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Review

Prefrontal cortex drives the flexibility of whole-brain orchestration of cognition

Morten L Kringelbach[1,2,3] and Gustavo Deco[4,5]

The brain is hierarchically organised across many levels, from the underlying anatomical connectivity to the resulting functional dynamics, which supports the necessary orchestration to ensure sufficient cognitive and behavioural flexibility. Here, we show how two emerging frameworks have been used to determine the brain's functional hierarchy and its reconfiguration in different cognitive tasks. One study used direct estimation of the information flow across a whole experiment to reveal the common top hierarchical regions orchestrating brain dynamics across rest and seven cognitive tasks. Another study used complementary, indirect spatiotemporal measures defining hierarchy as the asymmetry in the directionality of information flow to identify a set of regions within the prefrontal cortex (PFC) that serve as the common, unifying drivers of brain dynamics during tasks. Overall, these studies are beginning to reveal the orchestration of whole-brain dynamics and how specific PFC regions are key to driving our cognitive and behavioural flexibility.

Addresses
[1] Centre for Eudaimonia and Human Flourishing, Linacre College, University of Oxford, Oxford, UK
[2] Department of Psychiatry, University of Oxford, Oxford, UK
[3] Center for Music in the Brain, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[4] Center for Brain and Cognition, Computational Neuroscience Group, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Roc Boronat 138, Barcelona 08018, Spain
[5] Institució Catalana de la Recerca i Estudis Avançats (ICREA), Passeig Lluís Companys 23, Barcelona 08010, Spain

Corresponding author: Deco, Gustavo (gustavo.deco@upf.edu)

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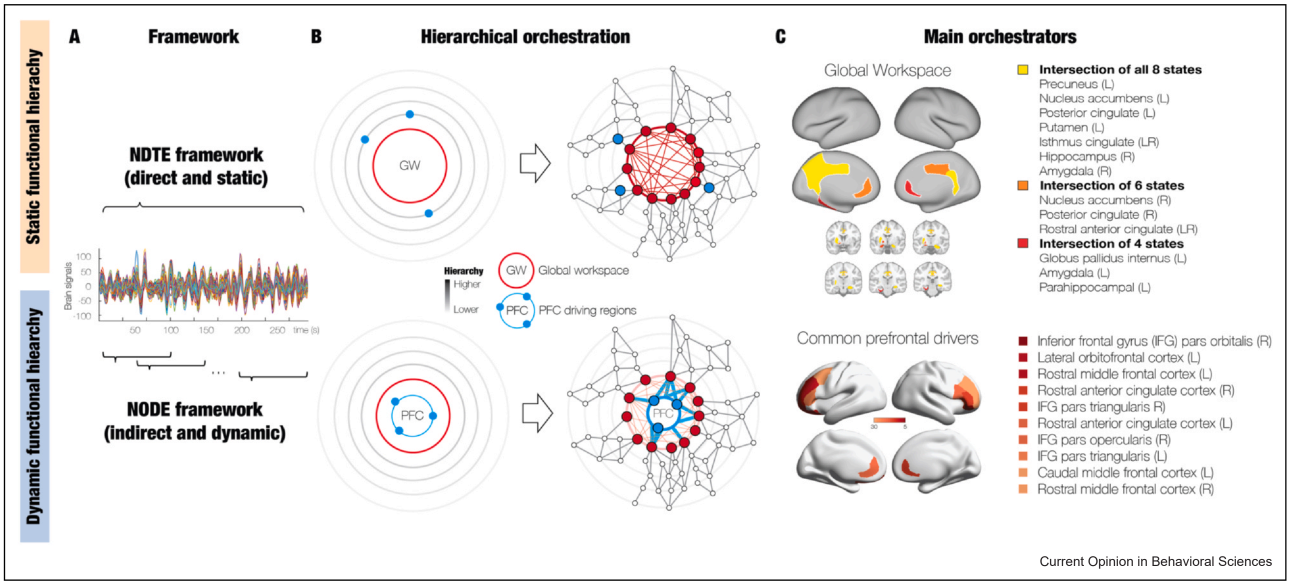
Introduction

In order to survive, the brain has to exhibit flexibility in terms of both cognition and behaviour when navigating complex environments [1]. This flexibility requires careful balancing of brain resources, and a large body of research has implicated the prefrontal cortex (PFC) in the necessary cognitive and emotional control [2], co-ordinating mental processes and actions in line with current goals and future plans, as shown by the extensive literature [3–10].

Mechanistically, this flexibility must rely on the hierarchical organisation of the brain, where information flows from distinct unimodal areas to integrative transmodal areas collaborating to orchestrate optimal brain communication and computation [11]. Evidence suggests the PFC sits at the top of the brain hierarchy [12–14], where it has a *unifying* role in directing the orchestration of complex brain dynamics [10], which includes interference control, response inhibition, mental set shifting, and working memory [6,7,10]. This is consistent with the literature showing that the PFC plays a role in the mediation of contingencies of action across time, which is important for the temporal organisation of cognition and behaviour in what is generally known as 'cognitive control' — or 'executive function' in the clinical literature [6,7]. Similarly, this recent evidence also confirms Fuster's hypothesis that the PFC serves an integral role in directing the 'perception–action cycle', where it orchestrates a cycle through the environment, sensory feedback, and to the cortex, to action and back [3]. This framework posits that the so-called 'cognits', cognitive networks formed originally by Hebbian rules, serve not only memory but also attention, perception, language and intelligence [9,15]. Importantly, the necessary flexibility in cognition and behaviour arises in the PFC from the intimate cooperation of the other cortical and subcortical participants in the perception–action cycle to create new actions [9]. More generally, it has been proposed that cognitive control is linked to the active maintenance of sequences of activity in the PFC, providing bias signals to other regions in the brain hierarchy [2]. It should be noted, however, that brain regions outside the PFC, such as, for example, cingulate, insular and posterior parietal cortices, have also been implicated in cognitive control [13,14,16].

Figure 1



Hierarchical orchestration of brain dynamics. **(a)** The NDTE framework provides direct estimations of the information flow between brain regions across the full timecourse of an experiment and thus a precise estimation of the static hierarchy [17]. In contrast, the NODE framework uses indirect estimations of the hierarchy using time-windowed measurements of the arrow of time [10]. This provides an estimation of the dynamic, spatiotemporal hierarchy. **(b)** The circular schematic illustrated the hierarchical organisation, moving from lower regions in the outer rings to the higher inner rings. The inner ring (in red) corresponds to top of the hierarchy, corresponding to the GW. The NDTE framework revealed how common, stable regions of the GW orchestrate the information over longer timescales, similar to how an administrative team would organise an enterprise. This static framework found that regions of the PFC (in blue) were located lower in the hierarchy. In contrast, on faster timescales, this administrative organisation is temporarily overtaken by prefrontal regions as revealed by the NODE framework. This temporary move of PFC regions to the top of the hierarchy is illustrated by how the blue regions temporarily move to form an inner circle. (c) The overall administrative GW revealed by NDTE consists of the left precuneus, left nucleus accumbens, left putamen, left posterior cingulate cortex, right hippocampus, right amygdala and left and right isthmus cingulate. Further regions are included if the threshold of intersection is lowered. In contrast, NODE revealed the spatiotemporal prefrontal drivers to consist of a set of PFC regions, including the Inferior frontal gyrus (pars orbitalis, opercularis and triangularis), lateral orbitofrontal, rostral and caudal frontal and rostral anterior cingulate cortices.

Here, we describe two frameworks for determining hierarchy in whole-brain dynamics and how these were used in complementary human neuroimaging studies to identify the orchestration of whole-brain dynamics. The first information-theoretic framework is *direct* but requires large amount of data both in terms of participants, each with long time series, producing a static hierarchy across the full experiment. The second thermodynamic framework is *indirect* and dynamic and can be used to investigate changes in hierarchy over time. Furthermore, this opens up for the possibility of using smaller data sets with fewer participants, creating the possibility to investigate smaller cohorts of patients with neuropsychiatric disease. But, as shown in this opinion paper, each framework has strengths.

Figure 1a (*top row*) shows the result of using a direct measure of information flow in the *normalised directed transfer entropy* (NDTE) framework to identify the common top hierarchical regions, called the 'global workspace' (GW), orchestrating brain dynamics across both rest and seven cognitive tasks [17], which were designed to capture the full span of human flexibility in cognition and behaviour. The information flow was measured using NDTE, which captured the *static* hierarchy over each of the eight experiments in the comprehensive Human Connectome Project (HCP) with over 1000 healthy people (Figure 1b, *top*). Interestingly, these results identified the GW consisting of midline cortical and deeper subcortical regions but not including PFC regions (Figure 1c, *top*).

Importantly, however, in order to go beyond this static measure and take into account flexibility *over time*, as shown in Figure 1a (*bottom row*), the second *Novel whole-brain modelling of Ongoing Dynamics Entropy production* (NODE) framework used a novel indirect, spatiotemporal measure inspired by thermodynamics, which defines hierarchy as the asymmetry in the directionality of information flow, or 'breaking the detailed balance' as it is commonly referred to in physics and systems biology [10]. When taking time into account, this framework identified regions within the PFC as the common, unifying drivers of brain dynamics during difficult tasks (Figure 1b, *bottom*). The key regions of the PFC included the inferior frontal gyrus, lateral orbitofrontal cortex, rostral and caudal frontal cortex and rostral anterior cingulate cortex (Figure 1c, *bottom*). Their causal mechanistic importance was demonstrated by selectively lesioning these regions in a whole-brain model. Overall, this study showed how specific PFC regions are key to driving the flexibility in orchestration of whole-brain dynamics, while a GW has more of an administrative role in promoting smooth functioning.

Hierarchical organisation of the brain and its dynamics

In the most general terms, hierarchy has been demonstrated to be an organising principle in all living systems [18]. This is perhaps best illustrated by thermodynamic modelling of biological systems as physical systems, where, in the most general abstraction, they can be described as thermodynamic open systems showing self-organised behaviour. The set–subset relations between dissipative structures are best characterised by a hierarchy across spatiotemporal scales.

In fact, a full understanding of the functioning of a complex system such as the brain can be shown to require the hierarchical integration of the underlying local parts into the whole [11,19,20]. Hierarchy in the brain can be assessed in terms of the underlying anatomy, which in turn provides the skeleton for whole-brain dynamics. As shown here, the hierarchy of these dynamics can be determined over the whole duration of the experiment or dynamically over time.

Traditional anatomical neuroscience research has identified the structural connectivity of the brain and how the hierarchy can be described in terms of topological modularity, where brain regions in the same module have dense intramodular connectivity with each other and sparser intermodular connectivity with nodes in other modules [21].

On top of this structural hierarchy, more recent research has started to characterise the underlying hierarchical dynamics by increasingly studying their spacetime evolution. Taking a bird's eye view, some prominent theories have proposed that the brain is optimising the balance between integration and segregation [22,23], while other accounts have focused on the orchestration by the 'GW', where integrated information is broadcasted to many other regions across the whole brain [24–26]. In both cases, this requires an efficient and robust hierarchical organisation [27–29].

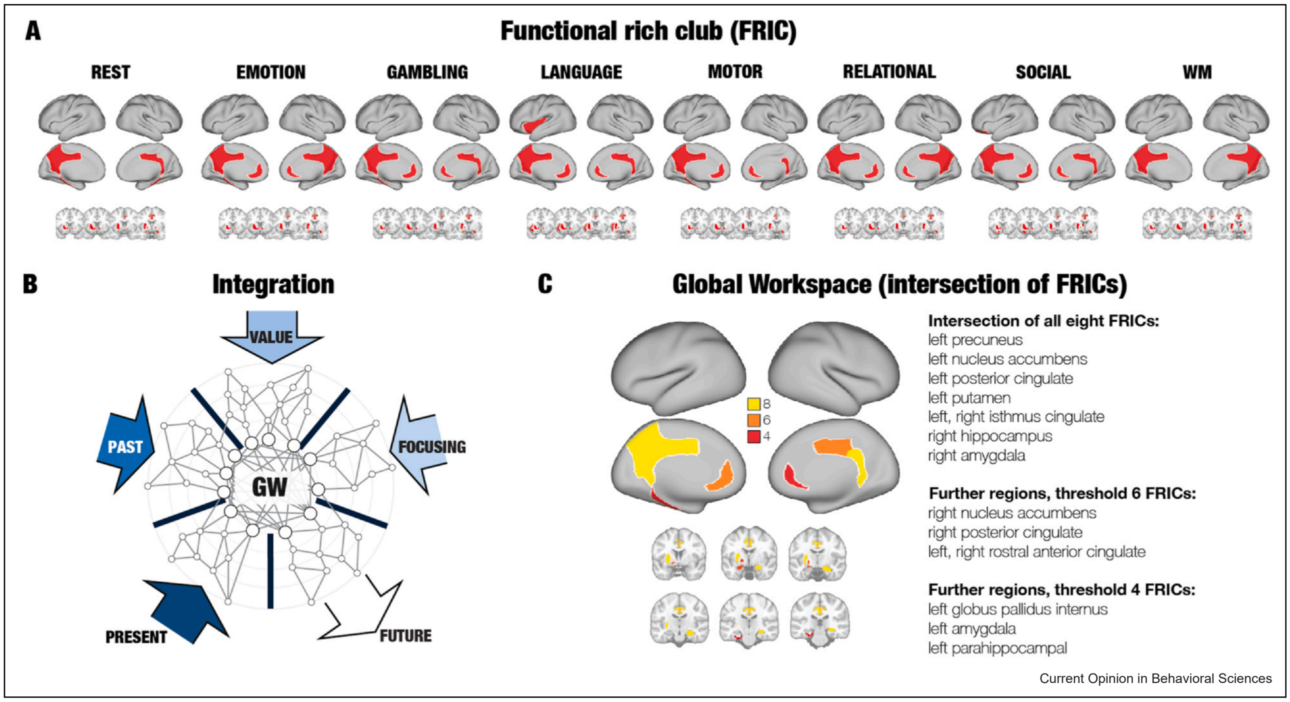
Hierarchy assessed by information flow

Discovering the hierarchical organisation of the brain requires measures for determining information flow between regions. In the simplest case, this measure should be able to determine the causal information flow between pairs of regions through the time series of each. One such measure is the classic Granger causality measure, proposed by Clive Granger [30], who won the Nobel Prize in Economics, trying to solve the challenging problem of determining how two time series are causally related. His solution can be shown to be a special case — for linear Gaussian systems — of the more general framework of *Transfer Entropy* [31–34], which is an information-theoretic measure able to capture the causal flow of information in any given system. This information-theoretical concept of causality was introduced in neuroscience by Schreiber [35] and subsequently by Brovelli et al. [32], who proposed a weaker form of causality allowing calculation of the involved entropies by just considering a Gaussian approximation, that is, by considering only second-order statistics. This has been further tailored in the NDTE framework to overcome specific challenges in neuroimaging data by controlling for spurious statistical effects using circular surrogate time series [36]. In addition, at the group level, the *P*-values corresponding to each pairwise NDTE flow are aggregated using the Stouffer method [37] and corrected for multiple comparisons. The NDTE framework can thus be thought of a normalised Granger causality measure optimised for the challenges of neuroimaging, and providing the exact information flow between all brain regions, allowing for the study of the functional hierarchical organisation of any brain state [17].

As shown in Figure 2, Deco et al. took advantage of the NDTE framework to provide a bidirectional description of the functional information flow underlying brain signals in resting and seven different cognitive tasks. From this comprehensive matrix of causal information flow between the brain regions in three different parcellations, the authors computed the 'Functional Rich Club' (FRIC) as the core set of regions, an array of functional hubs that are characterised by a tendency to be more densely functionally connected among themselves than to other brain regions from where they receive integrative information. FRIC is related to the idea of an anatomical rich club [38,39], which investigates the anatomy and includes nodes in a network with a tendency for high-degree nodes to be more densely connected among themselves than nodes of a lower degree. However, unlike the rich club, FRIC is a dynamic measure based on bidirectional flow of information and not constrained by anatomy. It will therefore change when applied to data arising from different tasks.

In other words, FRIC is one way of estimating the hierarchical organisation of brain dynamics. One way to think about FRIC is the colloquial example of a core assembly, where, for different tasks, some people remain through all executive meetings, while others are substituted in and out based on their expertise. In a similar manner, FRIC would include both common and task-

Figure 2



GW as the intersection of FRICs for rest and seven tasks. **(a)** The functional hierarchical organisation was computed for all seven tasks (emotion, gambling, language, motor, relational, social, and working memory) and rest in over 1000 HCP participants, and the FRIC was determined as the set of regions that define a 'club' of functional hubs characterised by a tendency to be more densely functionally connected among themselves than to other brain regions from where they receive integrative information [17]. The FRICs vary significantly between tasks and rest. **(b)** The GW is proposed as sitting on top of a hierarchical system integrating information from perceptual (PRESENT), long-term memory (PAST), evaluative (VALUE) and attentional (FOCUSING) systems. **(c)** The regions in the GW were computed as the intersection of the FRIC members across all possible tasks and resting state. This identified cortical and subcortical regions, including left precuneus, left nucleus accumbens, left putamen, left posterior cingulate cortex, right hippocampus, right amygdala and left and right isthmus cingulate. Lowering the threshold of participation in more than six FRICs adds two further regions: right nucleus accumbens and right posterior cingulate (in seven FRICs) and left and right rostral anterior cingulate (in six FRICs). Further lowering the threshold to four FRICs provides another three brain regions: left amygdala and left globus pallidus internus (in five FRICs) and left parahippocampal cortex (in four FRICs). Importantly, this did not reveal involvement of prefrontal regions, even at lower threshold.

specific brain regions as a result of the different flow of information for different kinds of tasks (Figure 2a). It was hypothesised that this would allow for the identification of the regions belonging to the 'GW' [24–26] (illustrated in Figure 2b) and which can be defined simply as the intersection of the different sets of resting and task-related FRICs (Figure 2c).

The results revealed that the GW, as the intersection of FRIC members for all seven tasks and rest, consists of the left precuneus, left nucleus accumbens, left putamen, left posterior cingulate cortex, right hippocampus, right amygdala and left and right isthmus cingulate. Further lowering the threshold of intersection to include areas only common to seven FRICs, added two further regions: right nucleus accumbens and right posterior cingulate and lowering to six FRICs adds left and right rostral anterior cingulate. Lowering the threshold even further to five FRICs, added the left amygdala and left globus pallidus internus, while lowering to four FRICs added the left parahippocampal cortex. Overall, these results point to a stable core of brain regions necessary in the GW where the PFC was not present even at low threshold (Figure 2c). Importantly, it should be noted that this intersection of FRIC members were taken from the static hierarchy across the whole experiment irrespective of the behavioural responses. This lack of dynamics is a fundamental limitation of the NDTE framework.

Still, this important result of finding the main orchestrators across eight different brain states was then strengthened by ascertaining its causal importance through the construction and selectively lesioning a whole-brain model accurately simulating the empirical functional hierarchy. The generative role of the GW in orchestrating function was demonstrated by systematically lesioning the whole-brain model. Only lesioning the FRIC regions in the GW at the top of the hierarchy, but not other regions at the bottom of the hierarchy, led to a significant breakdown in the ability of the whole model to fit the empirical data, demonstrating the causal significance of the FRIC regions.

Dynamic spatiotemporal hierarchy assessed by the arrow of time

As mentioned before, computing the spatiotemporal hierarchy over time using transfer entropy methods such as NDTE is difficult since this requires large amount of the data. Yet, Buzsaki et al. have pointed out that there is a simpler way to identify brain hierarchy, namely, by characterising the level of asymmetry in the directionality of information flow [40]. Thermodynamics can directly determine directionality in flow and is therefore an excellent tool for measuring hierarchy; since when the detailed balance of a complex system is broken, there is an increase in the directionality of information flow resulting in hierarchical reorganisation. Importantly, this hierarchy is not always vertically structured, that is, with a top and bottom of the hierarchy but could equally well be horizontal. This would, for example, be the case for a set of regions connected in a circle with information flowing around the circle. Still, there could be hierarchical reorganisation when the directionality of the information flow is changed. This definition of thermodynamic hierarchy allows for the determination of asymmetry in space (given by the information flow interactions), which gives rise to asymmetry in time (measured as the arrow of time or irreversibility) [41]. This complementary way of measuring hierarchy is consistent with a number of proposed theories, including core–periphery [42–44] and core synaptic hierarchy [11].

One particularly fruitful way of identifying unifying regions needed for brain dynamics to move away from equilibrium is given by the NODE framework [10]. In brief, as shown in Figure 3, this framework is designed to capture unifying drivers of task-driven brain dynamics by taking advantage of the key concept of *symmetry breaking*, where the fluxes of transitions between different interacting networks are more driven towards nonequilibrium than rest and thus more unbalanced [45,46].

The NODE framework is time dependent and extends whole-brain models by using sliding windows to estimate the time-varying global coupling parameter, $G(t)$ for each of the sliding windows of full functional magnetic resonance imaging data. Importantly, this framework is dependent on using linearised Hopf model at the edge of bifurcation to efficiently compute the fit to the windowed brain dynamics over time (Figure 3b). Specifically, as shown in Figure 3c, the time-varying global coupling $G(t)$ is obtained by fitting the whole-brain model to sliding windows of the functional empirical connectivity over the full timecourse of resting state and seven tasks. In thermodynamics, the forward and backward trajectories of a process can have different arrows of time, where their differences correspond to the level of irreversibility of the process (Figure 3d). As shown in Figure 3e, the NODE framework estimates the entropy production in the generative parameter space of the whole-brain model for each individual by using the time-varying global coupling to estimate the entropy production as the Kullback–Leibler distance between the forward and backward transition probabilities. Equally, for each individual, the global brain connectivity (GBC) is computed (Figure 3f). To reveal the main driving regions, the NODE framework correlates the entropy production with GBC across individuals. Similar to the strategy used for the NDTE framework, the intersection of the driving brain regions across tasks and rest directly reveals the main driving brain regions for cognition (Figure 3g). Figure 3h shows how cognition is being driven in a time-dependent manner by a common set of prefrontal drivers, including the inferior frontal gyrus (pars orbitalis, opercularis, and triangularis), lateral orbitofrontal, rostral and caudal frontal and rostral anterior cingulate cortices.

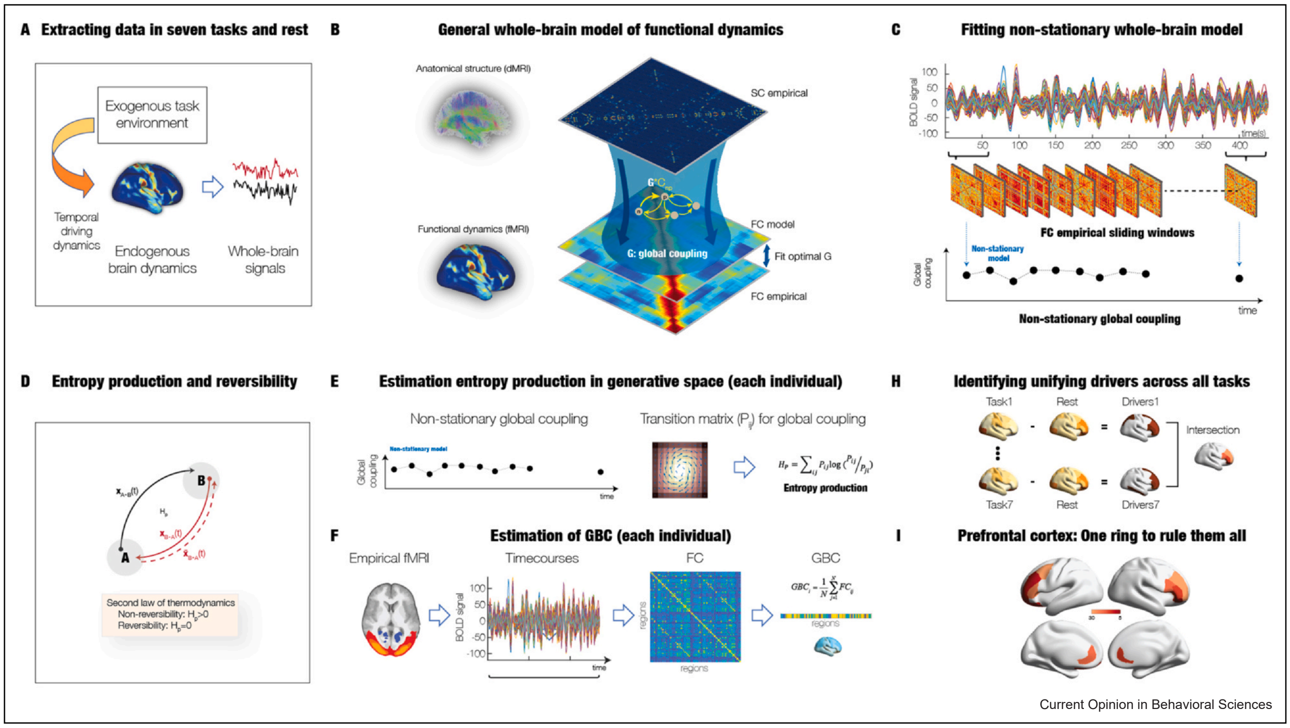
In other words, the NODE framework allows for the estimation of the level of irreversibility not for the empirical data but in the generative data created by the whole-brain model. This corresponds to estimating whether the states of $G(t)$ can be revisited by time-reversed global coupling, $G(-t)$. In turns, this opens for the computation of the GBC in each individual, which then allows the NODE framework to capture the main drivers breaking the symmetry for both rest and for the seven tasks.

One important caveat for these results is that they did not take into account the behavioural responses to the task. This should be explored in future studies. In that regard, it is of considerable interest to note that the focus on information flow in both NDTE and NODE frameworks is related to the proposal of Cole et al. that activity flow could be a linking principle between connectivity and activity [47]. Their important work shows how task-evoked activity flow over intrinsic networks is likely to be a large-scale mechanism, which could explain the relevance of resting-state functional connectivity to cognitive task activations. Linking NODE framework with a hierarchical investigation of the activity flow paradigm would be of considerable interest in the future.

Conclusion

In this opinion paper, we have discussed recent progress in discovering the hierarchical organisation and orchestration of whole-brain dynamics. This research has used various technical innovations inspired by information theory and thermodynamics, which have allowed the field to move beyond simple anatomical measures of

Figure 3



Discovering the common drivers of cognition over time. **(a)** The time-dependent whole-brain modelling of NODE framework allows for the discovery of the key brain regions and networks driving task-driven brain dynamics needed for survival [10]. This was used in the large-scale HCP with over 1000 participants engaged in resting and a battery of seven tasks designed to cover as wide a range of brain systems within realistic time constraints. These neuroimaging data were fitted in a time-dependent whole-brain model to the empirical data, which estimated the reversibility by measuring the entropy production in the time-evolving parameter space of the whole-brain model. **(b)** The whole-brain model links anatomical and functional information using a linearised Hopf model at the edge of bifurcation to fit windowed brain dynamics over time. The estimation of time dependency is made possible by the linearisation of the whole-brain model and the analytic derivation of the windowed functional connectivity. **(c)** The whole-brain model was fitted to sliding windows of the functional empirical connectivity over the full timecourse of resting state and seven tasks. This fitting produced a time-varying optimal global coupling parameter, $G(t)$ for the model at each sliding window. **(d)** In thermodynamics, the influence of the environment can be assessed through estimating the level of nonequilibrium by computing the production of entropy. In nonequilibrium, the balance is broken and revealing the asymmetry in causal interactions. The forward and backward trajectories of a process can have different arrows of time. The difference in forward and time reversal of the backward trajectories corresponds to the level of irreversibility of the process. If the entropy production is larger than zero, this corresponds to irreversibility of a nonequilibrium system. In contrast, if there is no entropy production, this is a reversible, equilibrium system. Here, this was used to estimate the entropy production in the generative parameter space of the whole-brain model. **(e)** Specifically, the time-varying global coupling was used to estimate the entropy production as the Kullback–Leibler distance between the forward and backward transition probabilities. **(f)** For each individual, the GBC was computed to capture the main drivers breaking the symmetry for rest and the seven tasks. **(g)** Correlating the entropy production with GBC across individuals allowed for the identification of the generative brain regions driving the entropy production. Comparing these driving brain regions in each task compared with rest and computing their intersection across the seven tasks reveals the main driving brain regions for cognition. **(h)** Finally, lesioning the common, unifying PFC regions in the time-dependent whole-brain model in cognitive tasks and in rest confirmed the causal, mechanistic nature of PFC regions in flexible cognition.

hierarchy to causal models of how the functional dynamics evolve over time. The NDTE framework used tools from information theory to discover the top of the hierarchy of brain processing, which revealed a common set of stable regions, conveniently termed ‘GW’ orchestrating dynamics over longer timescales, similar to how an administrative team would organise an enterprise. Moving beyond this primarily spatial method, the thermodynamics-inspired NODE framework revealed complementary, spacetime measures of hierarchy, where, on faster timescale, the administrative brain organisation is temporarily overtaken by prefrontal regions.

Going forward, the fertile theory of thermodynamics offers many novel ways of quantifying brain hierarchy. Implementations of the framework have already shed new light on the changes in orchestration and hierarchical organisation in health [48] and may in future help understand the breakdown in neuropsychiatric disease. One candidate for a better understanding could be the fluctuation-dissipation theorem (FDT), which describes the balancing forces of dissipation and spontaneous fluctuations. Using FDT with a generative, perturbative whole-brain model can estimate the violation of FDT in different brain states such as in wakefulness, cognitive tasks and deep sleep and bring new insights into the causal orchestration of hierarchy in these states.

Still, the results reviewed here offer new, unifying insights into the orchestration of cognitive flexibility. Metaphorically speaking, this provides a link to Tolkien's classic 'Lord of the Rings: Fellowship of the Ring' (Chapter 'The Shadow of the Past', p. 50) where the author suggests that not all rings are created equal but that there is one ring to rule them all [49]. The prefrontal drivers are perhaps analogous to Tolkien's 'one ring to rule them all', as they rise to the top of the hierarchy, similar to the top part of Fuster's ring of the perception–action cycle [15], and temporarily take over the orchestration of task-driven brain dynamics ensuring survival and enabling thriving.

Data Availability

This is a review article, and the data are described and available in the cited papers.

Declaration of Competing Interest

The authors declare that they do not have any kind of conflict of interest.

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