Taghia et al., 2017) and multiplication of temporal derivatives (Shine et al., 2015). Measures such as the time spent in a certain state and the transition probabilities between states can then be derived to better characterize connectivity-behavior relationships and how these change with disease (Quevenco et al., 2017). Using the sliding window approach, Wang and colleagues discovered high and low arousal dynamic connectivity states from rsfMRI data, that tracked temporal fluctuations of vigilance task performance after sleep deprivation (Wang et al., 2016).

In contrast to FC between remote brain regions described above, local FC metrics have been proposed to measure functional interactions or synchronization between

the neighboring voxels or vertices at a local spatial scale. Regional homogeneity (ReHo) (Fig. 1B) is one such local FC measure, defined as the Kendall's concordance coefficient between the time series of all nearest neighbors of a given node (Jiang and Zuo, 2015). Increased ReHo in parietal, frontal and occipital regions were found following sleep deprivation, suggesting altered regional functional organization (Dai et al., 2012).

Lastly, besides functional synchrony between regions, regional spontaneous activity at resting state may provide additional information of neural processing. Amplitude of low frequency fluctuation (ALFF) index, defined as the square root of power spectrum of BOLD signals averaged across low-frequency range, was proposed by Zang et al. (2007) (Fig. 1C). Alternatively, fractional ALFF index computes the ratio of power spectrum of low-frequency range to that of the entire frequency range (Zou et al., 2008). Using these measures in sleep deprivation has revealed inconsistent findings (Gao et al., 2015; Nilsonne et al., 2017).

3 Functional connectivity alterations following sleep deprivation

Overall, three of the most robust connectivity changes following a night of sleep deprivation are decreased integration within networks, decreased segregation between networks and an increase in global signal. "Integration" refers to the occurrence of correlated BOLD signals between functionally related brain areas even if they are spatially distinct, e.g., the Dorsal and Ventral Attention networks. It can also denote high signal correlation between different parcels within the same network, for example, within the default mode network. Segregation refers to decreased negative correlation (referred to as anti-correlation) between parcels belonging to networks that show opposite patterns of task-related signal.

Among cortico-cortical connections, stronger anti-correlations between Default and Attention networks have been observed during the well-rested state relative to the sleep-deprived state, i.e., the negative correlations were more negative during rested wakefulness(Yeo et al., 2015) (Fig. 2). Dorsal Attention network and Salience/Ventral Attention network are sometimes referred to as "task-positive" because they tend to activate during most cognitive tasks requiring a response whereas the default mode network deactivates at the same time (Fox et al., 2005). The loss of anti-correlation in the sleep-deprived state is sometimes discussed in terms of reduced cortical network segregation.

The second major change following sleep deprivation is a reduction in network integration. The brain evidences stronger correlations within parts of the Default Network in the well-rested state relative to the sleep-deprived state. There is also stronger connectivity between Dorsal Attention and Ventral Attention networks during the rested state relative to the sleep-deprived state (De Havas et al., 2012; Samann et al., 2010; Yeo et al., 2015).
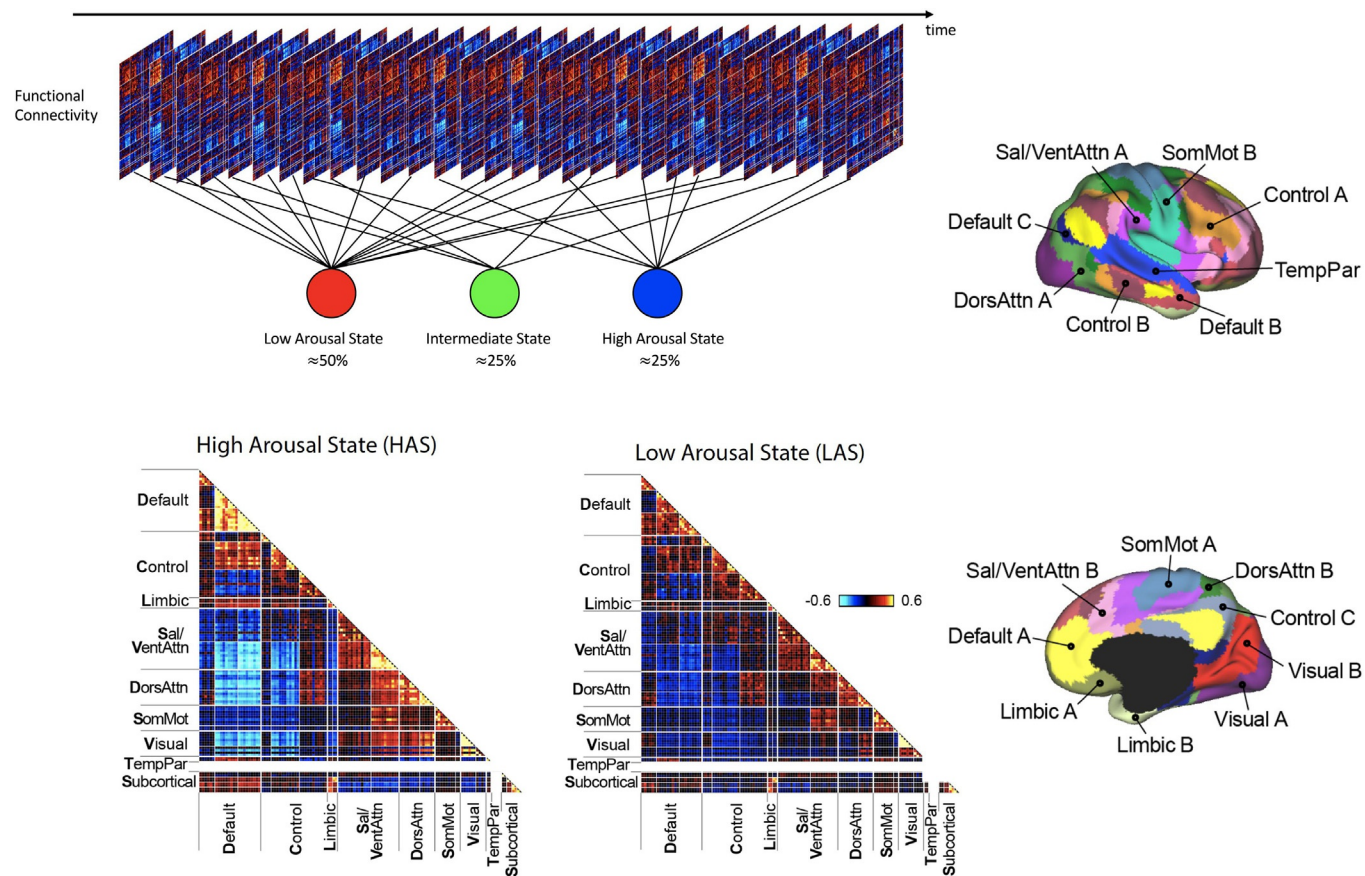
FIG. 2

Dynamic Functional Connectivity analysis of resting state connectivity obtained in the well-rested state showing a schematic of the sliding window method used to derive three functional connectivity "states" and the relative temporal distribution of these states. The functional connectivity matrices associated with the "high" and "low" arousal states and their corresponding anatomical locations are shown.

Among subcortical-cortical networks, empirical observations differ from the expectation that thalamocortical connectivity might be depressed following sleep deprivation corresponding to depressed thalamic function during sleep. Our group has found this expectation to hold for interactions between the thalamus and Dorsal Attention as well as Default networks (Yeo et al., 2015). Somewhat counter-intuitively, thalamus—Ventral Attention/Salience network connectivity increases with sleep deprivation. We found no significant state-related alteration in connectivity between the amygdala and cortical regions even though task-related studies suggest a weakening of amygdala to prefrontal connectivity (Chuah et al., 2010) that corresponds to decreased emotional regulation (Goldstein and Walker, 2014) in the sleep-deprived state. Two studies based on small samples found significant decreases in amygdala connectivity following sleep deprivation (Lei et al., 2015; Shao et al., 2014). At the present time, state changes in cortico-cortical connectivity appear to be more robust than the subcortical-cortical ones.

An increase in "global signal" is a third major type of signal change relevant to the characterization of state-related MR signal differences. Global signal refers to the mean time series (time course) of BOLD signal taken across gray matter, white matter and ventricle voxels (Liu et al., 2017). This global signal increases with decreased vigilance and sleep deprivation. However, the term "Increase" is some-what of a misnomer as it is often used to refer to the *extent of signal fluctuation* (Fukunaga et al., 2006) and not how the mean signal level changes across time, although the latter also tends to occur during the wake-sleep transition (Liu et al., 2018; Ong et al., 2015).

Why global signal increases with decreased vigilance is not clear, but one is reminded of accompanying dropouts of multi-unit activity (Vyazovskiy et al., 2011), increased EEG amplitude (Olbrich et al., 2009; Wong et al., 2016), fluctuation of pupil diameter (Massar et al., 2018; Wilhelm et al., 1998) and unstable response times during vigilance testing (Doran et al., 2001) (Fig. 3). On the one hand, global signal is a "nuisance" since contributions from white matter and ventricles are not of interest as these are not where neurons that contribute to cognitive brain activity reside. Depending on how the data is pre-processed, physiological cardiac and breathing signals included in "global signal" may or may not be adequately removed (Liu et al., 2017). While these themselves can be affected by sleepiness/sleep in that heart rate and breathing tend to be more regular with sleep onset, these are fundamentally signals unrelated to underlying brain connectivity. On the other hand, modulation of "global" signal with state and its correlation with behavioral markers of vigilance and EEG features clearly suggests physiological origins to signal increases that need to be explained in future studies.

The magnitude of the aforesaid "anti-correlations" between networks that con-currently activate and deactivate (show lower BOLD signal) in an opposing manner, is affected by whether global signals are regressed out in the analysis. Although such anti-correlations have been shown to persist following global signal regression (Chai et al., 2012), whether the latter still "artifactually" contributes to findings
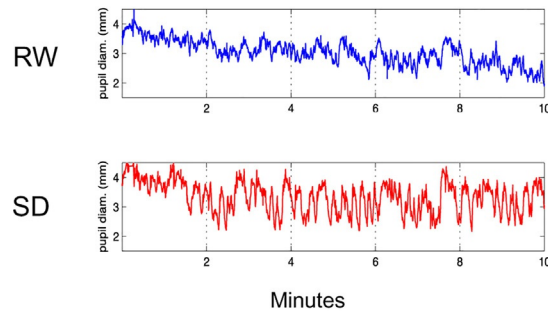
Multi-Unit Activity (Vyazovskiy 2011)
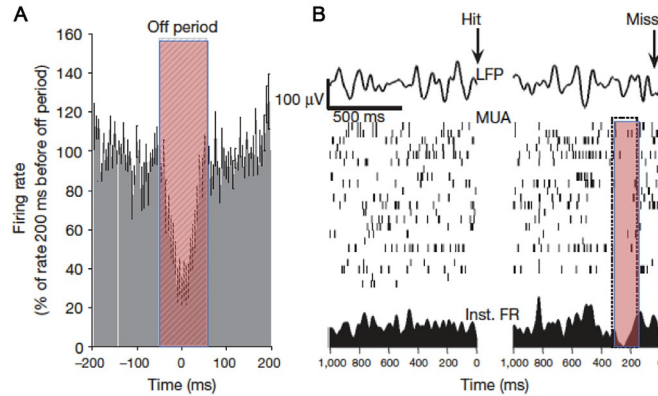
Behavioral lapses (Doran 2001)
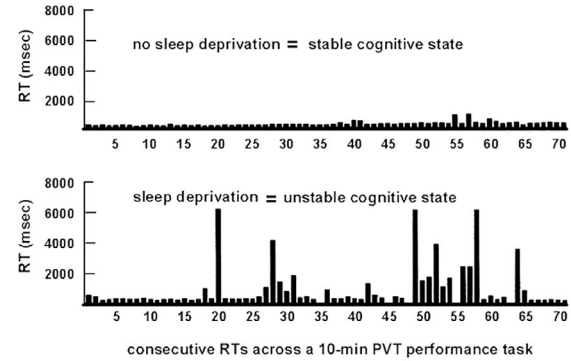
Pupil Diameter (Massar 2018)

fMRI Global Signal (Yeo 2015)

FIG. 3

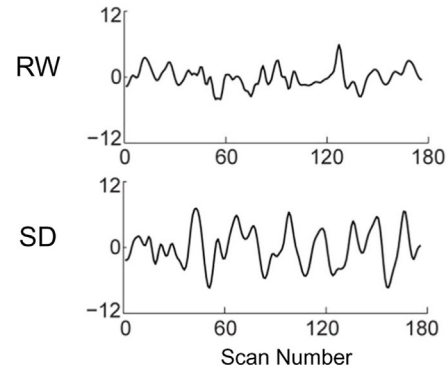Increased fluctuation of fMRI global signal in the context of other physiological fluctuations in the sleep-deprived state that indicate the occurrence of microsleep intrusions. These are associated with drop-outs in multi-unit activity, result in behavioral lapses, fluctuation in pupil diameter, and increased fluctuations in global signal. Abbreviations: RW, rested wakefulness; SD, sleep deprived.

remains contentious (Liu et al., 2017). We have argued that if we are specifically interested in brain connectivity and how this changes with state, global signals should be regressed out since they represent a type of signal change with a different physiologic origin—one that does not directly inform about connectivity (Yeo et al., 2015). A number of neuropsychiatric conditions have been associated with decreased network anti-correlation and since these can be made more apparent *with* global signal regression, GSR is often used as a standard processing step to enhance detection of such deviation from normality in patients.

Groups who do not perform global signal regression argue that as it is known to increase in the sleep-deprived state, it should not be removed (Xu et al., 2018a). Interestingly, despite its name, the "global signal" is not uniform across the brain and shows greater expression in sensorimotor and visual cortices (Xu et al., 2018b). This non-uniformity in regions of maximal expression is likely to affect the characterization of state changes in resting state connectivity. For example, a recent study found prominent state effects in sensorimotor cortex (Xu et al., 2018a) which are not apparent when GSR is performed.

Functional connectivity in the well-rested state is an indicator of a person's vulnerability to vigilance decline following sleep deprivation (Yeo et al., 2015). If participants are median split on the number of PVT lapses they have, persons showing less anti-correlation between default and task-positive networks were found to be more likely to exhibit vigilance decline after a $\sim$24 h of total sleep deprivation. Static FC was correct in predicting which half a participant would lie in about 60% of the time. Although not evaluated in a direct comparison, drift diffusion modeling of PVT data collected in the well-rested state has about a 65% prediction of median split data.

4 Dynamic functional connectivity and behavioral correlates

The characterization of functional connectivity to this point can be thought of as a summary of spatial patterns of correlated BOLD signals over the entire duration of the rsFC scan. However, just as signal fluctuations give rise to FC, the patterns of FC change in a repeating manner during the course of the time a person undergoes scanning. By taking contiguous scans over a temporal window and shifting this window one time point at a time across the duration of the study and evaluating FC within each window (which typically extends from 30 to 40s), one can uncover recurrent "dynamic connectivity states" (Hutchison et al., 2013), whose weighted average reconstitutes the "static connectivity" characterization described earlier.

Some form of mathematical clustering is used to tease out distinct "states" from the entire time series making up the rsfMRI dataset. The number of states thus derived is arbitrary but typically ranges from 3 to 7 with 5 being commonly used. There is at present no clear biological basis for determining state number. However, it is clear from the work of multiple investigators working independently and using

different approaches, that at least some states differ in their association with vigilance (Chang et al., 2013, 2016; Thompson et al., 2013; Wong et al., 2016).

In trying to correlate dynamic state to ongoing behavior, one is hampered by the fact that a behavioral probe disturbs ongoing behavior. Eyelid closures in the sleep-deprived state correspond to microsleeps associated with decreased likelihood of responding to an auditory stimulus (Ong et al., 2013). By observing the DFC state that had the best fit with the temporal pattern of eyelid closures, we were able to detect a state associated with "low arousal" and one corresponding to the eyes open condition signifying "higher arousal." These correspond to exaggerated versions of the patterns of static connectivity associated with sleep-deprived and well-rested scans reported in independent studies. Similar pairs of states could be recovered by regressing out task-related signal changes from FC data collected during performance of an auditory vigilance task. Periods where the ongoing connectivity pattern more closely resembled the "low arousal" DFC pattern were associated with slower response times and conversely, periods with quicker responses were more likely to exhibit the "high arousal" pattern of DFC (Wang et al., 2016). These findings reinforce the importance of examining anti-correlated BOLD signals as the extent of anti-correlated activity between task positive and task negative networks appears useful in differentiating persons with faster and slower response times. Further, within a subject, periods of greater anti-correlation correspond to epochs of faster responding.

Even in well-rested participants whose prior sleep history has been carefully controlled for, the "low arousal" state dominates, occupying on average slightly over 50% of the total time in a RSFC study (in a 3-state model of DFC) while the high arousal state occupies slightly less than 25% of this time (Patanaik et al., 2018). Network efficiency is higher in the high arousal state, but this comes at a cost, which is the reason for the brain spending more time in the low arousal state until required by task demands (Patanaik et al., 2018). Adolescents who are more resilient to the effects of multi-night sleep restriction evidence greater expression of an arousal index composed by subtracting the proportion of time spent in the low arousal state from proportion of time in the high arousal state and adding unity (Patanaik et al., 2018). The functional significance of other "intermediate" states is presently unknown. While it is tempting to ascribe a label of "transition" state, this is not clearly borne out by analyzing the temporal pattern of state transitions.

Vigilance is the cognitive domain that is most clearly associated with temporal preponderance of the two polar DFC states. The DFC arousal index computed from a rsFC scan obtained in the well-rested state differentiates sleep deprivation vulnerable and resilient participants in that it foreshadows the cumulative decline in vigilance in vulnerable persons when they are sleep restricted (Patanaik et al., 2018). DFC also seems to identify persons showing differences in speed of processing and working memory when sleep deprived though not as convincingly as in the case of vigilance. There is no association between DFC state with sleepiness or mood.

5 Functional connectivity changes in other neuropsychiatric conditions compared to sleep deprivation

Acute total sleep deprivation is a neurological and physiological stressor that produces cognitive and behavioral changes in healthy participants. Its short-term reversibility invites its use as a test platform for cognitive performance modulators (McEwen, 2006). Brain FC changes following sleep deprivation (Kaufmann et al., 2016; Yeo et al., 2015) somewhat resemble the vulnerability patterns of patients with Alzheimer's disease (see reviews Dennis and Thompson, 2014; Zhou et al., 2017), in particular, reduced FC within the DMN (Greicius et al., 2004) as well as decreased anti-correlations between the DMN and attentional networks (Brier et al., 2012; Wang et al., 2007). Recall that highly integrated brain regions become less integrated and highly segregated networks become less segregated with SD. A point of difference is that SD results in reduced FC within the attentional networks that is accompanied with lower vigilance whereas the findings concerning attentional network FC in Alzheimer's disease are rather mixed. For example, increased ventral attentional or salience network FC has been shown in patients with early Alzheimer's disease (Zhou and Seeley, 2014; Zhou et al., 2010).

Why the DMN is specifically affected by SD and whether and how this might relate to Alzheimer's disease?

Amyloid-beta (Aβ) is a peptide fragment of the amyloid precursor protein that accumulates extracellularly as plaques when misfolded, causing synaptic damage. Aβ accumulation is a hallmark of Alzheimer's disease (Gouras et al., 2015; Jack et al., 2013). Animal and human studies have demonstrated a bidirectional link between sleep disturbances and high Aβ burden (see review Kang et al., 2017). A recent human PET imaging study found that even a single night of sleep deprivation could elicit a significant increase in Aβ burden in the right hippocampus and thalamus. These increases were associated with mood worsening after sleep deprivation (Shokri-Kojori et al., 2018). It is hypothesized that sleep deprivation or disturbance may lead to decreased slow wave sleep (the sleep stage in which synaptic activity is lowest) facilitating the accumulation of Aβ (Cirrito et al., 2005). The precuneus which lies in the DMN is one of the most metabolically active brain regions during wakefulness (Raichle and Snyder, 2007). It becomes deactivated during slow wave sleep (Samann et al., 2011) and is the region most prone to Aβ accumulation (Buckner et al., 2005). Loss of functional segregation between the DMN and attentional networks has also been documented in slow wave sleep (Samann et al., 2011). It is currently thought that with disrupted sleep which is common in persons at risk of AD, reduced DMN deactivation and segregation from failure to obtain good sleep could accelerate the accumulation of Aβ in this network. Taken together with converging findings of higher Aβ deposition related to lower DMN connectivity (Drzezga et al., 2011; Kikuchi et al., 2011; Mormino et al., 2011), this could explain the similarity of reduced DMN functional integration following sleep deprivation and Alzheimer's disease.

Sleep problems are also common in persons suffering from depression. Longitudinal studies show that sleep complaints often precede the onset of depression and constitute an independent risk factor for its development. Impaired sleep may contribute to depression through an impairment of neuronal plasticity and neurogenesis, leading to altered connectivity and communication within and between brain regions involved in the regulation of mood (Meerlo et al., 2015). Indeed, depression has been thought to relate to altered neuronal plasticity and neuronal connectivity (Duman, 2002; Nestler et al., 2002). Meta-analysis of rsfMRI studies (Kaiser et al., 2015) reveals that major depressive disorder is characterized by reduced FC in the DMN, a network supporting internally oriented and self-referential thought. As well, decreased anti-correlation between fronto-parietal control network and DMN is observed. This pattern is mirrored by the FC changes after sleep deprivation. However, differentiating FC changes in major depressive disorder from those of sleep deprivation are the additional presence of hypoconnectivity within the fronto-parietal executive control network, hypoconnectivity between fronto-parietal network and parietal regions of the dorsal attention network and between prefrontal-limbic neural systems involved in processing emotion or salience (Wang et al., 2012).

Besides Alzheimer's disease and depression, sleep disturbance is also commonly involved in other neuropsychiatric disorders such as schizophrenia, bipolar disorder, and neuro-immune diseases. The FC studies in these disorders are limited and the findings are less consistent (Brady et al., 2017; Kambeitz et al., 2016; Pettersson-Yeo et al., 2011; Sbardella et al., 2015). For example, previous rsfMRI studies reported widespread functional dysconnectivity in psychosis, targeting multiple neural systems that include frontal regions (Hoptman et al., 2010), auditory cortex (Gavrilescu et al., 2010), DMN (Camchong et al., 2011), thalamocortical circuits (Klingner et al., 2014) and salience network (insula and anterior cingulate cortex) (Palaniyappan and Liddle, 2012). Again, the key convergence with FC changes following sleep deprivation is the reduced DMN FC.

Sleep disturbances often co-occur with neuropsychiatric disorders. Chronic sleep deprivation can result in impaired cognition such as memory and attention and mood problems such as increased anxiety and aggression (Meerlo et al., 2015), which are regulated by the high-order cognitive networks such as the DMN and DAN, salience, and limbic networks. Taken together, repeated bouts of sleep deprivation and/or disturbed sleep can be thought of contributing to brain functional connectivity alterations that could exacerbate pathways that lead to neuropsychiatric disease.

6 Importance of sleep during functional connectivity studies

A key advantage of rsFC studies, their ability to assay the functional status of multiple brain networks *without task performance,* can turn into a problem when seeking to characterize "normal" cognition or when comparing patient groups with healthy controls. Among "normal" participants, a third fall asleep in the scanner in historical multi-center data (Tagliazucchi and Laufs, 2014). This is unsurprising given that many volunteers are often sleep deprived or have irregular or unusual sleep-wake schedules.

Striking changes in BOLD signal, instantaneous FC (Ong et al., 2013; Poudel et al., 2018) and global signal (McAvoy et al., 2018) occur at the point of eye closure in sleepy persons and these can affect the evaluation of rsFC if frequent. Given that the characterization of "normal" usually means evaluation of persons when they are cognitively most able, inclusion of data where participants are falling asleep will affect the characterization of "normal" and affect the comparison of patient and "controls."

Some have advocated for the censoring of "asleep" data using machine learning techniques but this requires collecting prior simultaneous EEG-fMRI data for each centre, a time consuming and technically demanding task (Tagliazucchi and van Someren, 2017). Controlling for sleep history, screening for sleep disorders, conducting scans with eyes-open as opposed to eyes-closed (Ong et al., 2013, 2015) and using an in-scanner camera to monitor for epochs of involuntary sleep are three simple methods to reduce intrusion of sleep into rsFC studies.

With patients, it is more difficult to make recommendations as sleep disturbances accompany many neurodegenerative and psychiatric disorders and may be part of the abnormal brain network state for which characterization is sought. Nevertheless, it might be helpful to take note of how sleepy participants are in the scanner so that this information can be used as a co-variate.

7 Future directions

Complex preprocessing and data analytical steps are involved in rsfMRI-based FC mapping. To facilitate reproducible and meaningfully comparable data across multiple sites and across patient populations, it is important to ensure good practices in collection, analysis, and inference of rsfMRI data (Smith and Nichols, 2018). In particular, measures to reduce or control for the occurrence of sleep during rsFC studies must be implemented if the research goal is to probe awake cognition.

Longitudinal studies on the evolution of daytime sleepiness and its associated FC alterations might give insight into pathophysiological changes in the brain that evolve in the course of neurodegenerative or early phase psychiatric conditions. Evaluating how the severity of sleep intrusions modulates disease evolution or progression is another possibility. In turn, the effects of interventions like bright light exposure on long-term brain functional connectivity could be examined.

As regards the temporal dynamics of state transitions, the characterization of these in normal and diseased populations might contribute to characterizing disease evolution or the effects of intervention.

References

Allen, E.A., Damaraju, E., Plis, S.M., Erhardt, E.B., Eichele, T., Calhoun, V.D., 2014. Tracking whole-brain connectivity dynamics in the resting state. Cereb. Cortex 24 (3), 663–676.

Arslan, S., Ktena, S.I., Makropoulos, A., Robinson, E.C., Rueckert, D., Parisot, S., 2018. Human brain mapping: a systematic comparison of parcellation methods for the human cerebral cortex. Neuroimage 170, 5–30.

Ben Simon, E., Maron-Katz, A., Lahav, N., Shamir, R., Hendler, T., 2017. Tired and misconnected: a breakdown of brain modularity following sleep deprivation. Hum. Brain Mapp. 38 (6), 3300–3314.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34 (4), 537–541.

Biswal, B.B., Mennes, M., Zuo, X.-N., et al., 2010. Toward discovery science of human brain function. Proc. Natl. Acad. Sci. U. S. A. 107 (10), 4734–4739.

Brady Jr., R.O., Margolis, A., Masters, G.A., Keshavan, M., Ongur, D., 2017. Bipolar mood state reflected in cortico-amygdala resting state connectivity: a cohort and longitudinal study. J. Affect. Disord. 217, 205–209.

Brier, M.R., Thomas, J.B., Snyder, A.Z., et al., 2012. Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. J. Neurosci. 32 (26), 8890–8899.

Buckner, R.L., Snyder, A.Z., Shannon, B.J., et al., 2005. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J. Neurosci. 25 (34), 7709–7717.

Camchong, J., MacDonald 3rd, A.W., Bell, C., Mueller, B.A., Lim, K.O., 2011. Altered functional and anatomical connectivity in schizophrenia. Schizophr. Bull. 37 (3), 640–650.

Chai, X.J., Castanon, A.N., Ongur, D., Whitfield-Gabrieli, S., 2012. Anticorrelations in resting state networks without global signal regression. Neuroimage 59 (2), 1420–1428.

Chang, C., Liu, Z., Chen, M.C., Liu, X., Duyn, J.H., 2013. EEG correlates of time-varying BOLD functional connectivity. Neuroimage 72, 227–236.

Chang, C., Leopold, D.A., Scholvinck, M.L., et al., 2016. Tracking brain arousal fluctuations with fMRI. Proc. Natl. Acad. Sci. U. S. A. 113 (16), 4518–4523.

Chuah, L.Y., Dolcos, F., Chen, A.K., Zheng, H., Parimal, S., Chee, M.W., 2010. Sleep deprivation and interference by emotional distracters. Sleep 33 (10), 1305–1313.

Cirrito, J.R., Yamada, K.A., Finn, M.B., et al., 2005. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. Neuron 48 (6), 913–922.

Dai, X.J., Gong, H.H., Wang, Y.X., et al., 2012. Gender differences in brain regional homogeneity of healthy subjects after normal sleep and after sleep deprivation: a resting-state fMRI study. Sleep Med. 13 (6), 720–727.

De Havas, J.A., Parimal, S., Soon, C.S., Chee, M.W., 2012. Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance. Neuroimage 59 (2), 1745–1751.

Dennis, E.L., Thompson, P.M., 2014. Functional brain connectivity using fMRI in aging and Alzheimer's disease. Neuropsychol. Rev. 24 (1), 49–62.

Doran, S.M., Van Dongen, H.P., Dinges, D.F., 2001. Sustained attention performance during sleep deprivation: evidence of state instability. Arch. Ital. Biol. 139 (3), 253–267.

Drzezga, A., Becker, J.A., Van Dijk, K.R.A., et al., 2011. Neuronal dysfunction and disconnection of cortical hubs in non-demented subjects with elevated amyloid burden. Brain 134 (6), 1635–1646.

Duman, R.S., 2002. Pathophysiology of depression: the concept of synaptic plasticity. Eur. Psychiatry 17 (Suppl. 3), 306–310.

Erhardt, E.B., Rachakonda, S., Bedrick, E.J., Allen, E.A., Adali, T., Calhoun, V.D., 2011. Comparison of multi-subject ICA methods for analysis of fMRI data. Hum. Brain Mapp. 32 (12), 2075–2095.

Fornito, A., Zalesky, A., Breakspear, M., 2013. Graph analysis of the human connectome: promise, progress, and pitfalls. Neuroimage 80, 426–444.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102 (27), 9673–9678.

Fukunaga, M., Horovitz, S.G., van Gelderen, P., et al., 2006. Large-amplitude, spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep stages. Magn. Reson. Imaging 24 (8), 979–992.

Gao, L., Bai, L., Zhang, Y., et al., 2015. Frequency-dependent changes of local resting oscillations in sleep-deprived brain. PLoS One 10 (3), e0120323.

Gavrilescu, M., Rossell, S., Stuart, G.W., et al., 2010. Reduced connectivity of the auditory cortex in patients with auditory hallucinations: a resting state functional magnetic resonance imaging study. Psychol. Med. 40 (7), 1149–1158.

Goldstein, A.N., Walker, M.P., 2014. The role of sleep in emotional brain function. Annu. Rev. Clin. Psychol. 10, 679–708.

Gouras, G.K., Olsson, T.T., Hansson, O., 2015. Beta-amyloid peptides and amyloid plaques in Alzheimer's disease. Neurotherapeutics 12 (1), 3–11.

Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V., 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc. Natl. Acad. Sci. U. S. A. 101 (13), 4637–4642.

Hoptman, M.J., D'Angelo, D., Catalano, D., et al., 2010. Amygdalofrontal functional disconnectivity and aggression in schizophrenia. Schizophr. Bull. 36 (5), 1020–1028.

Hutchison, R.M., Womelsdorf, T., Allen, E.A., et al., 2013. Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage 80, 360–378.

Jack Jr., C.R., Knopman, D.S., Jagust, W.J., et al., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12 (2), 207–216.

Jiang, L., Zuo, X.N., 2016. Regional homogeneity: a multimodal, multiscale neuroimaging marker of the human connectome. Neuroscientist 22, 486–505.

Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiat. 72 (6), 603–611.

Kambeitz, J., Kambeitz-Ilankovic, L., Cabral, C., et al., 2016. Aberrant functional whole-brain network architecture in patients with schizophrenia: a meta-analysis. Schizophr. Bull. 42 (Suppl. 1), S13–S21.

Kang, D.W., Lee, C.U., Lim, H.K., 2017. Role of sleep disturbance in the trajectory of Alzheimer's disease. Clin. Psychopharmacol. Neurosci. 15 (2), 89–99.

Kaufmann, T., Elvsashagen, T., Alnaes, D., et al., 2016. The brain functional connectome is robustly altered by lack of sleep. Neuroimage 127, 324–332.

Kikuchi, M., Hirosawa, T., Yokokura, M., et al., 2011. Effects of brain amyloid deposition and reduced glucose metabolism on the default mode of brain function in normal aging. J. Neurosci. 31 (31), 11193–11199.

Klingner, C.M., Langbein, K., Dietzek, M., et al., 2014. Thalamocortical connectivity during resting state in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 264 (2), 111–119.

Kucyi, A., Davis, K.D., 2014. Dynamic functional connectivity of the default mode network tracks daydreaming. Neuroimage 100, 471–480.

Lei, Y., Shao, Y., Wang, L., et al., 2015. Altered superficial amygdala-cortical functional link in resting state after 36 hours of total sleep deprivation. J. Neurosci. Res. 93 (12), 1795–1803.

Lewis, C.M., Baldassarre, A., Committeri, G., Romani, G.L., Corbetta, M., 2009. Learning sculpts the spontaneous activity of the resting human brain. Proc. Natl. Acad. Sci. U. S. A. 106 (41), 17558–17563.

Liu, T.T., Nalci, A., Falahpour, M., 2017. The global signal in fMRI: nuisance or information? Neuroimage 150, 213–229.

Liu, X., de Zwart, J.A., Scholvinck, M.L., et al., 2018. Subcortical evidence for a contribution of arousal to fMRI studies of brain activity. Nat. Commun. 9 (1), 395.

Massar, S.A.A., Sasmita, K., Lim, J., Chee, M.W.L., 2018. Motivation alters implicit temporal attention through sustained and transient mechanisms: a behavioral and pupillometric study. Psychophysiology, e13275.

McAvoy, M.P., Tagliazucchi, E., Laufs, H., Raichle, M.E., 2018. Human non-REM sleep and the mean global BOLD signal. J. Cereb. Blood Flow Metab. https://doi.org/10.1177/0271678X18791070.

McEwen, B.S., 2006. Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. Metabolism 55 (10 Suppl. 2), S20–S23.

McKeown, M.J., Hansen, L.K., Sejnowski, T.J., 2003. Independent component analysis of functional MRI: what is signal and what is noise? Curr. Opin. Neurobiol. 13 (5), 620–629.

Meerlo, P., Havekes, R., Steiger, A., 2015. Chronically restricted or disrupted sleep as a causal factor in the development of depression. In: Meerlo, P., Benca, R.M., Abel, T. (Eds.), Sleep, Neuronal Plasticity and Brain Function. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 459–481.

Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn. Sci. 15 (10), 483–506.

Mormino, E.C., Smiljic, A., Hayenga, A.O., et al., 2011. Relationships between beta-amyloid and functional connectivity in different components of the default mode network in aging. Cereb. Cortex 21 (10), 2399–2407.

Nestler, E.J., Barrot, M., DiLeone, R.J., Eisch, A.J., Gold, S.J., Monteggia, L.M., 2002. Neurobiology of depression. Neuron 34 (1), 13–25.

Newman, M.E., 2004. Analysis of weighted networks. Phys. Rev. E Stat. Nonlin. Soft Matter Phys. 70 (5 Pt. 2), 056131.

Nilsonne, G., Tamm, S., Schwarz, J., et al., 2017. Intrinsic brain connectivity after partial sleep deprivation in young and older adults: results from the Stockholm sleepy brain study. Sci. Rep. 7 (1), 9422.

Olbrich, S., Mulert, C., Karch, S., et al., 2009. EEG-vigilance and BOLD effect during simultaneous EEG/fMRI measurement. Neuroimage 45 (2), 319–332.

Ong, J.L., Asplund, C.L., Chia, T.T., Chee, M.W., 2013. Now you hear me, now you don't: eyelid closures as an indicator of auditory task disengagement. Sleep 36 (12), 1867–1874.

Ong, J.L., Kong, D., Chia, T.T., Tandi, J., Thomas Yeo, B.T., Chee, M.W., 2015. Co-activated yet disconnected-neural correlates of eye closures when trying to stay awake. Neuroimage 118, 553–562.

Palaniyappan, L., Liddle, P.F., 2012. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. J. Psychiatry Neurosci. 37 (1), 17–27.

Patanaik, A., Tandi, J., Ong, J.L., Wang, C., Zhou, J., Chee, M.W.L., 2018. Dynamic functional connectivity and its behavioral correlates beyond vigilance. Neuroimage 177, 1–10.

Pedersen, M., Omidvarnia, A., Zalesky, A., Jackson, G.D., 2018. On the relationship between instantaneous phase synchrony and correlation-based sliding windows for time-resolved fMRI connectivity analysis. Neuroimage 2018 (181), 85–94.

Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., Mechelli, A., 2011. Dysconnectivity in schizophrenia: where are we now? Neurosci. Biobehav. Rev. 35 (5), 1110–1124.

Poudel, G.R., Innes, C.R.H., Jones, R.D., 2018. Temporal evolution of neural activity and connectivity during microsleeps when rested and following sleep restriction. Neuroimage 174, 263–273.

Quevenco, F.C., Preti, M.G., van Bergen, J.M., et al., 2017. Memory performance-related dynamic brain connectivity indicates pathological burden and genetic risk for Alzheimer's disease. Alzheimers Res. Ther. 9 (1), 24.

Rabiner, L., 1989. A tutorial on hidden markov models and selected applications in speech recognition. Proc. IEEE 77 (2), 257–286.

Raichle, M.E., Snyder, A.Z., 2007. A default mode of brain function: a brief history of an evolving idea. Neuroimage 37 (4), 1083–1090. (discussion 1097–1089).

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52 (3), 1059–1069.

Samann, P.G., Tully, C., Spoormaker, V.I., et al., 2010. Increased sleep pressure reduces resting state functional connectivity. MAGMA 23 (5–6), 375–389.

Samann, P.G., Wehrle, R., Hoehn, D., et al., 2011. Development of the brain's default mode network from wakefulness to slow wave sleep. Cereb. Cortex 21 (9), 2082–2093.

Sbardella, E., Tona, F., Petsas, N., et al., 2015. Functional connectivity changes and their relationship with clinical disability and white matter integrity in patients with relapsing-remitting multiple sclerosis. Mult. Scler. 21 (13), 1681–1692.

Shao, Y., Lei, Y., Wang, L., et al., 2014. Altered resting-state amygdala functional connectivity after 36 hours of total sleep deprivation. PLoS One 9 (11), e112222.

Shine, J.M., Koyejo, O., Bell, P.T., Gorgolewski, K.J., Gilat, M., Poldrack, R.A., 2015. Estimation of dynamic functional connectivity using multiplication of temporal derivatives. Neuroimage 122, 399–407.

Shokri-Kojori, E., Wang, G.J., Wiers, C.E., et al., 2018. Beta-amyloid accumulation in the human brain after one night of sleep deprivation. Proc. Natl. Acad. Sci. U. S. A. 115 (17), 4483–4488.

Smith, S.M., Nichols, T.E., 2018. Statistical challenges in "big data" human neuroimaging. Neuron 97 (2), 263–268.

Smith, S.M., Fox, P.T., Miller, K.L., et al., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. 106 (31), 13040–13045.

Sporns, O., 2013. Network attributes for segregation and integration in the human brain. Curr. Opin. Neurobiol. 23 (2), 162–171.

Sporns, O., Betzel, R.F., 2016. Modular brain networks. Annu. Rev. Psychol. 67 (1), 613–640.

Taghia, J., Ryali, S., Chen, T., Supekar, K., Cai, W., Menon, V., 2017. Bayesian switching factor analysis for estimating time-varying functional connectivity in fMRI. Neuroimage 155, 271–290.

Tagliazucchi, E., Laufs, H., 2014. Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. Neuron 82 (3), 695–708.

Tagliazucchi, E., van Someren, E.J.W., 2017. The large-scale functional connectivity correlates of consciousness and arousal during the healthy and pathological human sleep cycle. Neuroimage 160, 55–72.

Thompson, G.J., Magnuson, M.E., Merritt, M.D., et al., 2013. Short-time windows of correlation between large-scale functional brain networks predict vigilance intraindividually and interindividually. Hum. Brain Mapp. 34 (12), 3280–3298.

Vincent, J.L., Patel, G.H., Fox, M.D., et al., 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447 (7140), 83–86.

Vyazovskiy, V.V., Olcese, U., Hanlon, E.C., Nir, Y., Cirelli, C., Tononi, G., 2011. Local sleep in awake rats. Nature 472 (7344), 443–447.

Wang, K., Liang, M., Wang, L., et al., 2007. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. Hum. Brain Mapp. 28 (10), 967–978.

Wang, L., Hermens, D.F., Hickie, I.B., Lagopoulos, J., 2012. A systematic review of resting-state functional-MRI studies in major depression. J. Affect. Disord. 142 (1–3), 6–12.

Wang, C., Ong, J.L., Patanaik, A., Zhou, J., Chee, M.W., 2016. Spontaneous eyelid closures link vigilance fluctuation with fMRI dynamic connectivity states. Proc. Natl. Acad. Sci. U. S. A. 113 (34), 9653–9658.

Wig, G.S., Schlaggar, B.L., Petersen, S.E., 2011. Concepts and principles in the analysis of brain networks. Ann. N. Y. Acad. Sci. 1224, 126–146.

Wig, G.S., Laumann TO, Petersen, S.E., 2014. An approach for parcellating human cortical areas using resting-state correlations. Neuroimage 93 (Pt. 2), 276–291.

Wilhelm, B., Wilhelm, H., Ludtke, H., Streicher, P., Adler, M., 1998. Pupillographic assessment of sleepiness in sleep-deprived healthy subjects. Sleep 21 (3), 258–265.

Wong, C.W., DeYoung, P.N., Liu, T.T., 2016. Differences in the resting-state fMRI global signal amplitude between the eyes open and eyes closed states are related to changes in EEG vigilance. Neuroimage 124 (Pt. A), 24–31.

Xu, H., Shen, H., Wang, L., et al., 2018a. Impact of 36h of total sleep deprivation on resting-state dynamic functional connectivity. Brain Res. 1688, 22–32.

Xu, H., Su, J., Qin, J., et al., 2018b. Impact of global signal regression on characterizing dynamic functional connectivity and brain states. Neuroimage 173, 127–145.

Yeo, B.T., Tandi, J., Chee, M.W., 2015. Functional connectivity during rested wakefulness predicts vulnerability to sleep deprivation. Neuroimage 111, 147–158.

Zang, Y.F., He, Y., Zhu, C.Z., et al., 2007. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev. 29 (2), 83–91.

Zhou, J., Seeley, W.W., 2014. Network dysfunction in Alzheimer's disease and frontotemporal dementia: implications for psychiatry. Biol. Psychiatry 75 (7), 565–573.

Zhou, J., Greicius, M.D., Gennatas, E.D., et al., 2010. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. Brain 133 (5), 1352–1367.

Zhou, J., Liu, S., Ng, K.K., Wang, J., 2017. Applications of resting-state functional connectivity to neurodegenerative disease. Neuroimaging Clin. N. Am. 27 (4), 663–683.

Zou, Q.H., Zhu, C.Z., Yang, Y., et al., 2008. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J. Neurosci. Methods 172 (1), 137–141.