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Review

The Rediscovery of Slowness: Exploring the Timing of Cognition

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Slowness of thought is not necessarily a handicap but could be a signature of optimal brain function. Emerging evidence shows that neuroanatomical and dynamical constraints of the human brain shape its functionality in optimal ways, characterized by slowness during task-based cognition in the context of spontaneous resting-state activity. This activity can be described mechanistically by whole-brain computational modeling that relates directly to optimality in the context of theories arguing for metastability in the brain. We discuss the role for optimal processing of information in the context of cognitive, task-related activity, and propose that combining multi-modal neuroimaging and explicit whole-brain models focused on the timing of functional dynamics can help to uncover fundamental rules of brain function in health and disease.

Rediscovering Slowness

In his thoughtful and beautifully written book, *Die Entdeckung der Langsamkeit* (transl. '*The Discovery of Slowness*') [1], the German author Sten Nadolny meditates over the ultimate reasons for the success and failure of the English polar researcher John Franklin (1786–1847). Franklin was much celebrated during the Victorian era but perished on his third expedition to discover the mythical Northwest Passage, supposed to link the Atlantic and the Pacific Oceans above the northern coast of the American continent. In the novel, Nadolny suggests that Franklin's fatal attraction to the Arctic was linked to his desire to find an environment suited to his slowness of thought, which among other things manifested itself in his inability to speak fluently, memorizing instead 'entire fleets of words and batteries of response'. Nadolny makes the compelling argument that the slowness of cognition is an essential component of optimality of thought.

This literary view of slowness resonates well with dual-process theories [2,3], and in particular with the work of Daniel Kahneman and Amos Tversky, who collected intriguing behavioral evidence that the human mind consists of two competing fast and slow systems [4,5]. System 1 is fast, instinctive and emotional, whereas System 2 is much slower, more deliberative, and more logical. System 2 has limited access to System 1, which is the main source of impressions, intuitions, intentions, and emotions, but it will still consciously elaborate on these and eventually turn them into beliefs and voluntary actions. A firm neurobiological foundation of these systems has not yet been established, but there is mounting evidence that these systems are the result of the dynamics of interacting networks of brain regions over time rather than the contribution of any single region [6].

The separation of timescales of neural functioning has also been put forward in modern computational theories of information processing in human behavior [7–9] and in brain disorders

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such as epilepsy [10]. Inspired by the theory of nonlinear **dynamical systems** (see Glossary), timescale separation offers, first, a means to separate two sets of variables functionally and, second, to build hierarchies of processes constituting cognitive architectures. Intuitive examples include, for instance, handwriting comprising dynamic behavior on fast and slow timescales, from creating the individual letters forming words to generating sentences and paragraphs [11].

In this Review we expand on these ideas to show how slowness is not solely a literary construct but could be a fundamental principle of brain function, emerging from underlying brain dynamics as demonstrated by advanced whole-brain computational modeling. We briefly review the rise of resting-state studies that focus on intrinsic brain dynamics in basic and clinical neuroscience, but show how the analysis of time in the brain has become increasingly important. In particular, recent findings [12,13] have radically shifted the emphasis from static spatial correlation analysis to time-dependent analysis of the fluctuations and dynamics of functional processing. We then review the role of whole-brain computational modeling in the growing understanding of the dynamics of brain function, and emphasize how these models can lead to a deeper understanding of the spatiotemporal dynamics. We show how modeling has been used to shed new light on the **metastable** properties of the human brain, in other words states falling outside the natural equilibrium state of the system but persisting for an extended period of time. This has demonstrated that the healthy human brain is maximally metastable, which leads to a natural slowness of task-related cognition. Finally, we discuss how these new findings of slowness, in an era of relentless speed, may come to have a profound influence on our understanding of brain function in health and disease.

Characterizing Functional and Structural Brain Connectivity

Over the past decade there has been an explosion of empirical and theoretical interest in the spontaneous or intrinsic activity of the brain [14]. Initially, neuroimaging experiments assumed that this spontaneous activity was mainly noise and could be used simply as a control for discovering task-related activity [15,16]. However, careful experiments using a wide variety of neuroimaging techniques have found that spontaneous activity is highly structured in time and space [17–19]. Neuroimaging experiments uncovered large distributed networks of brain areas that are highly correlated, and were named resting state networks (RSN) [20,21] – although this is really a misnomer given that their very existence demonstrates that resting brains never rest [22,23]. These RSN can be quantified in terms of **functional connectivity** (FC), which can be expressed as a matrix containing the correlations across a long time-series between all pairs of brain areas (at the voxel level or more typically at the level of a given standard brain parcellation (e.g., [24,25]). Typically this FC matrix quantifies the average spatial structure of the RSN (Figure 1).

Nevertheless, the question remains of how these correlations emerge in the first place. One simple idea is that they could be tied to the underlying structure of the anatomical connections linking them; in many ways akin to the ideas of the medieval philosopher Thomas Aquinas who, in the spirit of Aristotle, wrote '*Quidquid recipitur ad modum recipientis recipitur*' – the container (or recipient) shapes the content. In the case of the brain, the underlying anatomy has been proposed to shape the functional activity [26,27]. The argument goes that even if the local neuronal dynamics in each single node (e.g., a voxel) is mainly noise (as evidenced by neurophysiological recordings [28–30]), these voxels are linked by anatomical myelinated fibers connecting them synaptically, and thus their correlations could be driven and shaped by those links.

This attractive idea would be testable if it were possible to extract the anatomical structural skeleton, in other words the structural connectivity (SC), that can be expressed in terms of a structural connectivity matrix. This can be mapped *in vivo* in humans on the scale of millimeters

Glossary

Attractor: a set to which a dynamical system evolves after a sufficiently long time. Points close to the attractor remain close, even under small perturbations.

Bifurcation: an abrupt qualitative change in the system's dynamics when one or more parameter pass through critical values, for instance loss of stability and the appearance of sustained oscillations.

Connectome: the complete description of the structural connections between elements of a nervous system.

Criticality: at the brink of a bifurcation, the system displays certain characteristic dynamic features, of which most are related to enhanced fluctuations.

Critical slowing down: the phenomenon that the return-time of a disturbance back to equilibrium increases close to a bifurcation.

Diffusion tensor imaging (DTI): an MRI technique that takes advantage of the restricted diffusion of water through myelinated nerve fibers in the brain to infer the anatomical connectivity between brain regions.

Dynamical systems: an area of applied mathematics that describes the behavior of complex (possibly chaotic) dynamical systems as described by differential or difference equations.

Edges: in a brain graph, an edge between nodes (regions or neurons) indicates that the nodes are anatomically or functionally connected.

Functional connectivity: statistical association – for example, significant correlations – between neurophysiological measurements recorded from anatomically distinct neurons or regions at several time-points.

Graph theory: a branch of mathematics that deals with the formal description and analysis of graphs. A graph is defined simply as a set of nodes (vertices) linked by connections (edges), and may be directed or undirected. When describing a real-world system, a graph provides an abstract representation of the system's elements and their interactions.

Hopf bifurcation: in nonlinear dynamics, a Hopf bifurcation is a local bifurcation (see above) in which an initially stable fixed point of a

(A) Structural connectivity

MRI + DTI

Tractography

AAL

SC

SC matrix

(B) Functional connectivity

EPI + Voxel tc

sec

EPI time-series

rs-MRI + AAL

Regional tc

FC matrix

(C) Structure–function relationship

Spontaneous correlation pattern

FEF — AS
CeS
IPS — SF
LIP
MT/MST — STS

3/4 — 4/4
Conjunction

Evoked response pattern

$P < 0.05$ — $P < 10^{-4}$
Activation

Anatomical connectivity pattern

Light — Strong
Density
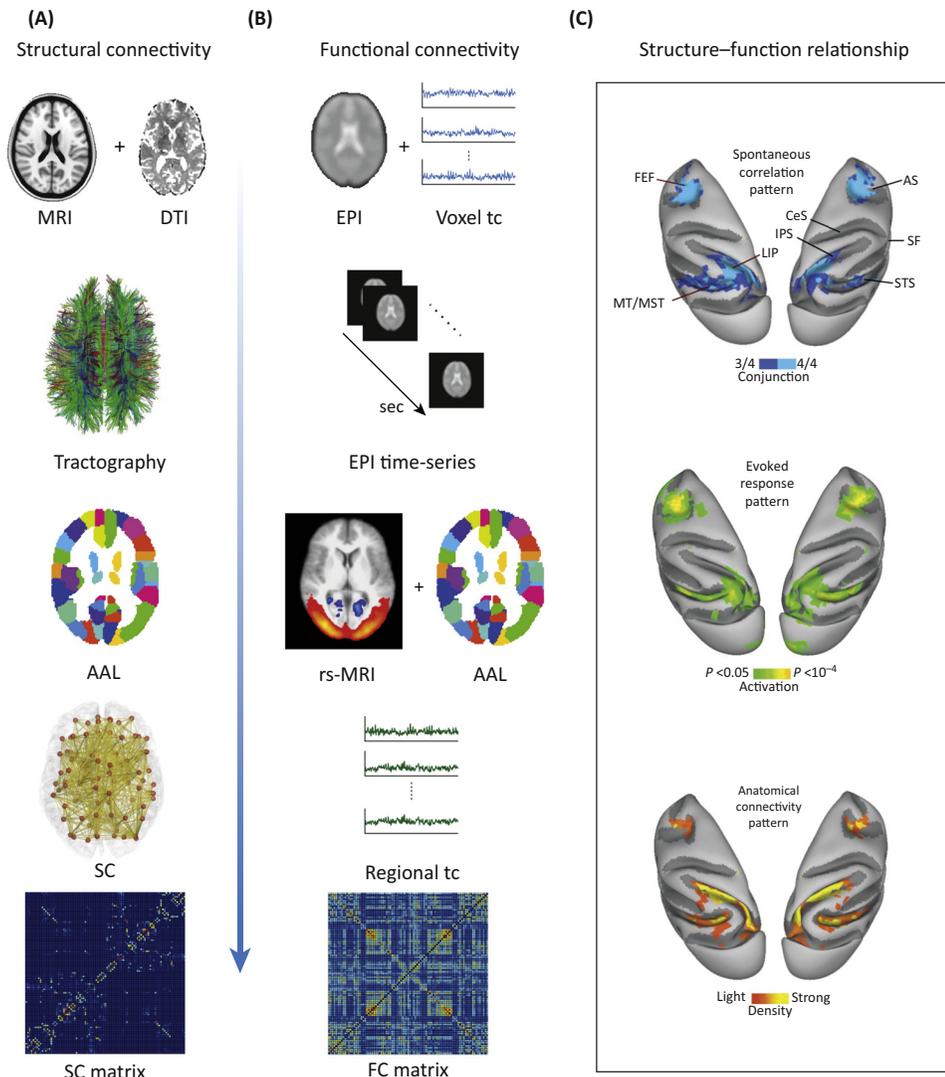
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Figure 1. Methods for Characterizing Functional and Structural Connectivity. Neuroimaging data can be used to extract the functional and structural connectivity *in vivo*. (A) Typically, obtaining the topological measures of structural connectivity (SC) requires structural MRI and diffusion tensor imaging (DTI), as well as a parcellation scheme (here we show the automatic anatomical labeling, AAL, parcellation), and the use of tractography measures to extract the SC matrix. (B) Similarly, functional connectivity (FC) can be obtained from functional neuroimaging measures of brain activity; for example, echo planar imaging (EPI) scans that sample the blood-oxygen-level dependent (BOLD) signal timecourse (tc) in each voxel. Combining this with a parcellation scheme can recreate the regional timecourses for each of the regions in the parcellation. The FC matrix is typically created from correlating the regional timecourses. (C) Evidence that SC is closely linked to FC has come from neuroimaging of primates, where cortical patterns of coherent spontaneous BOLD fluctuations are similar to those of task-evoked responses and anatomical connectivity [26]. The top panel shows a conjunction map of BOLD correlations within the oculomotor system on dorsal views of the monkey atlas left and right hemisphere surfaces. The middle panel shows task-related activity in a saccadic eye-movement task. The bottom panel shows the structural connectivity from the density of cells labeled by retrograde tracer injections into right lateral intraparietal area. Abbreviations: AS, arcuate sulcus; CeS, central sulcus; IPS, intraparietal sulcus; rs, resting state; SF, sylvian fissure; STS, superior temporal sulcus.

dynamical system loses its stability in an oscillatory fashion.

Kuramoto order parameter: a measure of the level of synchrony between oscillators in a network.

Magnetoencephalography (MEG): a method of measuring brain activity by detecting minute perturbations in the extracranial magnetic field that are generated by the electrical activity of neuronal populations.

Mean-field model: the mean-field approximation consists of replacing the temporally averaged discharge rate of a cell with an equivalent momentary activity of a neural population (ensemble average) that corresponds to the assumption of ergodicity. According to this approximation, we characterize each cell assembly by means of its activity population rate.

Metastability: in dynamical systems this refers to a state which falls outside the natural equilibrium state of the system but persists for an extended period of time.

Multistability: coexistence of more than two stable steady-states at given parameter values.

by using diffusion weighted imaging/**diffusion tensor imaging** (DWI/DTI) which can measure the white-matter fiber tracts constrained by the diffusion of water molecules [31,32], and where the connectivity between brain regions can be reconstructed by probabilistic tractography [33,34] (Figure 1A).

Over time, evidence for this hypothesis has accumulated from several sources, including seminal research in primates, showing that the average FC is significantly correlated with the SC during rest [26] (Figure 1C). However, this group and others only found low, albeit significant, structure–function correlations, suggesting that other factors also shape brain activity. Perhaps the most important clue to other potential influences comes from the fact that the typical FC matrix calculation ignores the importance of time. We and other researchers have argued that dynamics are indeed pivotal for understanding how the FC is shaped, in other words – in addition to the SC – others factors such as time-delays and the current global working point of the brain are crucial [13]. Thus, careful dynamical analysis is likely to improve our understanding of the underlying spontaneous brain activity.

Uncovering the Spatiotemporal Dynamics of Brain Activity

Studies have demonstrated that the correlations among brain regions, both within and between networks, evolve over time [35–37]. Important insights recently emerged from observations of fluctuations of the FC when calculated over relatively short sliding windows [12]. Further progress was made in quantifying the spatiotemporal structure of these fluctuations by introducing a careful dynamic analysis characterizing the FC dynamics (FCD) and explaining its nature based on large-scale network models [13]. The method for calculating the FCD is summarized in Figure 2.

When applied to empirical data, the FCD matrices show a characteristic checkerboard-like structure that signals when there is switching between different brain states or activity patterns (Figure 2C). In other words, the analysis can show when a brain network state recurs intermittently over time, across scanning sessions, and even across participants. These results suggest that spatial patterns are formed, dissolved, and reformed over time, such that periods of resting activity can be subdivided into subsets or 'communities' of brain regions that strongly interact over a period of time.

Research has demonstrated that the global phase synchrony of the time-series of brain activity evolves on a characteristic ultra-slow (<0.01 Hz) timescale, and that its temporal variations reflect the transient formation and dissolution of multiple communities of synchronized brain regions [38]. The level of variability of the global phase synchronization can be expressed by the standard deviation (SD) of the so-called **Kuramoto order parameter**, defining the metastability of a given system. Empirical measurements have confirmed that the brain is metastable [39].

Importantly, such time-varying functional connectivity has been reported both in awake humans and anesthetized macaques [36,40], thus the temporal variability of functional interactions is not likely to be produced by transitions between different mental states, but instead may be an emergent property of complex brain networks. These results suggest that the interplay between space and time in the brain is crucial to unraveling the mechanistic origins of spontaneous activity.

Whole-Brain Computational Modeling

One powerful way to investigate and model the non-stationary dynamics of whole-brain activity is to use whole-brain computational modeling (Box 1), which takes into account the interplay and mutual entrainment of local dynamics using the underlying structural connections, and results in global whole-brain dynamics (Figure 3A). Indeed, whole-brain models have been shown to be able to explain the spatial aspects of the resting FC by fitting the spatial correlation as extracted by the grand average FC [23,41]. Research has shown that the fitting of the grand average FC overemphasizes the influence of the SC, and that the resulting models are incapable of showing the non-stationary switching dynamics of the FC [13]. This difference is qualitative and cannot be

(A)

TS1
TS2

(B)

Time shift

TS2
TS1

Time shift

(C) Empirical FCD

Time shift (s)
200 400 600 800 1000 1200
Time shift (s)

(D) Simulated FCD

Time shift (s)
200 400 600 800 1000 1200
Time shift (s)

(E) FCD fluctuations

Kolmogorov–Smirnov distance

(F) Kuramoto order parameter

Time

Metastability of model

Metastability of data

Dynamical working point
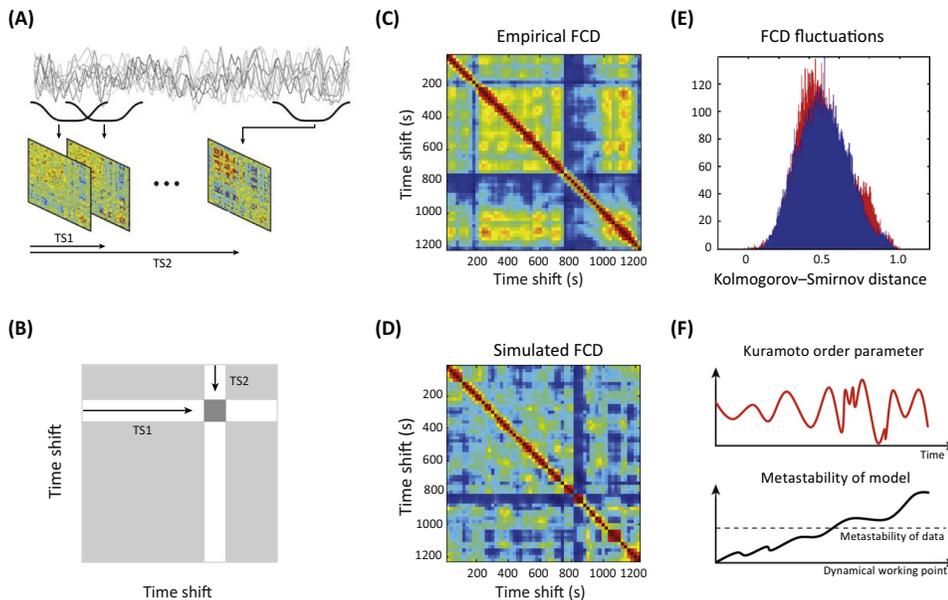
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Figure 2. Methods for Measuring Functional Connectivity Dynamics (FCD). (A) FCD captures the spatiotemporal organization of FC by representing the similarities between FC(t) matrices calculated in a short window of time (usually 60 s) located at different times, for example TS1 and TS2. This is accomplished by splitting each full-length BOLD time-series into several sliding windows, M. For each of these sliding window, centered at time t, a separate FC matrix, FC(t), can be calculated. (B) The FCD is thus a symmetric matrix with dimension M×M where the (ts1, ts2) entry is defined by the Pearson correlation between the upper triangular parts of the two matrices FC(ts1) and FC(ts2). (C) Thus epochs of stable FC(t) configurations are reflected around the FCD diagonal in blocks of elevated inter-FC(t) correlations. (D) Simulated FCD. (E) For comparing the FCD statistics, the upper triangular elements of the matrices are collected over all participants and sessions. The simulated and empirical distributions can then be compared by calculating the Kolmogorov–Smirnov distance between them, because this quantifies the maximal difference between the cumulative distribution functions of the two samples. (F) The metastability can be measured as the SD of the Kuramoto order parameter across time, which provides a measure the global level of synchronization of the oscillating signals.

simply addressed by quantitative parameter tuning. Following this insight the fitting of FC at one timescale only was abandoned; instead it was shown that a slight increase in nonlinearity of the node models suffices to create the non-stationary FCD as observed empirically. In fact, it appears that the slow switching of FC dynamics is the normal behavior of a nonlinear large-scale brain network and occurs naturally without any major parameter tuning.

The question therefore arises: what is the purpose, if any, of the slow FCD? Mechanistically, the most detailed models describe local spontaneous dynamics as **attractors** by means of explicit simulations of spiking neurons and their detailed synaptic connections, including the dynamics of specific neurotransmitter receptor types [42]. However, the emergent collective macroscopic behavior of brain models has been shown to be only weakly dependent on the details of individual neuron behavior [43].

This agrees with fundamental results from statistical physics, which have shown that macroscopic physical systems obey laws that can be independent of their mesoscopic constituents [44]. In turn, this allows whole-brain modeling to use reduced neural mass models, of which there are two main types: (i) oscillatory models [45–50] and (ii) asynchronous models [51–53]. These models can be unified by using a neural mass local model, such as the normal form of a **Hopf bifurcation**, to describe the transition from noise to oscillations, and this has been shown to exhibit both richness and generality in describing the temporal dynamics of EEG at the local node level [54,55].

Box 1. The Virtual Brain

The Virtual Brain (TVB) is a freely-available public tool based on an international neuroscience project that promotes the large-scale network perspective of brain function and dysfunction, and assembles the neuroinformatics competences for the computer simulation of individual brain networks [77] (Figure I). This level of description allows mimicking the empirical data sets obtained from invasive and non-invasive human brain imaging. TVB provides for the first time the possibility to feed computational neuronal network models with information about brain activity (EEG, MEG), spatially highly resolved whole-brain metabolic/vascular signals (fMRI), and global measures of neuronal connections (DTI) – for intact as well as pathologically altered connectivity. This enables the development of individual connectivity-dependent models of oscillatory activity and the characterization of network mechanisms that underlie the genesis of brain activity. The TVB platform allows performing either simulation with systematic parameter sweeps for hypothesis testing; or fitting of parameters against a participant's brain imaging data. These approaches can lead to the development of new diagnostic and therapeutic interventions. Currently ongoing projects are in the field of epilepsy, stroke, and aging. Beyond the direct implications for diagnosis, treatment, and prevention of network dysfunctions, the results of the Virtual Brain studies are likely to significantly contribute to the understanding of fundamental mechanisms of the brain's structure–function relationship.
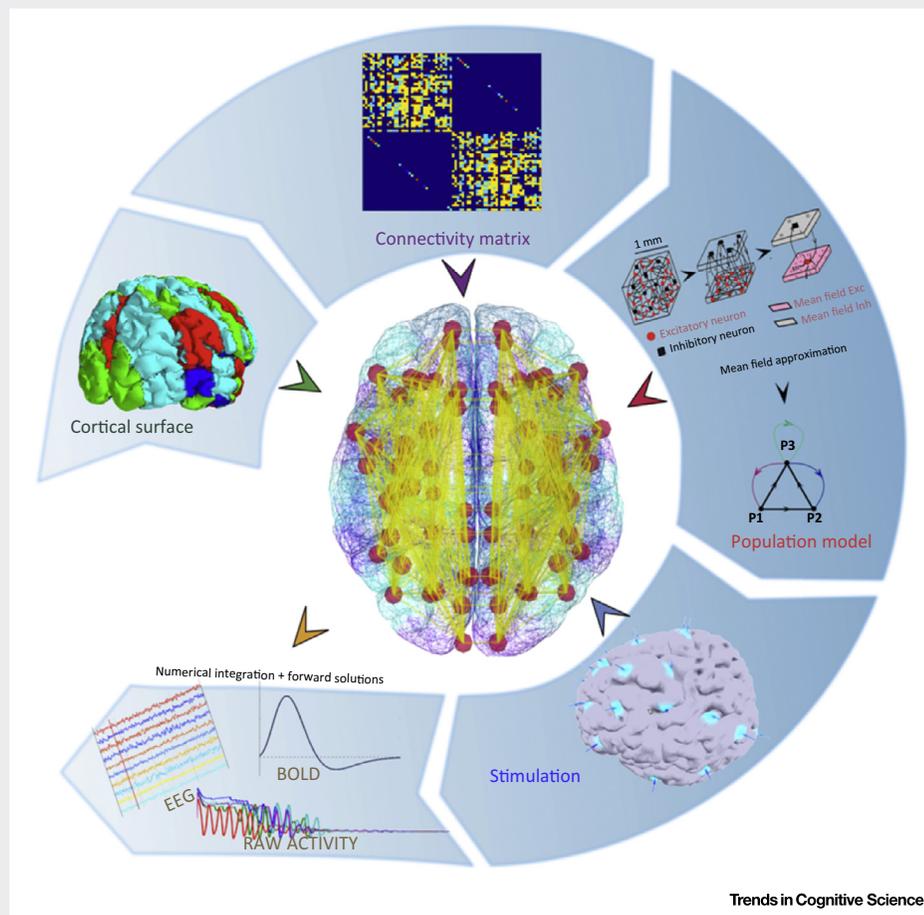
Figure I. Workflow in The Virtual Brain. A template for the cortical surface defines 3D geometry and parcellation. Methods of DTI allow reconstructing connections and tract lengths of fiber bundles to define a connectivity matrix and time-delays via signal transmission. Neural population models serve as network nodes generating dynamic signals owing to their intrinsic dynamics and interactions with other nodes. Interventions such as lesioning the connectivity, or stimulating brain regions, offer means to probe the brain dynamics in TVB. The resulting brain network dynamics is registered as raw local field potentials (LFP), BOLD fMRI, EEG, and MEG signals.

The Resting Brain Is Maximally Metastable and Slow

Evidence from a wide range of experiments suggests that the brain is metastable [39] (Box 2). Further empirical evidence has recently come from whole-brain computational models with oscillatory local nodes using the Kuramoto model [50,56]. These simulations fitting the model to
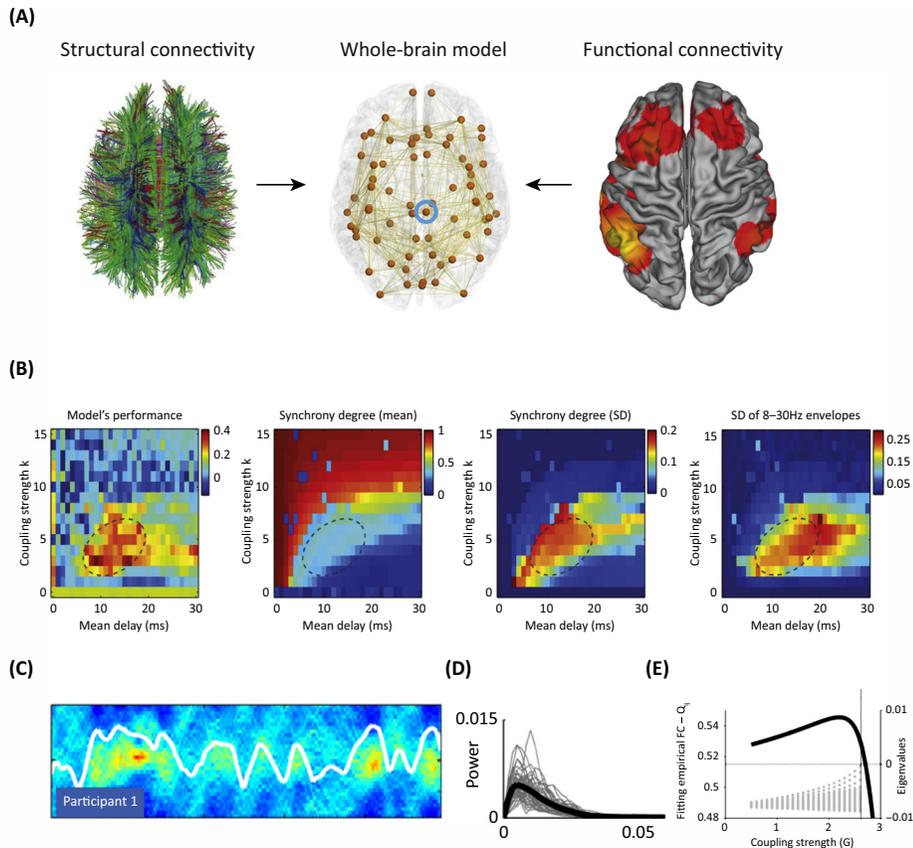
Figure 3. Metastability and Whole-Brain Computational Modeling. (A) Whole-brain computational models can be constructed using the structural connectivity (SC) between a given parcellation of brain regions, using either oscillatory or asynchronous local node models to fit the functional connectivity (FC) from neuroimaging data [e.g., fMRI or **magnetoencephalography** (MEG) data]. (B) Using an oscillatory local node model based on the Kuramoto model with only two parameters (global mean delay and coupling strength) showed maximal metastability and therefore maximal exploration of the dynamical repertoire [50]. The figures show the correlation between real and simulated FC profiles as a function of the coupling strength and the mean of the delay distribution. The area within the dashed line indicates the parameter range for which the model provides the best estimates of real MEG FC profiles. Fluctuations in the mean and SD of synchrony degree are indicative of a metastable synchronization regime (two middle figures). Similarly, in the presence of time-delays, the metastable synchronization induces a modulation of oscillator frequency, which generates envelope fluctuations of 8–30 Hz. (C) The temporal dynamics of phase interactions are shown for a typical participant [38]. (D) The power spectrum of the Kuramoto order parameter is shown across all participants, indicative of slow processing [38]. (E) Structured linear fluctuations around the spontaneous state show a characteristic slowing down before the bifurcation [51].

MEG data recorded over milliseconds importantly show that the brain is not only metastable, but maximally metastable, which implies the possibility for the widest exploration of the dynamical repertoire of the network. The Kuramoto model was implemented within the automatic anatomical labeling (AAL) parcellation of the structural connectivity of the human brain and used only two parameters, namely the global coupling strength and the mean delay between brain regions. As shown in Figure 3B, the model fits the data optimally within a limited combination of values of the two parameters as shown in the plots of (i) goodness of fit to empirical FC data, (ii) mean and (iii) SD of synchrony degree, and (iv) SD of the 8–30 Hz envelopes. Perhaps most importantly, at this particular working point of the whole-brain model, metastability is also maximal, which potentially has deep significance for our understanding of fundamental brain function.

It is important to realize that this type of discovery can only be made through a combination of integration and fitting of multimodal neuroimaging data with computational models [42]. Conventional correlational analyses are able to demonstrate that the brain is metastable, but crucially not whether it is maximally metastable – this is only possible with whole-brain computational modeling.

One of the important consequences of the brain being maximally metastable is that this implies a characteristic slowness of spontaneous dynamics (i.e., the switching transitions between brain states) upon approaching a bifurcation or state transition, a phenomenon termed '**critical slowing down**'. Although predicted by theory, only recently has this been demonstrated experimentally in elegant whole-cell patch-clamp recordings from pyramidal neurons and fast-spiking interneurons in rats [57]. Switching dynamics and co-occurring phenomena have been previously observed in human behavior [58] and human brain recordings [59,60]. It is the propagation of switching behavior across brain scales, in other words microscopic to macroscopic, that is relevant for cognition [61].

Whole-brain computational models can also be used to study the temporal evolution of resting state activity using the Kuramoto order parameter to measure the global level of synchronization of the oscillating signals between brain regions [38]. Figure 3C shows an example of this temporal evolution of the global level of synchronization in the human brain. Notably, the power spectrum of this evolves on an ultra-slow (<0.01 Hz) timescale (Figure 3D). Similarly, whole-brain computational models have demonstrated a critical slowing down on the **edge** of a **criticality** (Figure 3E) [51]. These findings imply that optimality, in the sense of maximally and wide exploration of the dynamical repertoire of the network, is a fundamental property of optimal task processing.

Beyond Resting: The Brain Is Slow During Stimuli/Task Processing

One must question the importance of slowness in the resting brain when it could be argued that cognition is more about engaging with tasks and stimuli than what is done at rest [16]. From the

(A)

(B)

(C)
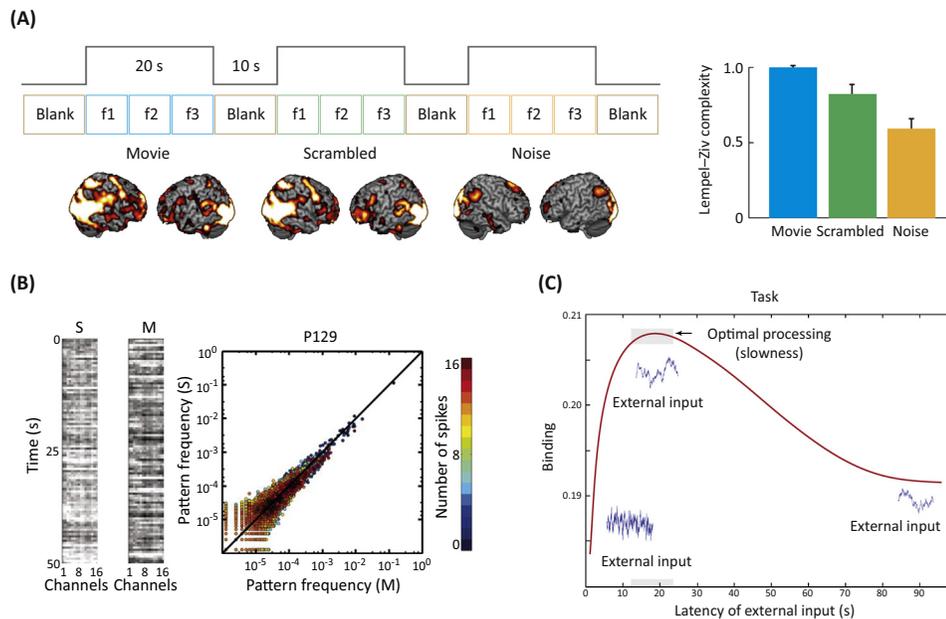
Figure 4. Slowness in Processing of Natural Stimuli. (A) The complexity of brain activity in response to natural sequence of images (movie) was significantly higher than to temporally and spatially scrambled images (with preserved first-order statistics). Adapted from [63]. This suggests that the temporal binding of information in human brain is better suited to the natural, slow timing/latencies of stimuli than to rapid unstructured noise. (B) Similarly, recordings of neural activity in awake ferrets to natural scenes stimuli (movie, M) show that the neural activity is well matched to the spontaneous neural activity (S). (C) We hypothesize that the binding (i.e., the level of encoding of information) is maximal when the brain is maximally metastable. This could be tested using a whole-brain computational model optimized to spontaneous activity but driven by external stimuli. This suggests that for the brain to optimally process external signals, the latencies should be on the order of the underlying latency of the timing of the resting brain, in other words of the switching between resting brain states, which existing data suggest would be with a latency of external input of around 20 s. At that point, the external signal 'resonates' with the underlying latency of the whole-brain dynamics, leading to optimal processing.

very start, neuroimaging experiments have – albeit mostly involuntarily – explored the link between spontaneous and task-related activity by pervasive use of subtraction paradigms. Nevertheless, it is only with the rise of resting-state paradigms that a better understanding has arisen of the link between them [23,62].

Neuroimaging experiments have started to reveal some of the key differences between spontaneous and task-related activity in further well-controlled ways and, in particular, have begun to quantify the speed of processing. One recent experiment assessed brain activity patterns in response to a natural slow, temporal sequence of images (movie), which was scrambled over time (scrambled movie) or space (noise); thus preserving the first-order statistics across stimuli [63] (Figure 4A). Strong and widespread cortical activity was found in all conditions, but selectively the Lempel–Ziv complexity of these activity patterns was found to have the highest value for the movie and was minimal for the noise condition. Thus, while the stimuli were carefully matched, meaningful integration and segregation of externally driven information over time clearly rely on slow processing of natural, temporally structured information.

Similarly, studies in other animals have established links between spontaneous activity and externally driven information. For example, a recording study in awake ferrets found a strong similarity between stimulus-evoked and spontaneous neural activities to responses evoked by natural scenes [64] (Figure 4B). They found improvements in this activity during development,

which demonstrates that the brain clearly adapts to the slowness of natural stimuli at the neural level.

Nevertheless, these are correlational results, and whole-brain computational modeling can provide new evidence for what happens during stimuli/task processing, where the evoked brain activity is designed for optimal processing and where the encoding of external information takes place at an optimal 'slow' range of latencies (i.e., at the timing of cognition).

We hypothesize that it should be possible to measure the binding ability of the human brain as a function of the latency of the external stimulation. Binding is defined as the amount of information of the input signal which is encoded in the network across time, in other words the entropy of all nodes across time [65]. The link to stimulus-evoked activity can be explored by simulating natural, external stimulation using the well-known independent stochastic (Ornstein–Uhlenbeck) process with equal variance but different latencies [66]. Subsequently, this would allow measurement of the binding of information over time by the brain activity using a sliding-window approach (Figure 4C) [65]. Existing evidence of ultra-slow activity [38] suggests that a clear maximum will emerge around at 20 s, which means that, around this relatively slow time-point, the brain is able to optimally process external inputs. In other words, to process optimally external time-signals, their latencies should be on the order of the underlying latency of the timing of the resting brain, in other words of the switching between resting brain states. At that point, the external signal 'resonates' with the underlying latency of the whole brain dynamics, and therefore the processing is optimal.

As shown earlier, this slowness in processing, or the latency of the metastability, is the result of the resonance of the latency of the external inputs with the crucial slowing down or intrinsic slowness of the switching between the different brain states (at rest). Thus, importantly, this finding is unlikely to be an artefact of, for example, low-pass filtering of the BOLD signal.

Concluding Remarks and Future Perspectives

Slowness is not obviously a desirable quality in a ruthless natural world built primarily on survival; even so, the relative evolutionary success of humans is evidence that a degree of slowness of cognition combined with fast reactions can be highly adaptive. The flexibility of human cognition for goal-directed behavior relies on our ability to build coherent, distributed dynamical states by segregating and integrating information on multiple timescales [65].

As an example, think about how helpless human infants are during infancy and childhood, and how caregiving behavior must be key to the survival of the human species [67,68]. Caregiving behavior depends partly on very fast processing of infant cues, exemplified by the fact that infant sounds elicit significant activity already after only 50 ms in the brainstem [69], and that infant facial features elicit activity in the orbitofrontal cortex within around 130 ms [70]. However, once this attentional, orienting response has taken place, it is replaced with careful, slow caregiving behavior that can address the specific needs of the infant. This slower, deliberate cognition has been shown to rely on much later brain activity in distributed networks which include the very same regions of the orbitofrontal cortex recruited earlier for the fast response [71]. This is potentially important for the future well-being of the infant given how slow, maladaptive parental cognitions such as rumination and worry can lead to significant disturbances in the parent–infant relationship [72]. More generally, the dual process of fast, attention-orienting activity followed and modulated by slower, conscious cognitive processes has been shown to be a recurrent theme across the sensory modalities that is highly dependent on intact reward processing [73–75].

What has been lacking is a mechanistic understanding of how the human brain achieves the right balance between the slow and fast processes across temporal hierarchies in cognitive

architectures [7]. We have presented here emerging evidence that, during task processing, the maximally metastable brain contains intrinsic brain activity that is designed for optimal processing, and can encode external information at an optimal 'slow' range of latencies.

This new insight into striking the optimal balance between fast and slow cognition may also be important for understanding the progression in brains from healthy to diseased. As such, it adds to current ideas of using connectomics in neuropsychiatry to discover new biomarkers and potential treatments [76] by using whole-brain computational models for understanding fundamental principles of brain function, especially to further understand the importance of time [53]. As a result, the field is now beginning to shift from using static grand averages (**mean-field model**; based on **connectomics**) to characterizing the time-dependent dynamics of whole-brain networks. It would be of considerable interest to test whether slowness could be an essential biomarker of a healthy brain (Outstanding Questions).

Overall, the rediscovery of time in cognitive neuroscience and connectomics is leading to new insights into the fundamental principles of brain function. Not only may this help to better understand the human brain's precarious balancing act of processing and predicting stimuli on different timescales, whether slow or fast – but it may also lead to a new appreciation of how slowness can help us deal with what may feel like an ever-accelerating pace of life. Nadolny suggests that Franklin may have sought the Arctic to match the speed of his thought processes, but ultimately the most important factor is the balance between fast and slow, between adequately processing the past to predict not only the now but the future. As observed by the Polish poet Wislawa Szymborska 'when I pronounce the word Future, the first syllable already belongs to the past.' Nonetheless, by learning to optimally balance fast and slow processes in the maximally metastable brain, we may be able to extend the 'now' into the 'long now'. This balancing act could potentially be extended to a Zen-like perspective of observing infinite gratitude for the past, infinite service to the present, and infinite responsibility for the future. Although such balanced states are rare, science reminds us that a potential route could be through the built-in slowness of the architecture of our brains.

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Outstanding Questions

What are the necessary and sufficient brain regions for balancing fast and slow processing?

How does the balance between slow and fast processing change between different conscious states, for example between being awake and different stages of sleep?

What are the neural mechanisms by which the reward system can bias the brain to change the balance between fast and slow processing?

What is the developmental trajectory of slowness?

How does the balance between slow and fast processing change in specific brain disorders?

Could slowness be a biomarker of a healthy brain?

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