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Biophysical Modulations of Functional Connectivity

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Abstract

Resting-state low frequency oscillations have been detected in many functional magnetic resonance imaging (MRI) studies and appear to be synchronized between functionally related areas. Converging evidence from MRI and other imaging modalities suggest that this activity has an intrinsic neuronal origin. Multiple consistent networks have been found in large populations, and have been shown to be stable over time. Further, these patterns of functional connectivity have been shown to be altered in healthy controls under various physiological challenges. This review will present the biophysical characterization of functional connectivity, and examine the effects of physical state manipulations (such as anesthesia, fatigue, and aging) in healthy controls.

Key words: aging; anesthesia; connectivity; fatigue; functional magnetic resonance imaging; modulation; resting-state

Introduction

Recent studies in functional magnetic resonance imaging (fMRI) have shown slowly varying time course fluctuations in resting-state data that are temporally correlated between functionally related areas. These fluctuations agree with the concept of functional connectivity: a descriptive measure of spatiotemporal correlations between spatially distinct regions of cerebral cortex (Friston et al., 1993). First shown in the fMRI literature by Biswal et al. (1995), these low-frequency oscillations have been shown to exist in the motor, auditory, visual, sensorimotor, and language systems, among others (Biswal and Ulmer, 1999; Cordes et al., 2000; Hampson et al., 2002; Hyde and Biswal, 2000; Lowe et al., 1998; Xiong et al., 1999). More recently, it has been investigated in the so-called "default-mode" network (Greicius et al., 2003; Raichle et al., 2001).

Studies examining the frequency characteristics have found the primary signal to lie under 0.1 Hz, in the frequency band of the blood oxygen level dependent (BOLD) response, with possible noise sources such as cardiac- and respiratory-induced noise having a higher frequency response, if sampled adequately (Cordes et al., 2000; De Luca et al., 2006). Further, studies employing multi-echo sequences have examined the T2* dependence of functional connectivity patterns. Our group found the linear echo-time dependence of functional connectivity patterns in the motor cortex to agree with the first-order BOLD signal equation, in the same way as task-induced activation (Peltier and Noll, 2002). Recently, Bianciardi et al. (2009) used multi-echo data at 7T to examine the relative contributions of possible confounds to the connectivity patterns. They found that after removing confounds, the dominant signal was from spontaneous activity, especially at the region of interest (ROI) level. Thus, both functional connectivity and "regular" task activation seem to arise from the same BOLD-related origins.

A limitation of BOLD fMRI is that it is an indirect measure of neuronal activity. However, research using other imaging modalities suggests that functional connectivity has neuronal origins. For example, in perfusion imaging, functional connectivity patterns have been found using both arterial spin labeling (Chuang et al., 2008) and $CMRO_2$ (Wu et al., 2009). Studies investigating resting correlates using electroencephalogram (EEG) have found that the different resting-state networks can be characterized by their corresponding EEG signatures (Laufs et al., 2003; Mantini et al., 2007). Further, recent animal studies have demonstrated coupling between the resting-state BOLD fluctuations and local neuronal activity employing simultaneous fMRI and neurophysiological recording (Scholvinck et al., 2010; Shmuel and Leopold, 2008), and spatiotemporal organization of resting-state neuronal activity using voltage-sensitive dye imaging (Kenet et al., 2003; Mohajerani et al., 2010). Thus, converging imaging evidence suggests that resting-state functional connectivity has underlying neuronal origins.

Reproducibility studies have shown resting patterns to be consistent over large numbers of healthy controls, repeated over time (Biswal et al., 1997; Shehzad et al., 2009; Van Dijk et al., 2010). This stability allows investigation of changes in resting-state patterns between controls and patients. Several

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recent studies have further shown decreased low-frequency correlations in pathological states such as callosal agenesis (Lowe et al., 1997) or Alzheimer's disease (Supekar et al., 2008), where there can be a disruption or degradation of the physical connections in the white matter. Further, resting-state functional MRI has shown differences in a wide variety of patient populations, such as depression (Berman et al., 2010), autism (Monk et al., 2009), and schizophrenia (Lynall et al., 2010). Low-frequency functional connectivity is thus important as a potential indicator of regular neuronal activity within the brain.

Another avenue of investigation is how the functional connectivity patterns change over time in a healthy brain, in response to internal or external modulation. This review will explore the change in resting connectivity under a variety of physiological changes, in the short term (fatigue, learning), medium term (sleep, anesthesia), and long term (development and aging). Finally, some future directions will be discussed.

Physiological Modulation in the Short Term

The resting-state activity of the brain is a dynamic, not static, entity. The evolving brain state may be influenced by its internal and external stimulus. It has been shown that prior cognitive states can influence subsequent "resting-state" activity (Waites et al., 2005). Experimental manipulations, as well, may modulate connectivity in the short term. For example, Napadow et al. (2008) examined resting-state data before and after acupuncture, and found increased connectivity with pain and memory regions following real, but not sham, acupuncture. This suggests that resting fMRI in the short term may exhibit change due to prior activity. Here, we examine short-term modulation in the specific cases of fatigue and learning.

Fatigue

Prolonged voluntary muscle fatigue can induce substantial neural signal changes in a number of primary, secondary, and association cortical areas (Liu et al., 2003). The brain can experience a disrupted process not only in processing a large amount of sensory (fatigue) information, but also in continuously forming new commands to drive the fatiguing muscle to maintain desired muscle output. It has been observed that the level of activity of the right and left primary motor cortices can increasingly differ during a repetitive unimanual task (Liu et al., 2003), indicating a fatigue-related disassociation of the two hemispheres. It is also known that recovery from fatigue does not occur immediately (Enoka and Stuart, 1992).

It was investigated whether the neural effects of muscle fatigue persisted after a fatiguing task, using resting-state fMRI (Peltier et al., 2005a). Resting-state acquisitions were acquired before and after a unimanual fatigue task (20 min of repetitive hand clenching) for eight subjects. The interhemispheric cross-correlation was calculated for voxels in the primary motor cortices (see Peltier et al., 2005a for more details). We observed that the resting-state time courses of the primary motor cortices are more dissimilar after the fatigue task (Fig. 1A). Moreover, the amount of significant interhemispheric correlations decreased significantly (Fig. 1B, C). Following the fatigue task, there was a 72% reduction of significant motor interhemispheric correlations ($p < 0.05$) over all subjects. This demonstrates that resting-state functional connectivity can reflect short-term changes in the state of neural networks.

Learning

Another short-term process that can be investigated with resting-state functional connectivity is learning (e.g., motor learning, perceptual learning). Neural plastic effects induced by training can result in modifications to the brain's function, which can persist after the training itself (Schwartz et al., 2002). The cognitive effects of learning can thus potentially alter resting-state functional connectivity, even after training has ended.

Dynamic changes in connectivity have further been seen in motor or visual learning studies. Albert et al. (2009) acquired resting-state scans before and after an 11 min motor session. Dummy tasks were used in between the motor task and the second resting-state scan. They demonstrated enhancement in frontoparietal circuit following motor learning, but not motor performance. Lewis et al. (2009) showed changes following visual perceptual learning in the visual cortex and frontoparietal areas involved in spatial attention (Fig. 2). By acquiring resting-state data before and after training on a visual shape-identification task constrained to one visual quadrant, they found that resting-state changes between the visual cortex and frontoparietal areas correlated with the degree of perceptual learning. In addition, they found that the effects could extend to visual areas not involved in the training. Taken together, these studies demonstrate that the prolonged effects of processes such as learning may be examined with resting-state functional connectivity.

Physiological Modulation in the Medium Term

Resting-state patterns are hypothesized to relate to neuronal activity, but their full relationship to conscious processes is not known (Fukunaga et al., 2006). Toward this end, several studies have investigated the effects of varying states of consciousness, including sleep (Fukunaga et al., 2006; Horovitz et al., 2008; Larson-Prior et al., 2009; Spoormaker et al., 2010), sedation and anesthesia (Alkire et al., 2000; Antognini et al., 1997; Boveroux et al., 2010; Kiviniemi et al., 2000; Martuzzi et al., 2010; Peltier et al., 2005b; Ramani et al., 2007; Schrouff et al., 2011), and vegetative states (Boly et al., 2004; Owen et al., 2006). In this section, sleep and anesthesia will be discussed, as reversible examples of physiological modulation in the medium term.

Sleep

Sleep is a rapidly reversible system-level process, characterized by loss of motor responsiveness, loss of consciousness, and reduced metabolism (Braun et al., 1997; Iber et al., 2007). These suppressive effects are also accompanied by increased memory consolidation (Stickgold, 2005). Stages of sleep include rapid eye movement (REM) and non-REM, which is further classified into multiple sleep stages based on EEG, electrooculography (EOG), and electromyography (EMG) activity (Iber et al., 2007). The reduced states of arousal in sleep afford an opportunity to investigate resting-state fluctuations in the absence of conscious activity (Fukunaga et al., 2006; Horovitz et al., 2008), as well as investigating possible mechanisms of sleep-induced loss of consciousness.

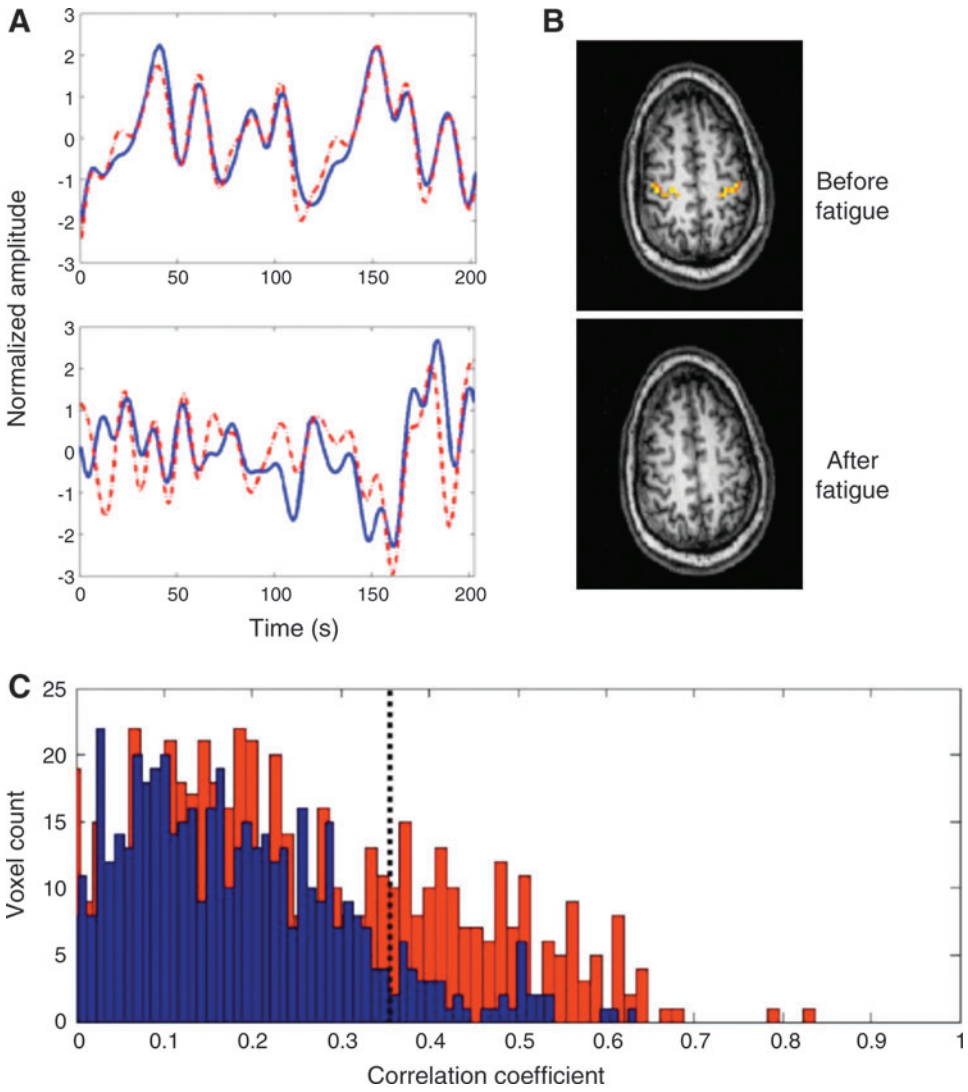

FIG. 1. Example of short-term modulation of functional connectivity after motor fatigue. **(A)** Average time courses for the left (blue, solid) and right (red, dashed) motor cortices for a typical subject, before (top) and after (bottom) fatigue. **(B)** The mean interhemispheric correlation for each voxel in the motor cortex for a typical subject, before and after fatigue. **(C)** Histogram of the mean interhemispheric correlation values over all subjects ($n = 8$). The dashed line corresponds to the significant threshold of $p < 0.05$. The number of significant correlations decreases after the fatigue task. Adapted from Peltier et al. (2005a).

Several studies have examined functional connectivity during awake and sleep states using simultaneous EEG/fMRI. This allowed simultaneous characterization of the sleep state while acquiring resting-state fMRI data. Fukunaga et al. (2006) found that the resting-state visual network persisted during sleep, and that the levels of signal fluctuation were higher in sleep compared to the awake state, and comparable to levels during visual stimulation. Horovitz et al. (2008) found that the resting-state default-mode activity persisted during light sleep (Fig. 3A). Further, Larson-Prior et al. (2009) found that connectivity in six resting-state networks (attention, default, executive, somatomotor, visual, and auditory) was maintained between awake and light sleep (Fig. 3B). In a recent study, Spoormaker et al. (2010) examined connectivity across sleep stages, and found that there was a loss in thalamic connectivity in moving from wake to sleep states, and a loss in general cortical connectivity in slow-wave sleep. This may help inform further investigations of consciousness.

These studies suggest that the resting-state activity, instead of being undirected conscious thought, does not require active cognitive processes, instead perhaps serving a critical role in cortical system integrity maintenance.

Anesthesia

Anesthesia is a (hopefully) reversible state of central nervous system suppression. However, the mechanism of anesthesia is not completely understood. Part of the problem is that it is not a uniform entity, and has several physiological endpoints of interest, including ablation of motor responses, memory function, and consciousness (Veselis, 2001). Both the regional suppressive effects on individual brain structures, as well as the global disconnective effects between brain networks, need to be explained (Veselis et al., 2002; White and Alkire, 2003).

Previous studies involving anesthesia-induced unconsciousness have suggested that disrupted thalamocortical networks are a central mechanism (Alkire et al., 2000; Ries and Puil, 1999). White and Alkire (2003) found reduced thalamic activity using halothane and isoflurane. However, Långsjö et al. (2004) found an increase in activity in the thalamus using ketamine as the anesthetic agent. These studies may support a hypothesis that disruption of the thalamocortical network plays a central role in anesthesia-induced unconsciousness.

In our previous work (Peltier et al., 2005b), we examined resting-state functional connectivity at different concentrations

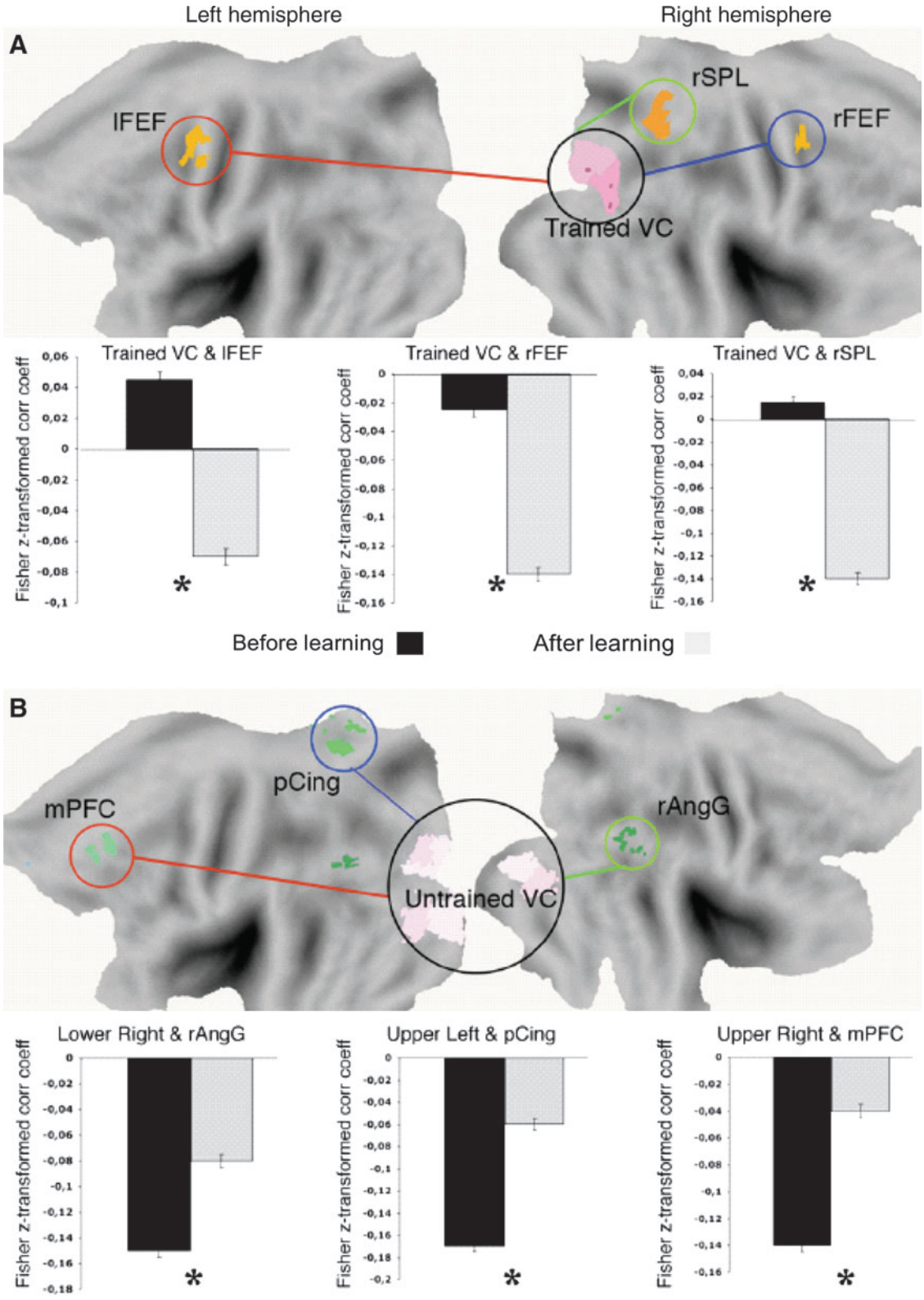

FIG. 2. Modulation of spontaneous functional connectivity after perceptual learning. The task involved training on a shape-identification task constrained to one visual quadrant. Flattened brain representation with ROIs in trained visual cortex and dorsal attention network **(A)** and in untrained visual cortex and default network **(B)**. Bar graphs report Pearson correlation coefficients between trained visual cortex and dorsal attention ROIs and untrained visual cortices and default network ROIs before (black) and after (gray) perceptual learning. Two-tail Student's *t*-test, $p < 0.05$; error bars ± SEM. Adapted from Lewis et al. (2009). The asterisk denotes significant difference in the graphed data.

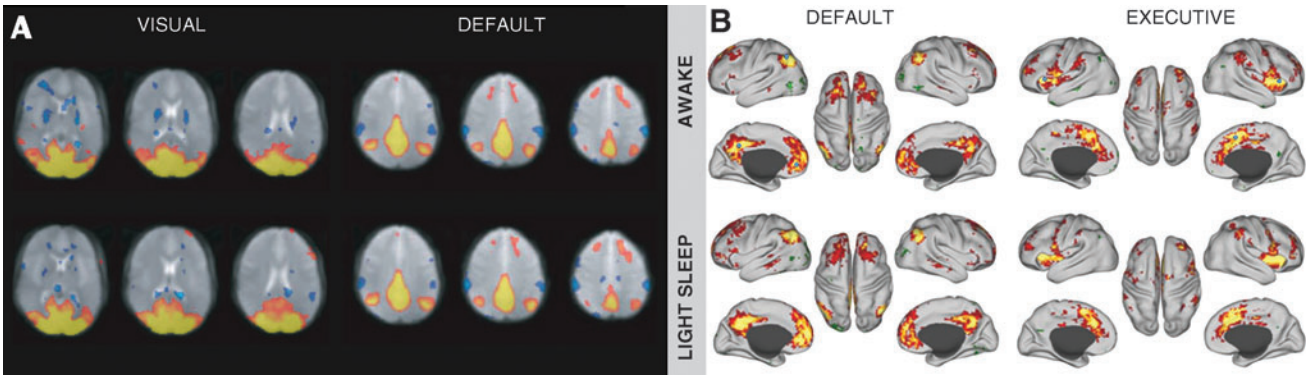

FIG. 3. Comparison of resting-state connectivity maps in awake (top) and light sleep (bottom) states. **(A)** Statistical composite maps showing temporal correlation with seed time courses in the visual cortex (visual) and posterior cingulate (default). Adapted from Horovitz et al. (2008). **(B)** Conjunction analysis of cognitive network seed correlations; locations of seed ROIs are located by blue circles. Adapted from Larson-Prior et al. (2009).

of sevoflurane (Fig. 4). By employing gradations of anesthetic influence, we were able to explore the effect of anesthesia on baseline, task-independent connectivity. In particular, changes in the functional connectivity of the motor network were analyzed. We observed a reliable resting-state motor network in the awake condition, as expected from previous studies (Cordes et al., 2000; Lowe et al., 1998; Peltier and Noll, 2002). In the deep anesthetic state, the network was first completely attenuated, and then, after recovering to the light state, the network response was confined to the hemisphere where the motor seed was placed. The observed reduction and recovery of functional connectivity complements previous work by Biswal et al. (1997) showing reversible reductions of functional connectivity during hypercapnia. The loss of temporal synchronization between motor cortices may impair motor performance (Serrien and Brown, 2004), and help to explain the suppressive effect of sevoflurane anesthesia on motor responsiveness (Galinkin et al., 1997; Ibrahim et al., 2001; Serrien and Brown, 2004). The circumscribed functional network during the light anesthetic concentration, as opposed to a global integrated network in the awake state, is reminiscent of reports on anterior–posterior dissociations of synchronized brain activity as measured by surface EEG (Lee et al., 2009).

These studies demonstrate that functional connectivity can be studied under anesthesia, and may be associated with changes in consciousness or network disassociation. Animal studies have also demonstrated coherent resting-state fMRI activity that may be altered under anesthesia (Moeller et al., 2009; Vincent et al., 2007). An open area of investigation is the effect of different anesthetic agents and/or different concentration levels. Results using sevoflurane, propofol, and so on, in humans have varied in the degree and direction of connectivity modulation (Table 1). These varied agents may have differing central effects and may be dose dependent (Alkire et al., 2000; Ries and Puil, 1999; Veselis et al., 2002), and thus modulate connectivity differently. Careful examination of agent type and dosage level will help to elucidate this matter further. Multimodal investigations using EEG and CBF

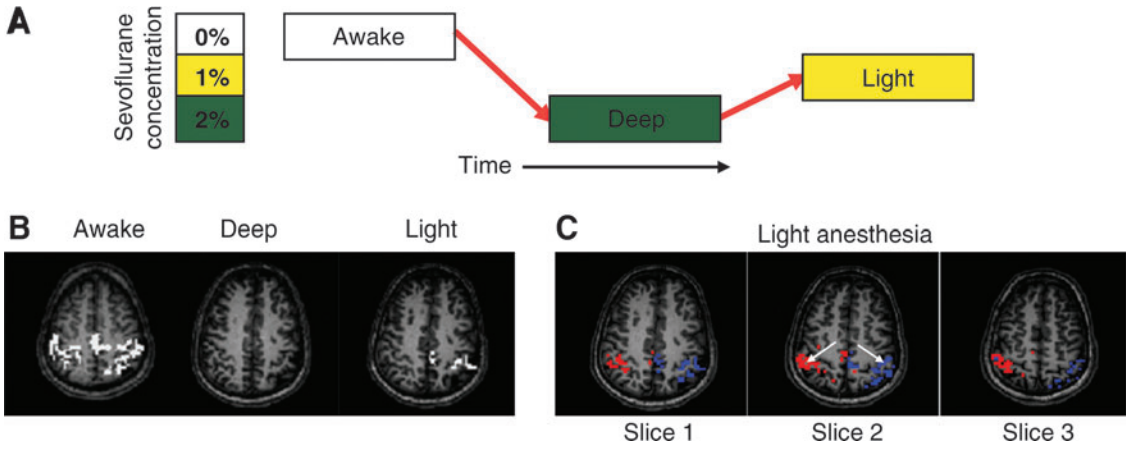

FIG. 4. Modulation of functional connectivity under graded levels of sevoflurane anesthesia. **(A)** Experimental paradigm; subjects had resting-state fMRI scan in awake state, followed by deep state (2% sevoflurane), followed by light state (1% sevoflurane). Subjects were held constant at each anesthetic level for 15 min before fMRI acquisition. **(B)** Functional connectivity results in the motor cortex under the awake, deep, and light states. **(C)** Functional connectivity results for three contiguous slices in a representative subject under light anesthesia, for left (red) and right (blue) motor cortex seed ROIs. Arrows indicate the location of the seed ROIs. Adapted from Peltier et al. (2005b). fMRI, functional magnetic resonance imaging.

Table 1. Resting-State Functional Magnetic Resonance Imaging Studies Examining the Effects of Anesthesia in Humans

Author	*Anesthetic*	*Findings*
Schrouff et al. (2011)	1.5–2.8 μg/mL propofol	Total integration within brain networks was significantly lower during deep sedation as compared to resting-state wakefulness.
Boveroux et al. (2010)	1.5–2.8 μg/mL propofol	Decrease in consciousness linearly correlated with decreased corticocortical and thalamocortical connectivity in frontoparietal networks.
Martuzzi et al. (2010)	1% end-tidal sevoflurane	fc-fMRI patterns did not significantly differ in sensory cortex and in the DMN, whereas, in high-order cognitive regions (memory and pain circuits), it was significantly altered by anesthesia.
Peltier et al. (2005b)	1% and 2% end-tidal sevoflurane	A network involving the primary motor cortex, sensorimotor area, and SMA was found in the awake state. Connectivity of this network was diminished under light anesthesia and virtually absent under deep anesthesia.
Kiviniemi et al. (2000)	6.3 mg/kg/h intravenous thiopental boluses	Concentrated signal fluctuations were observed near the primary sensory areas. Thiopental was suspected to cause an increase in the amplitude and reduction in the frequency of these fluctuations.

fMRI, functional magnetic resonance imaging.

measures, while controlling for physiological variables such as blood pressure (Kannurpatti et al., 2003), can also help ascertain the underlying mechanism of anesthesia (Liu et al., 2011). For further review of the effects of anesthesia on functional connectivity, please see Nallasamy and Tsao (2011).

Physiological Modulation in the Long Term

When considering functional and structural connectivity in younger and older subjects, brain maturation needs to be considered as a factor. Changing white matter and gray matter volumes in early childhood, during adolescence, and in old age can alter the functional and structural networks, with consequent possible age-dependent differences between target groups of interest. It has also been shown that structural and functional connectivity are correlated; a high degree of structural connectivity can imply a higher degree of functional connectivity (Honey et al., 2009; Koch et al., 2002; Skudlarski, et al., 2008; see also Honey et al., 2010 for review). In this section, the effects of development and aging on the resting-state networks are considered.

Development

Studies investigating human cerebral development have investigated white matter structural changes that occur

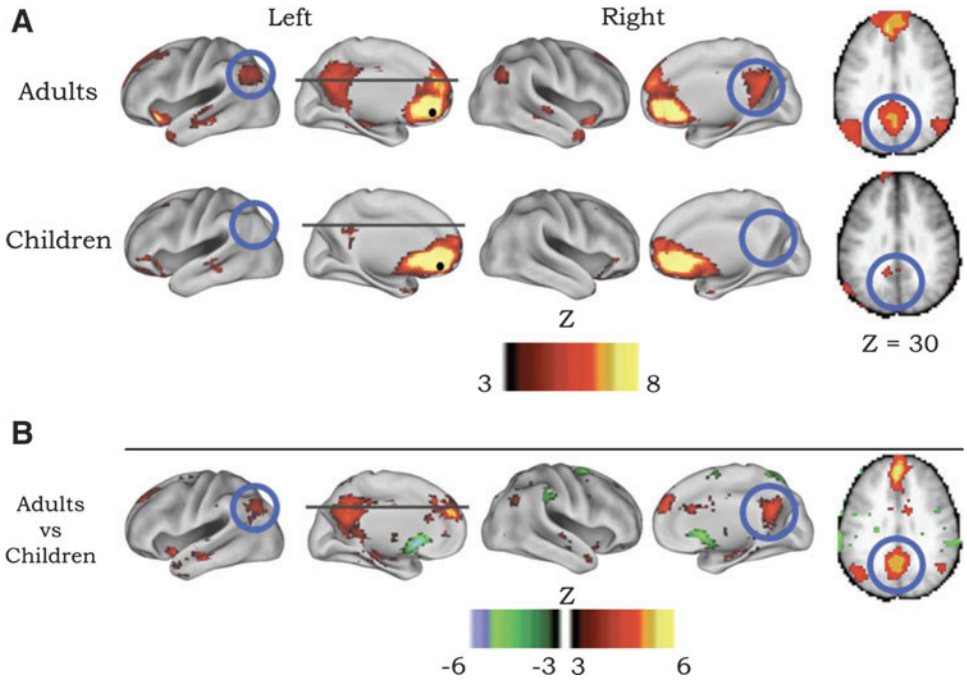

FIG. 5. Comparison of resting-state functional connectivity maps in adults and children. Seed region (solid black circle) in mPFC (ventral: -3, 39, -2). **(A)** Adult connectivity pattern exhibits expected response in default-mode network. However, the connectivity map in children significantly deviates from that of the adults. Functional connections with regions in the posterior cingulate and lateral parietal regions (highlighted with blue open circles) are present in the adults but absent in children. **(B)** These qualitative differences between children and adults are confirmed by the direct comparison (random effects) between adults and children. mPFC (ventral) functional connections with the posterior cingulate and lateral parietal regions are significantly stronger in adults than children. Adapted from Fair *et al.* (2008).

prior to adulthood. White matter volume increases approximately linearly with age until early adulthood, while gray matter volume increases into adolescence, then decreases postpubescence into adulthood (Gogtay et al., 2004; Sowell et al., 2003), with total cerebral volume similar in adults and adolescents (Giedd, 2004; Giedd et al., 1999). These structural changes appear to be region specific, occurring with differing temporal courses across adolescence, with the frontal lobes maturing later than other cortical regions (Romine and Reynolds, 2005). The observed differences arise due to multiple processes including loss of synapses, increases in myelination, and changes in receptor density (e.g., glutamate receptors in the prefrontal cortex) (Giedd et al., 1999; Spear, 2000). In addition, diffusion tensor imaging has demonstrated changes in white matter microstructure (i.e., increased density) with increasing age (Barnea-Goraly et al., 2005; Schneider et al., 2004; Snook et al., 2005).

The developing brain thus has dynamic changes in the underlying structural connectivity that may alter the activity of resting-state networks. Several studies have started to investigate effects of development using fMRI resting-state connectivity. Fransson et al. (2007) found incomplete default-mode networks in infants. Fair et al. (2008) investigated the default-mode network in children of ages 7–9 and in adults of ages 19–31. They found that the network is only loosely connected in children, while being highly integrated in the adult population (Fig. 5). Both these studies indicate a developmental effect on the resting-state brain. Even further, Dosenbach et al. (2010) used resting-state data from over 200 subjects to predict physical age from the resting-state data. Using multivariate pattern analysis, they achieved 92% accuracy in classifying children from adults, controlling for brain volume and movement, with brain maturity being predicted by weakening of short-range connections between functional networks, and strengthening within networks. This pattern of network "pruning" and consolidation with increasing age may also be accompanied by a reduction in power of the resting-state fluctuations (Littow et al., 2010).

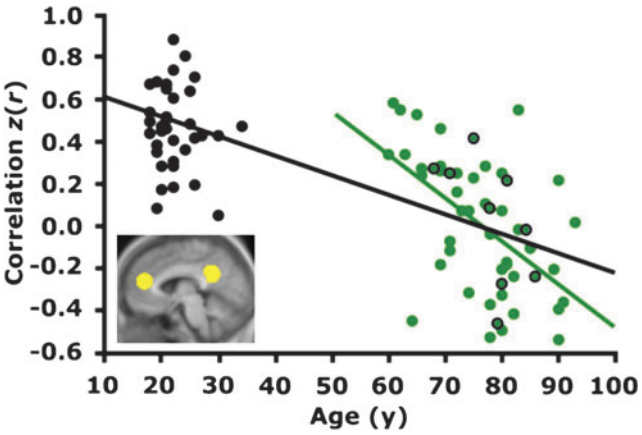

FIG. 6. Reduction of anterior to posterior functional correlations with aging. The time course within the medial prefrontal cortex (mPFC) was correlated with the time course within the posterior cingulate/retrosplenial cortex (pC/rsp) for young (black) and old (green) participants. The resulting z-transformed correlation coefficient z(r) for each participant is plotted against age. The black regression line, shown for illustrative purposes only, indicates a strong negative relationship between anterior-posterior functional correlations and age across both groups. The green regression line indicates a negative relationship with age in the older group alone ($r = -0.53$, $p < 0.001$). Green data points outlined in black represent individuals without amyloid beta deposition as determined by positron emission tomography. Adapted from Andrews-Hanna et al. (2007).

Aging

Cortical aging brings reductions in memory, inhibitory control, and processing speed. These may be the results of neurotransmitter receptor depletion, gray matter atrophy, and white matter deterioration (Reuter-Lorenz and Cappell, 2008). Gray matter decreases with age, with regionally variant losses, with increased reductions in the frontal lobes (Good et al., 2001; Jernigan et al., 2001; Raz et al., 1997). Age-associated white matter loss and/or demyelination can also lead to cognitive decline (O'Sullivan et al., 2001; Pfefferbaum and Sullivan, 2004).

Functional MRI aging studies have begun to apply MR connectivity to examine age-related declines. Andrews-Hanna et al. (2007) showed reductions in the default-mode network and dorsal attention network during a semantic task in older subjects, compared to younger subjects (Fig. 6). These reductions were associated with white matter degradation and reduced functional performance, and were present even in those older subjects screened against having preclinical Alzhiemer's disease. Following this, Damoiseaux et al. (2008) reported reduced activity in the default-mode network for older versus younger subjects. In addition, they correlated this reduction with age and reduced processing speed in the older subjects. Langan et al. (2010) demonstrated increased interhemispheric connectivity in the bilateral motor network. This correlated with increased bilateral recruitment during a motor task in older adults, suggesting loss of interhemispheric inhibition (please see Fling et al., 2011, for further discussion). These studies suggest that alterations to brain network connectivity may play an important role in gauging the effect of physical aging.

Discussion

The physiological manipulations discussed in this review have modulations of functional connectivity over a range of time scales. It is likely that the underlying biophysical mechanism in each case may be different. In the short term, tasks such as fatigue and learning may affect cortical excitability, which in turn may suppress or enhance network communication (Lewis et al., 2009; Peltier et al., 2005a). The medium-term effects of anesthesia can involve neural activity, metabolism, and neurovascular coupling (Liu et al., 2011; Williams et al., 2010), leading to both suppressive and disconnective effects on functional networks (Alkire et al., 2000; Peltier et al., 2005b). Finally, the effects of development and aging may reflect the long-term changes in white matter connectivity. Further work may better define the time signature of these different biophysical processes, and their resultant effect on spontaneous functional connectivity patterns.

In addition to time-dependent signals of interest, there are also potential time-varying confounds in resting-state functional MRI. Cardiac- and respiration-induced variations can

cause artifacts in resting-state analyses (Birn et al., 2006). Changes in blood pressure can also alter the resting-state fluctuations (Kannurpatti et al., 2003). In addition, time-varying psychological processes such as mental fatigue should be considered when designing resting-state experiments.

Resting-state functional connectivity is an emergent field, with continual refinement of techniques. Besides the seed correlation method that is used in a large number of studies, data-driven approaches can also be used to detect resting-state networks with reduced user bias (Beckmann and Smith, 2004; Calhoun et al., 2008; Peltier et al., 2003). Additionally, new acquisitions that can acquire brain volumes with sub-second TRs can also help with separating out physiological noise, as well as acquire data with greater temporal degrees of freedom (Feinberg et al., 2010). The dynamic nature of functional connectivity networks may also be exploited further. As noted in Chang and Glover (2009), functional networks are a dynamic entity, with temporal variations and changing spatial associations over the time course of an fMRI scan. Applying real-time and pattern classification approaches (LaConte et al., 2005, 2007) in the monitoring of these dynamic changes may help to explore the full range of resting-state activity. Advances in all of these areas will help to increase the sensitivity and accuracy of resting-state analyses.

Conclusion

Resting-state MRI functional connectivity seems to arise from ongoing spontaneous brain activity; thus, low-frequency functional connectivity is important as an indicator of normal neuronal activity. This review has dealt with physiologic changes in functional connectivity in healthy brains, and demonstrated that resting-state connectivity can monitor physiological changes in the short, medium, and long term. Application of these same techniques to patient populations and animal studies can help develop to better characterize disease states, functional loss and recovery, and develop predictive imaging biomarkers of disease states (Craddock et al., 2009).

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Author Disclosure Statement

The authors have no conflicts of interest to declare.

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