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REVIEW ARTICLE

A historical perspective on the evolution of resting-state functional connectivity with MRI

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Abstract In this review article, I discuss initial and recent studies of the assessment of functional connectivity in the human brain using low-frequency BOLD fluctuations in the resting state. By putting the studies in their historical context, the goal is to give the reader an appreciation of the evolution of the field and the pivotal events and studies that have led to the widespread acceptance of the method as a neuroscience tool for investigating functional connectivity in the human brain.

Keywords Functional connectivity · Resting state · fMRI · Anatomic connectivity · Default mode

Introduction

It is not the intent of this article to provide an exhaustive review of the resting-state fMRI literature. Indeed, as will be discussed at the end of this article, this has become impossible to do given the enormous amount of activity going on in this field currently. Rather, the goal of this article is to give a historical overview of the evolution of resting-state fMRI as a neuroimaging technique and attempt to give some insight into its gradual acceptance in the field of neuroscience.

Observations of the existence of colored "noise" in BOLD-weighted data date to almost the inception of fMRI. The usual citations for these observations are from the proceedings of the 1992 SMRM meeting, in particular by Robert Weisskoff et al. and Peter Jezzard et al. [1,2]. The observed color was attributed largely to what is now referred to as "physiologic noise" and was thought to be largely cardiac and respiratory related.

While studying these background effects in fMRI, Biswal and colleagues were investigating methods to remove the effects of cardiac and respiratory fluctuations in fMRI data (this led to a 1996 MRM paper on digital filtering of fMRI data [3]). In the process, they discovered that, even after filtering out cardiac and respiratory direct effects, interesting, functionally relevant spatiotemporal patterns were still present in rapidly sampled BOLD- weighted data [4].

Because they were initially studying the effects of physiologic noise, such as cardiac- and respiratory-related effects, the sampling rate of the data was fast enough to directly sample those effects. Since they directly sampled cardiac and respiratory noise, after digitally filtering the timeseries data, they could be relatively certain that those effects were not responsible for the residual spatiotemporal correlations they observed. In the 1995 study, however, they reported using repetition times of 250–1,000 ms. The frequency of the effect appeared to be specific to the frequency regime below 0.08 Hz. Briefly, they applied a FIR filter to remove fluctuations faster than 0.08 Hz from all voxels' time series. They then selected a "seed" region in left hemisphere primary sensorimotor cortex. The mean time series was calculated for this seed region. They calculated the cross correlation of this reference time series to all other voxels low-pass filtered time series. Observed correlation magnitudes exceeded 0.35 for many voxels in the homologous region contralateral to the seed region (see Fig. 1a, b). This seed-based correlation analysis remains a very common method for assessing functional connectivity using Resting-state BOLD-weighted data.

To understand the evolution of the study of resting-state fMRI, it is important to put this first observation of the phenomenon in context. At the time of the initial resting-state report, fMRI was only a few years old and still had not

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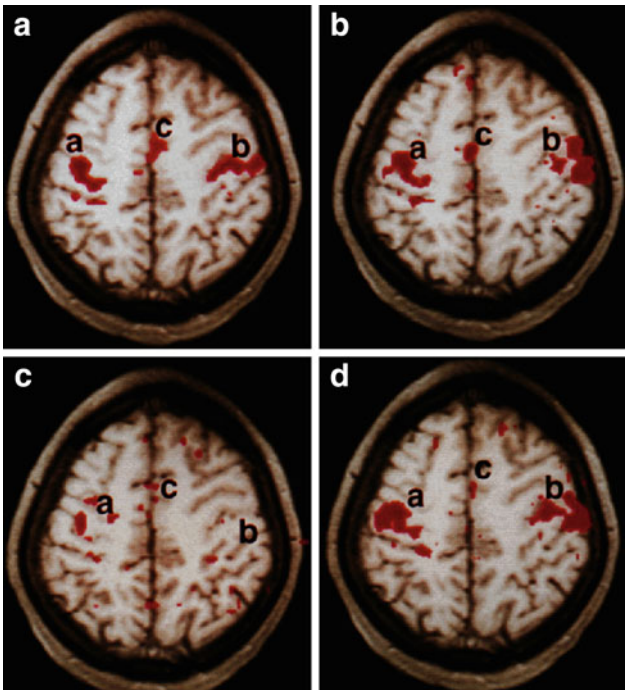

Fig. 1 **a** fMRI task-activation response to bilateral left and right finger movement (scan 5) superimposed on a GRASS anatomic image. **b** Functional-connectivity map obtained by choosing a reference waveform from the left motor cortex (scan 1). **c** Functional-connectivity map obtained during hypercapnia (scan 2) using the time course in the same pixel location as the reference waveform. **d** Functional-connectivity map obtained after resumption of breathing room air (scan 3). Regions, *a*, *b*, and *c* in each of the images represent left primary motor cortex, right primary motor cortex, and supplementary motor areas (SMA), respectively. A substantial overlap between the task-activation map and the functional-connectivity map during each of the room-air scans was obtained. However, maps generated during hypercapnia had less overlap. Overlaps between the task-activation and the first rest scan while breathing room air for the left motor cortex, right motor cortex, and SMA were 74, 67, and 53%, respectively. These dropped to 48, 26, and 31%, respectively, during hypercapnia. Reproduced with permission from Ref. [5]

been fully embraced by the neuroscience community. People working on the technical development of fMRI methods were fully aware that there were very interesting and ill-understood features of the data, and there was understandably a lot of resistance to accept the observed spatiotemporal correlations as being directly related to function. Conferences were punctuated with a lot of lively discussion about the possible sources of the spatiotemporal correlations. I would also like to point out that now, 15 years later, there is still not a very good model for the noise characteristics of resting-state BOLD-weighted MRI data. At any rate, Bharat Biswal and colleagues deserve a lot of credit for recognizing and pursuing this as a neuronally based phenomenon.

To expand on this point, in the very early years after the initial discovery, almost all of the effort was in validating the empirical observation of spatiotemporal correlations in low-frequency BOLD fluctuations as being neuronal in origin. After 15 years and much improved understanding of the neurovascular coupling between neuronal activity and BOLD signal, there is still no firm understanding of the neuronal basis of the low-frequency oscillations. As will be discussed later, there is a picture beginning to come together related to electrical power oscillations at the neuronal level that may be related to the effect, but the coupling mechanism and the propagation method are still completely unknown.

Over the next couple of years, the Medical College of Wisconsin group continued to investigate and validate the resting-state spatiotemporal correlations as a measure of functional connectivity. In this time, they published a couple of other studies that established the observed correlations as being consistent with a BOLD-based contrast effect [5,6].

In 1994–1995, our group at UW-Madison was studying the effect of subanesthetic ketamine challenges (in Monkeys) with fMRI. It is known that ketamine has a psychoactive effect in subanesthetic doses and we were looking for limbic system blood flow responses and were looking at whole-brain correlations as an exploratory method. We were using whole-brain acquisitions and noticed that, even with control (i.e. resting, or saline-challenge) data, there were interesting, functionally relevant spatiotemporal patterns in the data.

After the report of Biswal and colleagues, we pursued these observations in human subjects using a new (at the time) GE 1.5 T MRI scanner with 3-axis echoplanar capability.

To further put this work in historical context, it is also useful to mention here that, prior to 1995 or so, echoplanar capability was not a common MRI technique and was not easily done in anything remotely resembling the manner that it is done today. The work at Medical College of Wisconsin was done using a specially built 3-axis head-only gradient coil that was developed by Eric Wong [7]. This was combined with a custom-built RF coil to make the measurements used in their studies. Our group started out using a similar coil that had become a product from Medical Advances around 1994, but by the end of 1995 we had a new, fully echoplanar-capable whole-body GE MRI scanner.

BOLD contrast-to-noise ratio at 1.5 T tends to be around 1 (the signal change is on the same order as shot-to-shot noise fluctuations in signal). It is absolutely necessary to know the time of a neuronal event in order to effectively detect the signal change in BOLD-weighted MRI data. Of course, to examine the resting data for spontaneous fluctuations, one cannot use the timing of the events. Thus, in order to see the effect, it was necessary to scan for a very long time and average across subjects (original scan time was 17:40). We published this result in 1998, but it was necessary to account for many possible systematic effects in order to get it published [8]. If one reads through our 1998 paper, you will see a fairly in-depth discussion of many possible contributions to spatiotemporal correlations, including motion,

motion-correction, and aliased cardiac and respiratory effects. This was due, in part, by our own skepticism that the effect was real, but also by understandably skeptical reviewers. The manuscript was over a year in review.

Another point to be made here is that the acquisition and analysis of these data were at the limit of technology available at the time. Scanners could not record this much data, and special acquisition methods had to be employed to allow the collection of large data sets. Similarly, off-line processing was confounded by the large memory, disk space, processing time, etc. needed for the analysis of such large datasets. This limited the access to this technique to the highly motivated researcher.

Over the next couple of years, several other papers were published by the Medical College of Wisconsin group [9,10], the UW-Madison group [11–13], and one paper confirming the 1998 whole-brain observation, published by Xiong et al. from UT-San Antonio [14].

By the end of 2000, 5 years after the initial observation, there were 10 published studies using the effect, most of them from the state of Wisconsin in the United States.

In the early years of resting-state fMRI, prior to general acceptance as a methodology, much of the work being done after the initial and confirmatory observations was directed toward understanding the nature of the effect.

As mentioned above, one of the earliest such studies was a hypercapnia study published by Biswal et al. [5]. In this study, they demonstrated that the right/left hemisphere-symmetric correlation patterns observed in the motor system were diminished under the hypercapnia condition and returned after normal air-breathing was established. This result was taken to be evidence that the effect was a blood oxygenation-related phenomenon, similar to activation-based BOLD signal (see Fig. 1).

Another study, published at about the same time as the hypercapnia study by the Medical College of Wisconsin group, showed that the observed correlations were present in a direct measure of blood flow. Using a newly developed arterial spin labeling technique, they demonstrated that the temporal correlations between right and left hemisphere sensorimotor regions were present in ASL data [6].

Another study, performed by Peltier and Noll in 2002, demonstrated that the fluctuation amplitude of the correlated regions had a monotonic exponential dependence on the echo time used in the data acquisition [15]. Using activation-based fMRI data in the same study, they showed that the echo-time dependence of the resting-state correlations was similar to that of the BOLD signal amplitude in the activation-based data. This study was further evidence that the resting-state correlations were a blood oxygenation contrast-based phenomenon.

In 1999, we demonstrated that network modeling approaches could be applied to resting-state BOLD-weighted data [16]. This was one of the first studies to use an approach other than seed-based correlation. Using the motor circuit model of Alexander et al. [17], we constructed a pathway model of the intrahemispheric connectivity of the cortical and subcortical motor regions. We measured the low-frequency BOLD fluctuations of these brain regions at rest and during rapid, continuous tapping. Using structural equation modeling and the pathway model, we demonstrated that the connection strength between the cortical and subcortical motor regions was higher when tapping than at rest.

In 2000, our group demonstrated that the spatiotemporal correlations changed when the functional network changed. In particular, we took advantage of the fact that regions of dorsolateral prefrontal cortex (DLPFC) that moderate executive function will become active during the performance of very different tasks. We compared the correlation pattern to right hemisphere DLPFC when performing a 2-back spatial working memory task, to the correlation pattern when performing a complex patterned finger opposition task. We took advantage of the fact that the functional connectivity-related fluctuations are very slow (<0.1 Hz). The tasks were performed continuously at a rate much faster than 0.1 Hz and the resulting fMRI data were temporally filtered to remove the direct effects of activation. The resulting correlation patterns were strikingly different (see Fig. 2).

There were a number of studies that addressed the issue of the relationship between anatomic connectivity (i.e., white matter pathways) and functional connectivity. It was realized by many people that if spatiotemporal correlations in low-frequency BOLD- weighted MRI data were reflective of functional connectivity, then these correlations should depend on anatomic connectivity.

The first of these studies was a case study in a subject with callosal agenesis [18]. This is a developmental abnormality

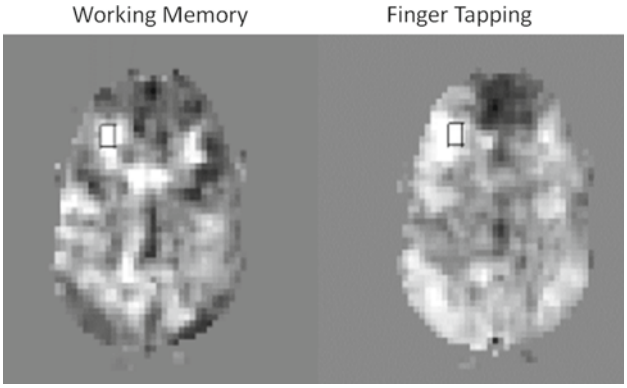

Fig. 2 Gray scale image of temporal correlation to right hemisphere dorsolateral prefrontal cortex (*black box*). *Left panel* is for BOLD-weighted data obtained during continuous performance of a 2-back spatial working memory task. *Right panel* is for data obtained during continuous performance of a complex finger opposition task

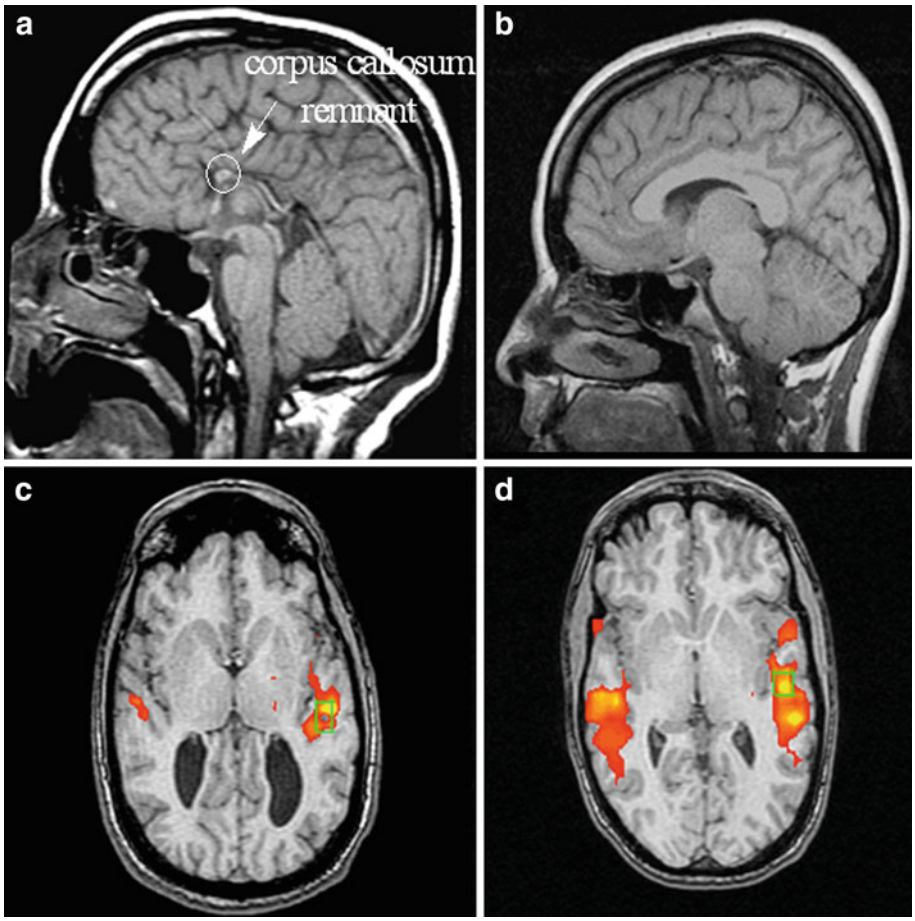

Fig. 3 **a** midsagittal T1-weighted image illustrating the callosal remnant in the agenesis subject. **b** midsagittal T1-weighted image for a subject with a normal corpus callosum. **c** false-color overlay indicates the temporal correlation of all pixels to the left hemisphere auditory cortex (*green box*) for the agenesis subject. **d** the same as (**c**) for the healthy control subject

resulting in partial or total lack of a corpus callosum—the major white matter structure connecting the two cerebral hemispheres. People with callosal agenesis often exhibit dramatic dysfunctions related to tasks requiring coordination of the two hemispheres, particularly language-related tasks such as reading. This study showed dramatically reduced spatiotemporal correlations between the right and left auditory cortices in the acallosal subject as compared to healthy control subjects (see Fig. 3). The subject also exhibited severe learning disabilities as well as dyslexia, confirming that the missing pathways were likely affecting brain function. Quigley et al. published a study in 2003 that replicated this result seen in auditory cortex functional connectivity in three acallosal subjects [19].

Studying callosal agenesis as it relates to functional connectivity is problematic for a couple of reasons: (1) it is a rare condition that often goes undiagnosed since the symptoms relate to learning and intelligence measures, thus making it difficult to find subjects and (2) since it is a developmental abnormality, compensatory pathways can be developed (callosal agenesis is often accompanied by hypertrophy of the anterior and posterior commissures, two other, smaller hemisphere-connecting pathways). Thus, functional deficits would need to be confirmed by detailed neuropsychologic testing, making the condition a spectrum disorder of disconnection.

Multiple sclerosis is an adult onset idiopathic disease of the white matter. It is known that white matter plaques, localized areas of disease that are typical in MS, interrupt axonal signaling [20]. Since the disease normally develops in adulthood, compensatory pathways are an unlikely confound in these subjects. It was demonstrated in 2002 that MS patients, generally, have lower functional connectivity between the bilateral sensorimotor regions than age- and gender-matched control subjects [21].

Recently, research into the relationship of anatomic connectivity and functional connectivity has been stimulated by the development of MRI methods to assess white matter integrity and to track white matter pathways. Several recent studies have shown that functional connectivity as assessed with resting-state fMRI correlates highly with MRI diffusion methods of evaluating white matter connectivity [22–26]. This is discussed in more detail below.

In the early part of this decade, Marcus Raichle and colleagues at Washington University in St. Louis postulated a coherent, interacting network of brain regions that are more

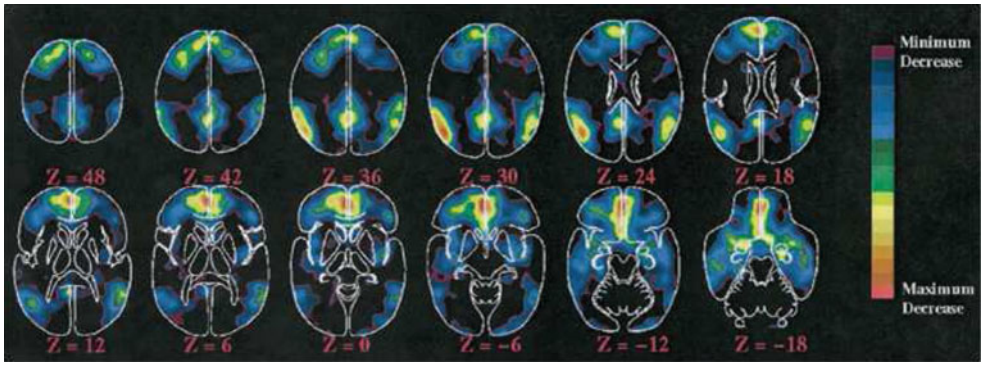

Fig. 4 Regions of the brain regularly observed to decrease their activity during attention demanding cognitive tasks. These data represent a metaanalysis of nine functional brain imaging studies performed with PET. In each of the studies included, the subjects processed a particular visual image in the task state and viewed it passively in the control state. One hundred and thirty-two individuals contributed to the data in these images. These decreases appear to be largely task independent. The images are oriented with the anterior at the top and the left side to the reader's left. The numbers beneath each image represent the millimeters above or below a transverse plane running through the anterior and posterior commissures. Reproduced with permission from Ref. [24]

active when not engaged in a specific task [27]. This was based primarily on observations they made with a large body of PET data of regions of the brain that routinely had a reduction in metabolic activity when engaging in cognitive tasks—largely independent of task details (see Fig. 4).

Almost coincident with the work by Raichle and colleagues, Jeff Binder and colleagues at Medical College of Wisconsin showed in an fMRI study that these same brain regions were more active during the resting period between performance of a perceptual task, but equally active during a semantic task [28]. They concluded that the regions of "deactivation" often seen during cognitive fMRI studies are likely from an interruption of this network involved in conceptual processing. This network bears a striking resemblance to the regions identified by Raichle and colleagues.

In 2003, Greicius et al. demonstrated that many of the regions that Raichle and colleagues were referring to as the "default mode" network showed high correlations in resting-state fMRI data [29]. Grecius et al. used a seed-based correlation analysis to demonstrate this. This result has since been confirmed by many groups, including the Raichle group [30–32].

Since the initial reports, several studies have demonstrated that this network is routinely separated as a source using spatial ICA methods on resting data [33,34]. This has continued to be a prolific avenue of discovery in resting-state studies. More importantly, the robustness of this network and the ease with which it is observed in resting-state data have done as much as any other single development to spur the acceptance and utilization of resting-state fMRI as a legitimate neuroscience tool.

Regarding experimental evidence for a neuronal mechanism for 0.1 Hz fluctuations, it was pointed out a number of years ago that the BOLD effect correlates with fluctuations in local field potential rather than firing rate at the neuronal level [35]. Leopold et al. subsequently discovered that there were modulations in the power amplitude of local field potential that were temporally coherent over much larger spatial distances than the raw local field potential [36]. A Fourier analysis showed that this coherence was enhanced below 0.1 Hz (Fig. 5). This constitutes a possible mechanism for a 0.1 Hz spatiotemporal coherence in BOLD fluctuations that is based on neuronal signaling.

In another 2003 study, Kenet et. al., using voltage sensitive dye imaging in the visual cortex of cats, compared the patterns of cortical activity due to specific visual orientation stimuli to spontaneous patterns observed in the absence of stimuli [37]. They saw that spontaneous activity in the region of visual cortex resulted in the same extended spatial patterns of cortical activity as that observed in response to specific orientation stimuli (Fig. 6). This result nicely demonstrates that spontaneous brain activity can have spatiotemporal coherence reflective of functional connectivity.

Taken together, these two electrophysiology studies form the basis for an argument that low-frequency resting-state BOLD fluctuations (LFBF) could represent neuronal connectivity.

Some of the most compelling evidence for the electrophysiologic basis of the low-frequency BOLD fluctuation connectivity signature comes from the studies of simultaneous EEG- and BOLD-weighted MRI. Laufs et al. showed in a couple of studies that there are widespread cortical regions whose resting MRI fluctuations are strongly temporally correlated with the power in certain EEG bands [38]. In this study, they demonstrated that some regions had positively correlated LFBF and EEG power in the alpha band, while other regions were negatively correlated. Although the EEG signal was not spatially resolved, when the regions that had EEG/LFBF correlations were examined for spatiotemporal correlation within the fMRI data itself, the same regions were

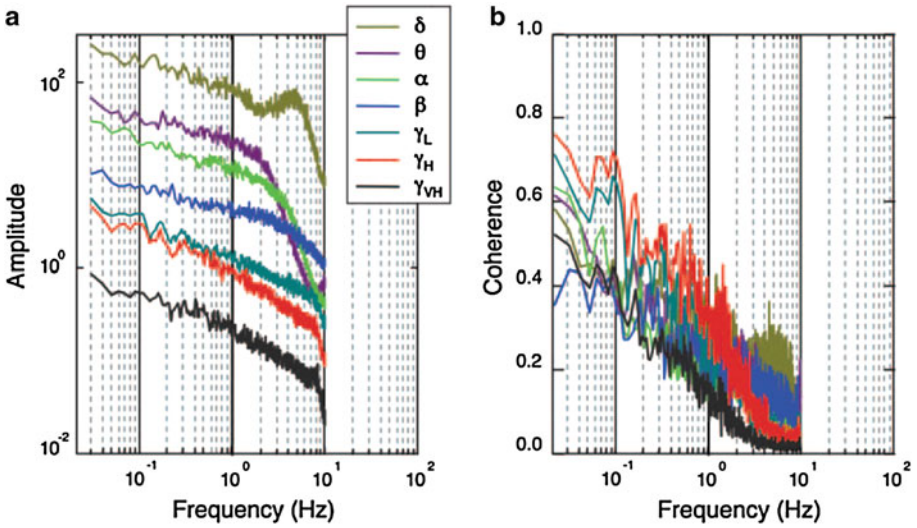

Fig. 5 Grand mean power spectrum and coherence of power (rectified) LFP signals during resting condition. **a** The power spectrum reveals increased power at lower frequencies resulting from the rectification process. **b** As suggested by the example in Fig. 5, the coherence between electrodes at long time-scales is also very high for the power signal. Thus, the LFP power displays slow, coordinated changes at long time-scales. Reproduced with permission from Ref. [32]

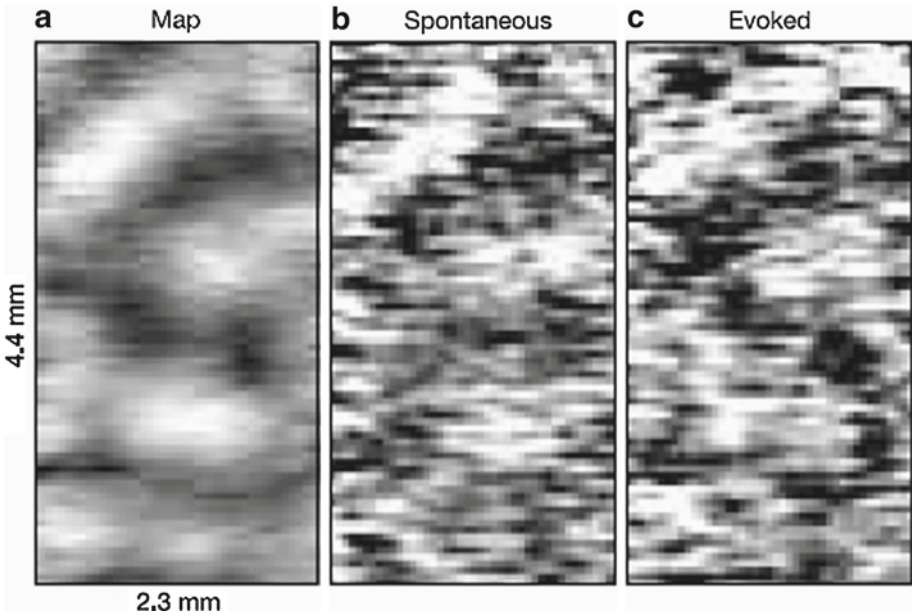

Fig. 6 Comparing instantaneous patterns of spontaneous and evoked activity to the averaged functional map. **a** The orientation map using full-field gratings of vertical orientation, obtained by averaging 165 frames (5 frames from each trial starting from 100 ms after stimulus onset, over 33 stimulus presentations). **b** A map obtained in a single frame from a spontaneous recording session. **c** A single frame from an evoked session using the same orientation as for the map. Amplitude was computed as described in Methods. Reproduced with permission from Ref. [33]

shown to be highly correlated, indicated that these likely represent networks of correlated electrical activity.

As stated above, MRI diffusion methods have matured to the point where it is possible to perform in-vivo measurements of anatomic connectivity. Although it is still unclear what the relationship is between diffusion-based measures of anatomic connectivity and true axonal pathways, it is possible to use DWI-based tractography to delineate plausible white matter pathways that correspond to known anatomic pathways [39–44]. Using these methods, several groups have investigated the relationship between resting state-based functional connectivity and anatomic connectivity.

In combining DWI measures of anatomic connectivity with the measures of functional connectivity, it is important to understand the different limitations of both methods. A major confound to DWI-based fiber tracking is the substantial fraction of voxels, even in state-of-the-art DWI acquisitions, that contain axonal fiber bundles that are oriented in different directions. This is known as the crossing-fiber problem. Many tracking methods are inefficient at tracking across these complicated white matter pathways. Thus, long-range connections, such as interhemispheric pathways, become difficult to measure. In addition, the comparison of functional connectivity to anatomic connectivity introduces the problem of indirect connections. Fiber tracking methods are by nature one-to-one, while most functional connectivity measures are simply assessing connectivity, direct or indirect. These issues should be kept in mind when trying to interpret studies comparing the two measures.

The first of these appeared shortly after the introduction of probabilistic fiber tracking approaches. In 2002, Koch et al. used a probabilistic fiber tracking approach to attempt to

relate resting-state functional connectivity to the pathway connectivity across adjacent gyri in the cerebral cortex [26]. They found no correlation between their measure of white matter connectivity and functional connectivity, but reported a general observation that high values of white matter connectivity were always associated with high functional connectivity. They conclude that the fact that the inverse did not hold as being due to a contribution of indirect connections to high values of functional connectivity.

There was little activity using fiber tracking approaches for a number of years. The next study appeared in 2008 [23]. This was a population study comparing MR-DWI-based measures of white matter integrity in the transcallosal sensorimotor pathway to functional connectivity. Functional connectivity was defined as the fraction of voxels in right hemisphere primary sensorimotor cortex (SMC), defined from task-based fMRI, over a given correlation to low-frequency fluctuations in left hemisphere SMC. The correlation threshold corresponded to $p < 0.05$. The measure of anatomic connectivity was taken to be the mean radial diffusivity over the voxels along the transcallosal pathway determined from tracking. The study demonstrated a significant inverse correlation in radial diffusivity along the white matter connecting pathway and resting-state functional connectivity in a population of MS patients. Since increased radial diffusivity is commonly taken to be related to demyelination in MS [45–47], this was taken as evidence that a reduction in anatomic connectivity is related to reduced functional connectivity. Interestingly, although no such correlation was seen in healthy controls, when the control subjects were combined with the patients, the significance increased, implying that the lack of correlation observed in healthy control subjects may have been due to a lack of range in transverse diffusivity—i.e., it would take a larger study, but the same effect may be observed in the general population with larger numbers of subjects.

Shortly thereafter, Skudlarski et al. published a study in a population of healthy control subjects demonstrating a very strong correlation between DWI-fiber tracking-based anatomic connectivity and resting-state functional connectivity. The study assessed connections between many different brain regions in each subject, thus accruing a large statistical range of pathway connectivities. The study found a very striking degree of correlation between their fiber tracking-based measure of anatomic connectivity and resting-state functional connectivity (see Fig. 7).

Although it did not specifically assess pathway-dependent anatomic connectivity measures, there is one other recent study of note with regard to resting-state functional connectivity and anatomic connectivity. In 2008, Johnston et al. showed that complete section of the corpus callosum (callosotomy) resulted in lateralization of functional connectivity in a single subject, when compared to pre-callosotomy functional connectivity (Fig. 8) [48]. The subject was a six-year-old epileptic patient with chronic seizures. Although the patient was interictal at the time of both scan sessions, there is the possibility that interictal electrical activity related to the epilepsy could have been present and, in that case, the effect would not necessarily be a resting-state phenomenon.

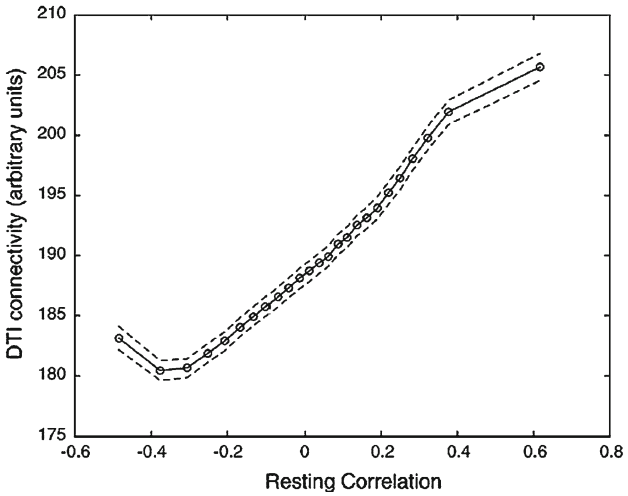

Fig. 7 Mean DTI estimated anatomic connectivity as a function of mean functional resting-state connectivity. The whole connectivity matrix was divided based on the resting connectivity values into 25 bins. The average value of DTI connectivity of each of those bins is plotted against mean resting connectivity. It is apparent that anatomic connectivity (measured by DTI) increases for most of the range, with exception of the lowest resting connectivity bin. This suggests that it is the resting connectivity and not its absolute value that corresponds to the actual functional connectivity, that negative resting connectivity should not be interpreted as representing real functional connectivity. Reproduced with permission from Ref. [21]

The demonstration of the relationship between anatomic connectivity and functional connectivity in the human brain has been greatly beneficial in demonstrating the validity of resting-state functional connectivity.

As an alternative to seed-based correlation analysis, spatial ICA has become a leading analysis technique for functional connectivity using resting-state BOLD data. This data-driven method analyzes whole-brain data to derive spatially independent sources of non-gaussian behavior [49]. The method was first applied to activation-based fMRI studies and proved to be a very effective method for that. The complex and ill-understood noise structure of spontaneous fluctuations in BOLD-weighted data makes it much more problematic to apply in resting-state data. The Oxford University fMRI group was the first to focus method development on application to resting-state BOLD data [33,34,50]. There are now two relatively complete spatial ICA software distributions that are in routine use for resting-state data analysis, the Melodic software from the FSL distribution of the Oxford group [51], and the GIFT toolbox from Vince Calhoun's group at University of New Mexico [52].

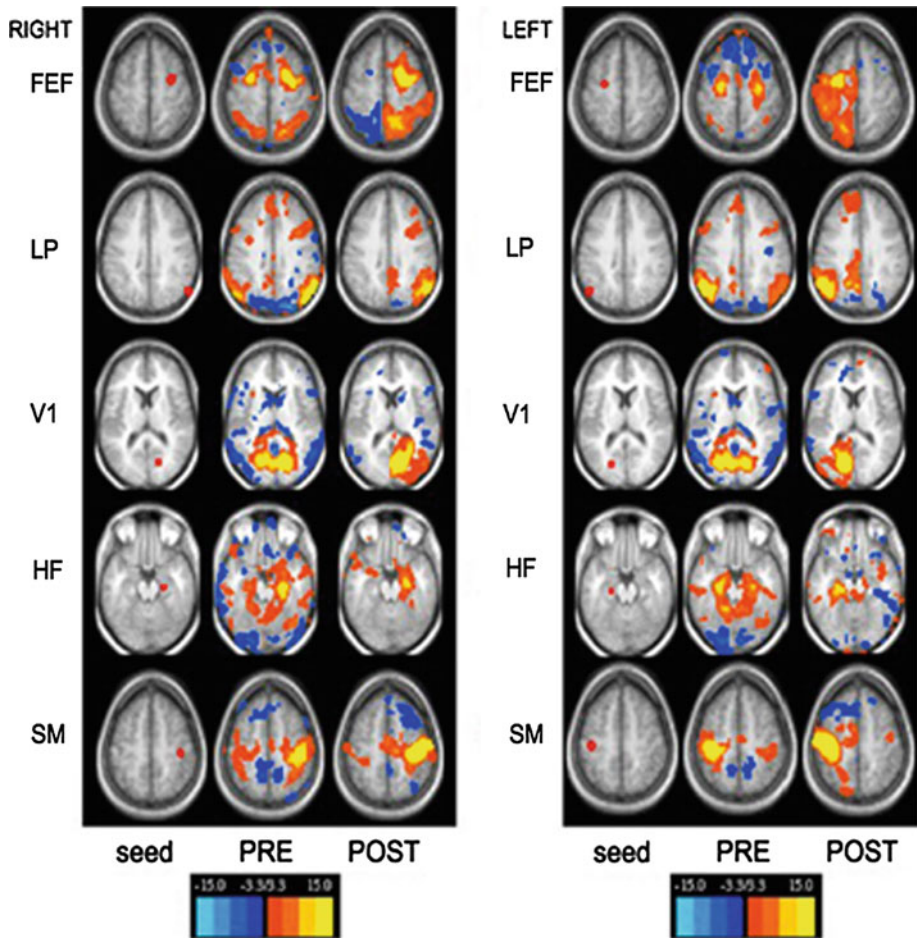

Fig. 8 Functional connectivity computed before and after corpus callosotomy for *right-* and *left-sided* seed regions. Seed regions defined in the right hemisphere (first column of each set) were used to generate correlation maps both before (second column) and after (third column) complete transection of the corpus callosum. Seed ROIs were placed laterally in the hemispheres to avoid confusion that might arise due to partial volume averaging associated with ROIs close to the midline. Pre-surgery, functional connectivity maps using the selected seed regions revealed a pattern of correlations that is consistent with published literature, including near symmetric correlations with the contralateral hemisphere. For example, a seed in right lateral parietal region demonstrates correlations with the left lateral parietal as well as with medial prefrontal cortex and posterior cingulate/precuneus (row 2). Post-surgery, contralateral correlations that were present before transection prominently disappear (FEF: row 1; LP: row 2; V1: row 3). Correlations with the hippocampal formation seed and the somatomotor seed do not show complete loss of contralateral correlations. These regions have neuroanatomical connections with the opposing hemisphere through fibers that do not cross in the corpus callosum. The temporal lobe, for example, is able to communicate with the contralateral hemisphere through the anterior commissure (Schmahmann and D.N., 2006). Findings were similar for both *right-* and *left*-sided seeds. FEF = frontal eye field, z = 55.5; LP = lateral parietal, seed: z = 36.5; V1 = primary visual cortex, z = 12.5; HF = hippocampal formation, z = −13.5; SM = somatomotor, z = 51.5. Reproduced with permission from Ref. [44]

It has become clear that spontaneous neuronal activity has to be accounted for in any noise analysis of BOLD-weighted data. As evidence of this, one recent study was published by Bianciardi et al. in 2009 [53]. In this study, the authors modeled the sources of in-vivo temporal variance in BOLD-weighted MRI signal at 7 tesla. They separated the sources of low-frequency scanner drifts, respiratory- and cardiac-related effects, variability in these rates, and spontaneous neuronal activity. They determined that spontaneous neuronal activity was the second leading source of variance at 7 T. Thus, spontaneous neuronal activity appears to be a major source of variance at high field, and high-field MRI holds high promise for resting-state fMRI.

In a couple of studies using concurrent electrophysiological monitoring and resting-state fMRI, Leopold and colleagues have shown that low-frequency BOLD-weighted fluctuations in resting macaque brain are correlated with gamma-band local field potential signals, albeit with a 6–8 s lag between electrical signal and BOLD signal [54,55]. In the most recent work, they demonstrate that the gamma-band LFP signals are highly correlated with 6 s lagged low-frequency (<0.1 Hz) BOLD fluctuations across the entire

cerebral cortex [54]. Importantly, this implies that the widely observed global correlations observed in resting-state fMRI (see Murphy et al. [56] for an example) may be directly related to neuronal activity.

As further evidence of the importance of the gamma band in resting- state fMRI, Nir et al. observed a high correlation in the gamma-band LFP power between the interhemispheric auditory regions [57]. Similarly, the spatial organization of the correlation in gamma- power fluctuations has been shown to be similar to that of resting- state BOLD correlations [58].

Generally speaking, the consensus of the electrophysiology studies that relate to the low-frequency BOLD fluctuations in the resting brain seems to indicate some relationship with either alpha bands [36,38] or gamma bands [36,54,55,57]. This forms a coherent picture in that these two bands are relevant to conscious experience and directed attention [59–61].

In summary, the current level of activity in resting-state fMRI is the culmination of over fifteen years of work in the field. The early years of investigation into this phenomenon laid the groundwork for the current state of the field by establishing important validation milestones. A number of developments in other fields, such as the discovery of the "default mode," the discovery of spontaneous coherent firing of extended neuronal networks, the discovery that band-limited power in the electrophysiologic signal is modulated at 0.1 Hz and is spatially coherent over long distances, helped establish a plausible neuronal basis for resting-state fMRI. All of these, together with the validation work and eventual application to clinical populations, have led to the acceptance of resting-state fMRI as a valid tool for neuroscience research.

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