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Review

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How networks communicate: propagation patterns in spontaneous brain activity

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Initially regarded as 'noise', spontaneous (intrinsic) activity accounts for a large portion of the brain's metabolic cost. Moreover, it is now widely known that infra-slow (less than 0.1 Hz) spontaneous activity, measured using resting state functional magnetic resonance imaging of the blood oxygen level-dependent (BOLD) signal, is correlated within functionally defined resting state networks (RSNs). However, despite these advances, the temporal organization of spontaneous BOLD fluctuations has remained elusive. By studying temporal lags in the resting state BOLD signal, we have recently shown that spontaneous BOLD fluctuations consist of remarkably reproducible patterns of whole brain propagation. Embedded in these propagation patterns are unidirectional 'motifs' which, in turn, give rise to RSNs. Additionally, propagation patterns are markedly altered as a function of state, whether physiological or pathological. Understanding such propagation patterns will likely yield deeper insights into the role of spontaneous activity in brain function in health and disease.

This article is part of the themed issue 'Interpreting blood oxygen level-dependent: a dialogue between cognitive and cellular neuroscience'.

1. Importance of intrinsic activity

As observed by Hans Berger, in reporting on the first measurements of the human electroencephalogram, spontaneous (intrinsic) neural fluctuations are a dominant feature of the brain's electrical activity [1]. In the context of studying task-evoked neural responses, spontaneous activity was long considered merely to be 'noise'. Thus, most early studies of neural activity employed computational strategies to suppress spontaneous activity. More recently, it has been appreciated that investigating spontaneous activity is essential for understanding brain function [2–4]. At the systems level, this paradigm shift was prompted by two major findings. First, although the human brain represents only 2% of total body mass, its intrinsic activity consumes 20% of the body's energy, most of which is used to support ongoing neuronal signalling ([5–9], but see also [10]). Task-related increases in neuronal metabolism are generally small (less than 5%) when compared with this large intrinsic energy consumption (for a recent review, see [9]). Thus, to understand how the brain operates, we must take into account the component that consumes most of the brain's energy: spontaneous activity.

The second set of findings has been derived from resting state functional magnetic resonance imaging (rs-fMRI) of the blood oxygen level-dependent (BOLD) signal [11]. Biswal et al. used human rs-fMRI to discover that spontaneous infra-slow (less than 0.1 Hz) fluctuations of the BOLD signal are highly correlated within the somatomotor system [12]. This basic result has since been extended to multiple functional networks spanning the entire brain ([13–17]; figure 1*a*,*b*). Spatial correlations within intrinsic activity are widely referred to as functional connectivity; the associated topographies are known as resting state networks (RSNs [2]). The discovery of RSNs revealed that spontaneous activity is highly structured and can be related to brain function in health [18–21] and disease [22–25].

Yet, despite these advances, functional connectivity analyses do not address the temporal dimension of brain communication, that is, propagation of signals between regions. Instead, the correlation measure (e.g. functional connectivity) integrates over time to provide a static spatial view of brain organization

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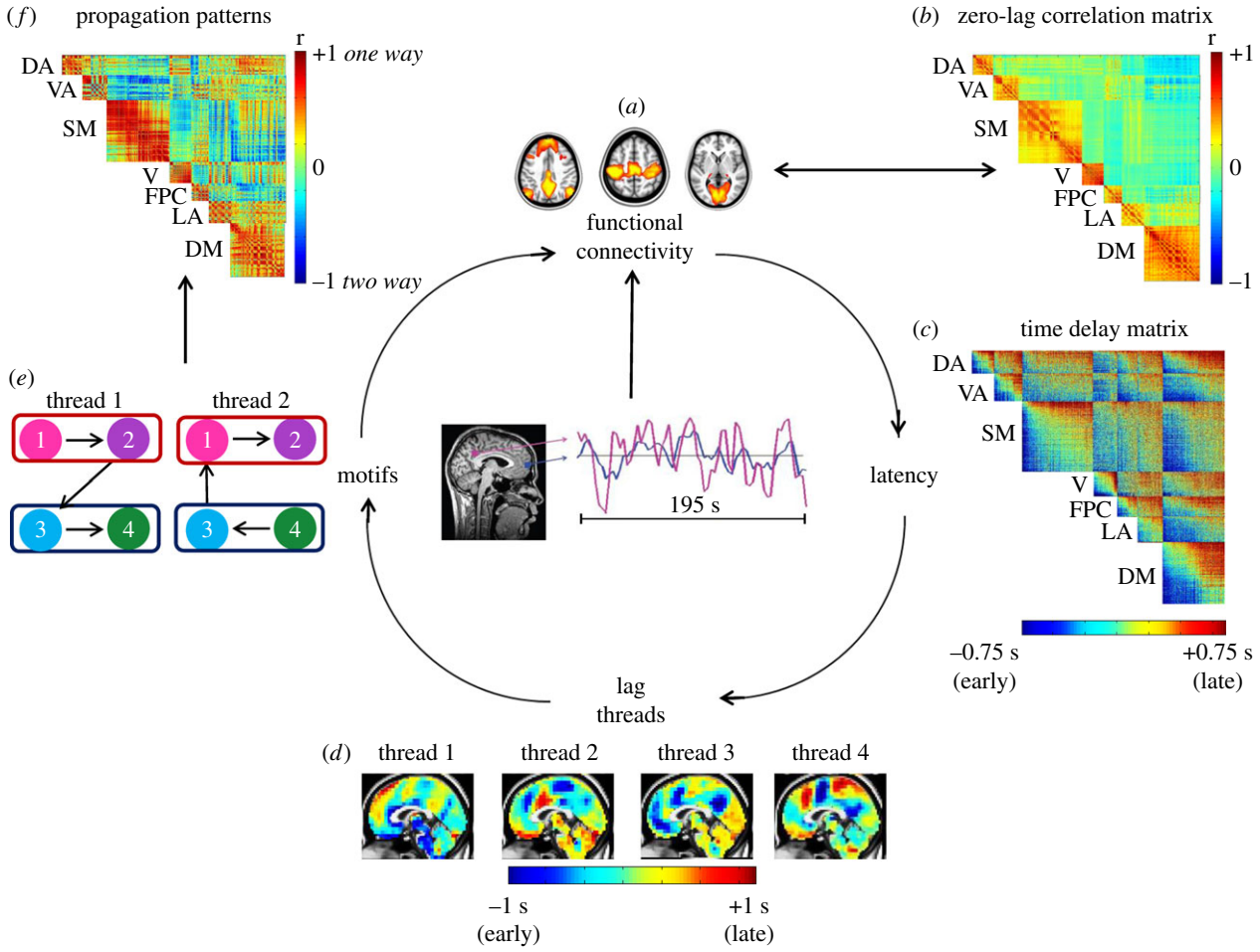

Figure 1. A conceptual, evolving view of the spatio-temporal organization of spontaneous BOLD signal activity. (*a*) The first evidence of organization in spontaneous BOLD signal activity was the discovery of functional connectivity, or zero-lag correlations, within RSNs, including the default mode network, motor network and visual network, illustrated in that order from left to right. RSNs demonstrate that spontaneous activity carries a signature of network segregation. (*b*) Functional connectivity illustrated in a zero-lag correlation matrix; each pixel depicts the correlation between a pair of voxels. Voxels are grouped into networks (RSNs) on the basis of highly correlated spontaneous activity. (*c*) Propagation structure illustrated in a time delay (TD) matrix. Each pixel depicts the temporal lag between a pair of voxels. The TD matrix reveals propagation of spontaneous activity between and within RSNs, a signature of network integration. (*d*) The TD matrix propagation structure is composed of multiple propagation sequences, or lag threads. Four lag threads are illustrated here, in mid-sagittal view. (*e*) Embedded within lag threads are 'one-way streets' (or lag thread motifs), representing conserved regions of unidirectional propagation across distinct propagation sequences. (*f*) By analysing propagation sequences (figure 3), we find that lag thread motifs correspond to and give rise to RSNs. DA, dorsal attention; VA, ventral attention; SM, sensory motor; V, visual; FPC, fronto-parietal control; LA, language; DM, default mode.

[18,20,26]. However, ample evidence of structured propagated intrinsic activity has been reported in the mouse using voltage sensitive dyes as well as genetically encoded calcium imaging [27–33]. These observations raise the question: can evidence of temporal propagation be found in the spontaneous BOLD signal?

2. Dynamics in the resting state blood oxygen level-dependent signal

Several approaches can be taken to understand BOLD signal propagation. For example, vector autoregressive (VAR) methods, including Granger causality [34,35] and dynamic causal modelling [36,37], can be used to infer signal directionality. Although these methods are highly effective for testing causal models in small numbers of time series, VAR-based analyses have computational limits which prevent extending these approaches to account for the tens of thousands of voxel time series necessary to describe propagation in the whole brain [26].

Thus, we have opted to study BOLD signal propagation by analysing temporal lags across the whole brain. Given a pair of nodes, if the first node transmits a signal to the second, then there will be a temporal delay (or lag) between the signals. These temporal lags can be detected by computing lagged correlation (or, equivalently, lagged covariance) curves between time series pairs (figure 2). If there exists a non-zero temporal delay which maximizes (or minimizes, in the case of anti-correlation) the lagged correlation, we can then infer directed propagation between the two voxels. The existence of a non-zero-lag in peak correlation between voxels does not reveal the route (e.g. direct or indirect) or biological mechanism of propagation (see Future directions section for further discussion). All we can conclude is the existence of propagation through some mechanism. Despite this limitation, lagged correlations are commonly used in the electrophysiology literature to characterize directed propagation/communication between neuronal assemblies [38–41].

3. Temporal lags analysis

There is one technical hurdle that complicates applying lagged correlations to resting state BOLD signals: the low

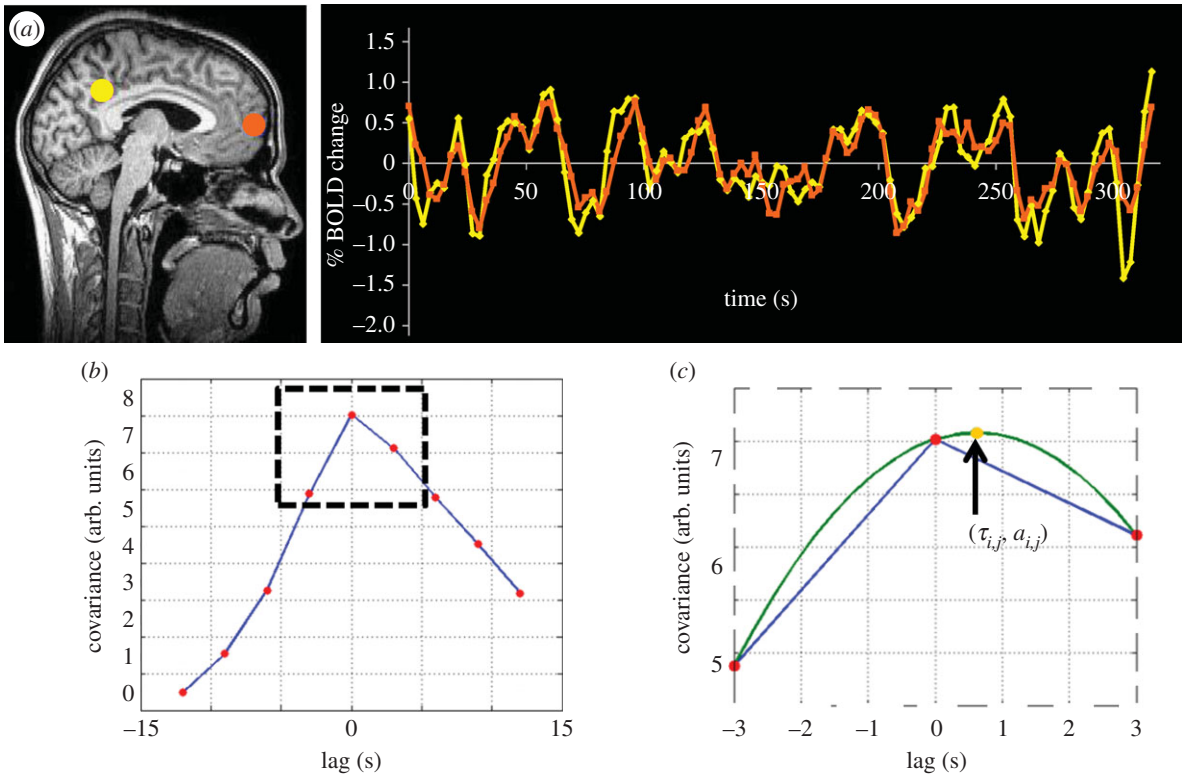

Figure 2. Calculation of lag structure using lagged cross-covariance functions and parabolic interpolation. Lags are defined by analysis of time series derived from two loci. (*a*) Two exemplar loci (both in the default mode network). (*b*) The corresponding lagged cross-covariance function. The range of the plotted values is restricted to $\pm$15 s, which is equivalent to $\pm$4 frames (red markers) as the repetition time was 3 s. The lag between the time series is the value at which the absolute value of the cross-covariance function is maximal. (*c*) This extremum can be determined at a resolution finer than the temporal sampling density by parabolic interpolation (green line) through the computed values (red markers). This extremum (arrow, yellow marker) defines both the lag between time series *i* and *j* ($\tau_{i,j}$) and the corresponding amplitude ($a_{i,j}$).

temporal sampling density of fMRI. We can only empirically calculate lagged correlations in intervals of the time between measurements. If the signals of interest are sampled rapidly, then the peak of the lagged correlation curve is well estimated simply by finding its empirical peak. However, in most conventional fMRI sequences, the temporal resolution is one measurement every 2–3 s. To circumvent this problem, we apply parabolic interpolation to lagged correlation curves. This allows us to measure temporal lags at a resolution finer than the temporal sampling density of our data (figure 2). BOLD signal temporal lags computed through interpolation are highly reproducible [26,42].

To analyse whole brain propagation, we extend this approach to compute the temporal delay between every pair of voxel time series in grey matter. The set of all such delays forms a time delay (TD) matrix [26]. Figure 1*c* illustrates a TD matrix derived from rs-fMRI data collected in 100 awake, healthy young adults. The voxels comprising the TD matrix in figure 1*c* are drawn from an RSN parcellation as defined by Hacker *et al.* [43]. After sorting voxels by cortical RSN affiliation, voxels within RSNs were then sorted from 'early' to 'late'. Blue hues indicate negative lag values (i.e. when one voxel is earlier than another), whereas red hues indicate positive lag values (i.e. when one voxel is later than another). The diagonal blocks in the TD matrix represent propagation within RSNs (e.g. within the DMN, lower right corner); the off-diagonal blocks represent propagation among RSNs (e.g. between the DMN and DAN, upper right corner). The TD matrix in figure 1*c* is highly reproducible at the group level in awake adults, as previously shown using a cohort of nearly 1400 subjects [42] indicating that the propagation structure of rs-fMRI data is highly conserved across individuals.

Two key functional features are highlighted by figure 1*c*. First, the range of temporal lags is approximately $\pm$1 s over the entire cortex. Thus, the propagation speed of the spontaneous BOLD signal is much slower than classical axonal transmission via myelinated fibre tracts, which transmit signals over tens to hundreds of milliseconds [44]. Instead, the propagation speed of BOLD signal fluctuations is in the range of propagated changes in regional cortical excitability [32,39] (see Future directions section for further discussion).

Second, the TD matrix reveals equivalent propagation of BOLD signal activity both within and among RSNs. No RSN wholly leads or follows the others. Rather, there is reciprocal signalling between every pair of RSNs. To gain an intuitive appreciation of this pattern, note that a uniform, well-ordered early-to-late organization is seen in every diagonal TD matrix block, representing ordered within-RSN propagation. When we analysed CSF voxels (not shown here; see Fig. 9 in [26]), we found intra-CSF voxels to be much less well ordered even though they were analysed identically to the true RSNs, indicating that the observed intra-RSN lag structure is not mathematically imposed [26]. Each off-diagonal (cross-RSN) TD matrix block also contains well-ordered early, middle and late components, indicating ordered cross-network propagation. Again, this organization is not seen in off-diagonal blocks involving CSF [26].

Critically, the mean value in each of the off-diagonal blocks in the TD matrix is very nearly zero [26,45]. If one RSN were systematically earlier than another RSN, the expected off-diagonal block mean would be non-zero. For example, if the

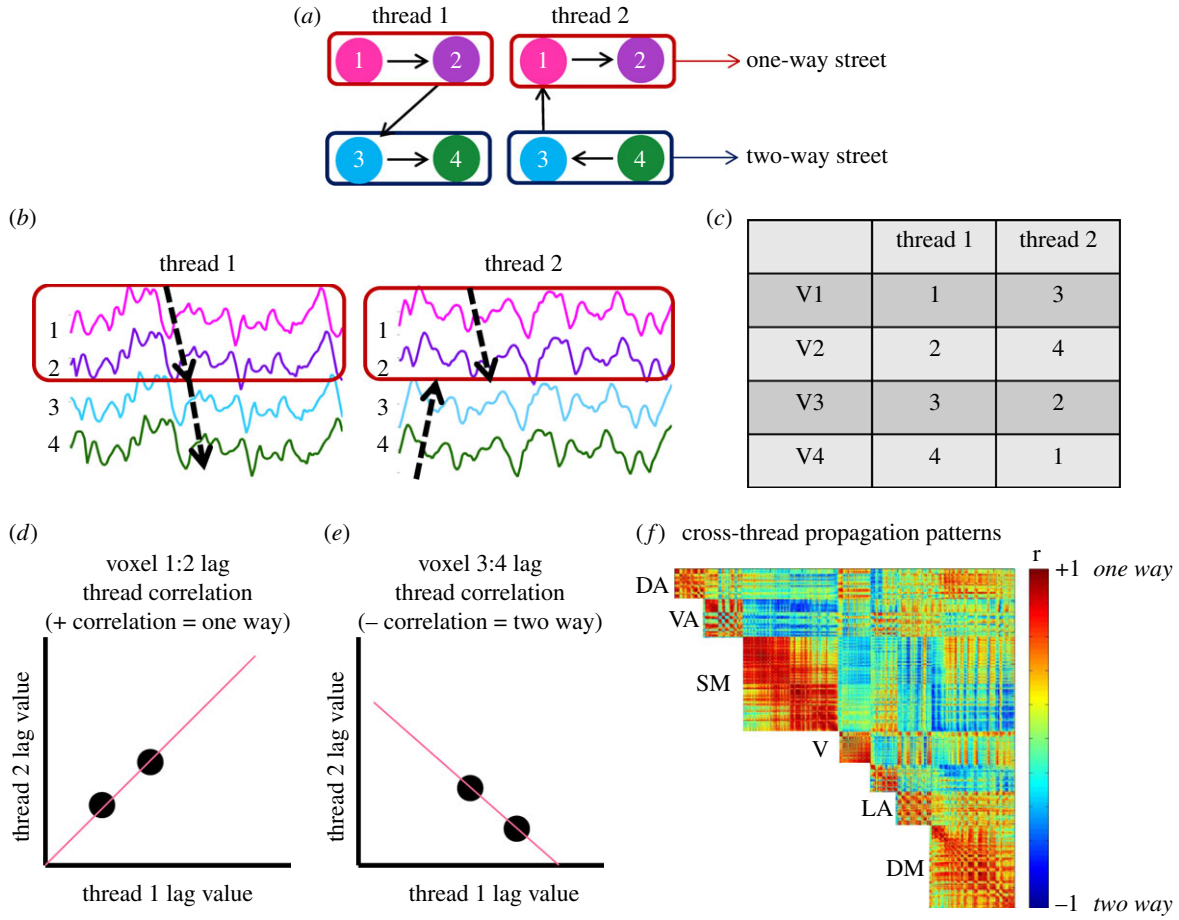

Figure 3. Lag thread motifs, or 'one-way streets', correspond to resting state network topographies. (*a*) Schematic of two lag threads propagating through four voxels. The overall pattern of propagation differs in the two threads, but the sequences through voxels 1 and 2 are identical (red box). Thus, voxels 1 and 2 represent a lag thread motif or 'one-way street'. By contrast, the propagation directions between voxels 3 and 4 (blue box) are reversed across the two example threads, depicting a 'two-way street'. (*b*) The lag threads in (*a*) realized as time series. (*c*) Temporal ordering of the voxels in the illustrated lag thread schematic. (*d*) Correlation of temporal orderings, across lag threads, for voxels 1 and 2. Note that the correlation is positive in the case of a 'one-way street' or motif. (*e*) Correlation of temporal orderings, across lag threads, for voxels 3 and 4. Note that the correlation is negative in the case of a 'two-way street'. (*f*) Voxel-wise correlation matrix computed over latency values in the four lag threads derived from real data, as shown in figure 1*d*. Blocks of high correlation are found on the diagonal, or intra-RSN, blocks, implying that BOLD signal propagation is largely unidirectional within networks. By contrast, negative correlations (and lower positive correlations) are found in the off-diagonal, or inter-RSN, blocks, implying that cross-RSN propagation is generally bidirectional.

default mode (DM) network were wholly leading or following the dorsal attention (DA) network, then the off-diagonal block of the TD matrix representing DM : DA lags would either be wholly 'blue' or wholly 'red'. Instead, what we observe is an even distribution of blue and red. Hence, some components of the DM network lead the DA network (blue), but other components of the DM network follow the DA network (red). This principle plays out in all cross-network off-diagonal blocks in the TD matrix. Thus, infra-slow activity propagates both within and among RSNs, and cross-RSN signalling is predominantly reciprocal. The reciprocal propagation patterns between RSNs provide a possible framework for communication between networks which, traditionally, have been considered distinct, spatially segregated entities.

4. Relationship between temporal and spatial organization

The propagation (TD matrix, figure 1*c*) and RSN structures (zero-lag correlation matrix, figure 1*b*) of the BOLD signal highlight temporal and spatial features of brain organization, respectively. However, both temporal lags and functional connectivity are derived from precisely the same underlying signal, raising the question: can we unite our descriptions of space and time? Or, more specifically, do RSNs arise from patterns of propagated activity, and, if so, how?

The simplest hypothesis is that voxels with the smallest temporal delays comprise RSNs. That is, short temporal lags could imply high zero-lag correlation. However, we found no empirical relation between temporal lag and Pearson's *r* correlation over pairs of voxels in grey matter (Fig. in [42]). The reason this relationship does not exist is that the range of temporal delays within and among RSNs is quite similar ([26]; figure 2). If high correlations were associated with shorter temporal delays, the range of the lags in the diagonal blocks in TD matrix would have to be smaller than the range of the lags in the off-diagonal blocks. As this is not the case, a more complicated relation is required to unify our description of RSNs and propagations.

We next explored whether RSNs emerge from patterns embedded within propagation sequences. We can identify individual propagation sequences in the data by applying matrix decomposition to the TD matrix. In the same way that matrix decomposition of a correlation matrix yields spatial network topographies [46], matrix decomposition of

the TD matrix reveals propagation sequences (figure 1*d*, [42]). We refer to these propagation sequences as 'lag threads' by way of analogy with modern computer programming practice, where single applications contain multiple, independent thread sequences.

By examining lag threads, several features of BOLD signal propagation become clear. First, based on an analysis of 688 subjects, we identified the presence of eight significant lag threads or propagated temporal processes in rs-fMRI data [42]. The first four lag thread topographies are depicted in figure 1*d*. We found that lag thread propagation patterns do not strictly respect RSN borders and that the propagation patterns are bilaterally symmetric. Second, lag threads are very consistent across independent groups of subjects. This replicability is demonstrated in two groups of 688 subjects in [42] and a group of 39 subjects in [45]. Thus, the propagation structure of rs-fMRI data is defined by a set of remarkably conserved, bilaterally symmetric propagation sequences. This finding is in accordance with data collected using voltage sensitive dyes and genetically encoded calcium in mice and rats, where preserved patterns of slow, bilaterally propagating processes have been described [27–33].

Having isolated lag threads from the TD matrix, we serendipitously[1] pursued the hypothesis that although in general there is reciprocal signalling between brain regions (e.g. in figure 1*d*, subcortical structures lead the cerebral cortex in lag thread 1, but the reverse is true in lag thread 2), the direction of propagation within RSNs may be preserved across lag threads. In other words, RSNs may represent 'one-way streets' with respect to propagation of the spontaneous BOLD signal. An example of a one-way street embedded in lag threads in shown in the schematic in figure 3. In a system where the propagation speed is fast relative to the frequency of the signals, as is the case with the spontaneous BOLD signal (whole brain propagation of the order of approximately 1 s, fluctuations of the order of approximately 10–100 s), activity within 'one-way streets' will be highly correlated at zero-lag (see Fig. 7 in [42]).

To investigate whether the 'one-way streets' explain the emergence of RSNs from propagation patterns, we asked three questions: (i) is there evidence for 'one-way streets' in the spontaneous BOLD signal? (ii) Do these one-way streets correspond to conventionally defined RSNs? (iii) Can RSNs be recovered solely using the lag structure and spectral content of the BOLD signal?

To answer the first two questions, we need a computational technique to detect 'one-way streets'. Recognizing that lag threads are simply propagation sequences that order voxels from early to late, one-way streets can be recovered by looking for correlations in voxel-wise temporal ordering across lag threads (figure 3*d*,*e*). Intuitively, 'landmarks' (e.g. voxels) on a one-way street are always visited in the same order. Hence, regardless of whether the one-way street is traversed early or late in a specific path (e.g. lag thread), the ordering of landmarks will be highly correlated over all paths (e.g. over all lag threads). When we compute the voxel-wise propagation sequence correlation across lag threads, we in fact find topographies of high correlation, indicating the presence of one-way streets (figure 3*f*). We refer to these 'one-way street topographies' as 'lag thread motifs'. Comparing the propagation sequence correlation matrix (figure 1*f*) against a conventional zero-lag (functional connectivity) correlation matrix (figure 1*b*), we find substantial agreement [42]. Thus, not only do we find evidence of 'one-way street' motifs in BOLD signal propagation, these lag thread motifs match the topographies of RSNs. Interestingly, the voxel-wise propagation sequence correlation matrix also exhibits anti-correlations, predominantly in the off-diagonal blocks. These anti-correlations correspond to 'two-way streets' (figure 3*e*), again demonstrating reciprocal signalling between networks.

Having found lag thread motifs (one-way streets) in BOLD signal propagation patterns which correspond to RSNs, we are left with the final question: can RSNs be recovered solely on the basis of propagation patterns? We approached this question through simulation. By constructing synthetic resting state BOLD time series in which we determined temporal structure, but did not constrain zero-lag correlations, we found that the zero-lag correlation matrix in the synthetic data is substantially similar to the zero-lag correlation matrix derived from real data (Fig. 8 in [42]). Hence, RSN organization can arise as a consequence of the temporal organization of rs-fMRI data.

Critically, the reverse is not true, that is, the RSN organization of the BOLD signal does not give rise to its temporal structure. We can demonstrate this point by altering the previous simulation to produce synthetic data in which we pre-determine the zero-lag correlation structure, but not the temporal structure. Comparing TD matrices, we found that the real and synthetic data did not agree (see Fig. 9 in [42]). The implication of this finding is that spatial RSN topographies emerge from patterns of propagation in the resting state BOLD signal. That is, the spatial organization of the resting state BOLD signal is a consequence of its temporal organization.

5. Neural origin of blood oxygen level-dependent signal propagation

Despite the evidence for propagating low frequency activity across multiple modalities [31,32,47,48], concern lingers that regional variations in the kinetics of neurovascular coupling could largely account for BOLD signal propagation [49,50]. We have previously articulated two reasons that BOLD signal lags are likely of neural origin. First, we find focal state-dependent changes in BOLD signal propagation. These changes are found in normal physiology, such as pre- versus post-motor learning [26] and sleep versus wake [45], as well as pathophysiology, such as resting state data in autism spectrum disorders (ASD) versus typical controls [51]. A vascular explanation for this result implies focal changes in the dynamics of neurovascular coupling found during learning, wake versus sleep, as well as ASD. There is no evidence of such systematic, long lasting, state-dependent shifts in vascular kinetics [26,52]. By contrast, altered neural communication has been implicated in learning, sleep, and ASD, supporting the view that changes in BOLD signal propagation reflect neural activity. Second, a fixed set of varying haemodynamic delays across the brain can only account for one propagation sequence in the data [26,42,53]. As the BOLD signal consists of multiple propagation sequences [42,53], only a minor component of BOLD signal propagation can be attributed to vascular effects.

The aforementioned arguments provide indirect evidence for the neural origin of BOLD signal propagation. More recently, Matsui and colleagues directly tested the basis of

BOLD signal propagation through simultaneous optical imaging of spontaneous fluctuations in neuronal calcium and vascular haemoglobin (the optical equivalent of the BOLD signal [54]) in the mouse [33]. Matsui *et al.* compared propagation patterns in neural calcium versus the BOLD signal using multiple analytic techniques, including computation of TD matrices in both signals. In each analysis, Matsui *et al.* found substantial agreement in propagation patterns between neural calcium and haemoglobin, directly demonstrating that BOLD signal propagation indeed reflects neural activity [33].

6. Summary

Since the advent of fMRI, our understanding of spontaneous activity has progressed from regarding it as merely noise, to primarily focusing on spatially segregated RSNs (spatial topographies of signals correlated at zero-lag), to now, an appreciation of its exquisite propagation structure. An in-depth tutorial for applying propagation analyses to rs-fMRI, including more discussion of pre-processing strategies required for lags computations, can be found at: http://www.nil.wustl.edu/labs/raichle/propagation_analysis.html. In particular, fMRI data must be slice-timing corrected prior to temporal lags analysis. Slice-timing correction is not currently implemented in several extant publically available datasets, including the human connectome project [55]. Thus, investigators wishing to explore propagation analysis must ensure their data has been slice-timing corrected.

7. Future directions

Patterns of propagated neural activity found in the resting state BOLD signal open an exciting new avenue for understanding brain function. Here we summarize some of the questions raised by our findings and the directions these findings suggest for future research.

1. *Biological mechanism:* It is presently not known what biological mechanisms underlie propagation of low-frequency activity (whether detected using the BOLD signal or electrophysiological means) [31,32,47,48]. Low-frequency phenomenon have generally been understood as modulations in cortical excitability [56–58] and previously proposed mechanisms for such propagation include balance in excitatory : inhibitory activity [59], astrocytic signalling [60,61], as well as fluctuations in cell metabolism [62,63]. These findings suggest that observed BOLD signal propagation likely corresponds to widespread, propagating shifts in excitability, the mechanisms of which are yet to be understood. Although we cannot presently elucidate propagation mechanisms, extant findings do offer some hints. First, the two cortical hemispheres are completely synchronous, with no lag in activity [33,42]. Second, as shown in figure 1*c*, unidirectional propagation within RSNs takes nearly the same amount of time regardless of whether the RSN is spatially contiguous (like the visual network) or spatially distributed (like the DM network, which has spatially separated posterior and anterior components). One explanation for these observations is that neural activity represented in the BOLD signal does not physically propagate across the cortex, but is organized subcortically, a heretofore unexplored possibility. Future experiments which record cortical activity during subcortical manipulations, for example, using DREADDs (designer receptors exclusively activated by designer drugs) in a mouse model [64], can directly test this hypothesis.
2. *Physiological function:* Neural communication in the brain is generally associated with fast axonal signalling along myelinated fibres, with temporal delays of the order of tens of milliseconds [44]. Fast, high frequency signalling underlies our ability to quickly perceive and react to environmental stimuli [65]. However, the existence of patterned slow, low-frequency propagation begs the question of the physiological significance of these phenomena. A theory proposed by Gyorgy Buzsaki, in the context of cortico-hippocampal function, suggests that in order to carry information, neural signals must be segmented into 'packets' conveying discrete messages [66,67]. Thus, whereas information may be conveyed quickly through high-frequency signals, slower propagation of low-frequency activity may act to coordinate signaling by creating a *routing structure* for higher frequency activity which delineates distinct 'packets' of information.

   For example, sharp wave ripples (SPW-Rs) rapidly convey high frequency (greater than 100 Hz) signals from the hippocampus to cortex [68], but the onset of SPW-Rs is modulated by slower (1–4 Hz) signals propagating from cortex to hippocampus [69,70]. Similarly, we speculate directed propagation of spontaneous infra-slow activity as reflected in the BOLD signal (e.g. back to front propagation in the DMN), may coordinate higher frequency information transfer in the opposite direction (e.g. front to back in the DMN). Future studies which explicitly compare the directionality of infra-slow and higher frequency signals are required to test how infra-slow propagation routes higher frequency information flow.
3. *Propagation sequences and neural processes:* It has been hypothesized that resting state BOLD activity may reflect specific neural processes (or events) which occur on the sub-second scale [3]. For example, Logothetis and colleagues demonstrated that hippocampal SPW-Rs have a distinct rs-fMRI signature, including inter-regional temporal delays of the order of those found in our resting state studies [71,72]. Hence, we speculate that rs-fMRI propagation sequences (e.g. lag threads) may correspond to distinct neural processes. If this hypothesis was true, we would expect state-dependent changes in rs-fMRI propagation structure, as spontaneous neural events are known to be altered across state. For instance, SPW-Rs, slow waves, and many other neural processes are enriched in (awake) post-task learning periods as well as sleep [68,73,74]. In fact, we have indeed found that propagation patterns in rs-fMRI are sensitive to physiological changes in state, including before versus after motor learning tasks [26], eyes open versus closed [26] and most dramatically, wake versus slow wave sleep [45]. These findings suggest that the propagation structure of rs-fMRI can be used to reveal fundamental neural 'events' or processes in spontaneous activity; however, future multi-modal studies are necessary to investigate whether events such as SPW-Rs underlie distinct BOLD signal propagation patterns.
4. *Relations to pathophysiology:* Altered neural communication is widely assumed to be a critical component of neurological and psychiatric illnesses [75–77]. The propagation

structure of rs-fMRI presents a much expanded way to study neural communication in human pathology. As a proof of principle, we recently studied high-functioning adults with autism spectrum disorder (ASD) and found significant group differences in propagation structure (ASD versus typical controls) [51]. Moreover, we found specific relationships between propagation abnormalities and behaviour. For example, altered cortico-striatal propagation in the ASD cohort was highly correlated with repetitive behaviours in individual subjects. By contrast, we did not observe significant group differences in conventional functional connectivity, in line with other recent reports [78,79]. Therefore, propagation may be a more sensitive marker of some pathologies than conventional functional connectivity. These findings also raise the possibility of therapeutic interventions. For instance, directed stimulation of neural populations has shown therapeutic promise in a host of diseases, but identifying proper stimulation loci has remained a challenge [80]. In the future, alterations in the propagation structure in rs-fMRI may be used to identify specific neural circuits or regions for targeted interventions and, also, a means of evaluating the results of those interventions.

Authors' contributions. A.M. and M.E.R. contributed equally to this article.

Competing interests. We declare we have no competing interests.

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Endnote

[1]A co-author of our earlier lag threads paper [42] suggested examining spatial correlations across lag thread topographies. He had intended to suggest computing spatial correlations between RSNs and lag threads, but A.M. mistook his meaning, and thus surprised the group by finding that voxel-wise correlations across lag threads mimicked RSN organization. We next struggled to interpret what the meaning of this computation might be. We did not know how to interpret high spatial correlations across temporal sequences. After several weeks of false starts, A.M. happened to be walking along a one-way street and wondered if the concept may explain the result. Through simulation, we were able to demonstrate that 'one-way streets' do in fact provide a way to explain the emergence of RSNs from lag threads.

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