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REVIEW

A whole new world: embracing the systems-level to understand the indirect impact of pathology in neurodegenerative disorders

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Abstract
The direct link between neuropathology and the symptoms that emerge from damage to the brain is often difficult to discern. In this perspective, we argue that a satisfying account of neurodegenerative symptoms most naturally emerges from the consideration of the brain from the systems-level. Specifically, we will highlight the role of the neuromodulatory arousal system, which is uniquely positioned to coordinate the brain's ability to flexibly integrate the otherwise segregated structures required to support higher cognitive functions. Importantly, the neuromodulatory arousal system is highly heterogeneous, encompassing structures that are common sites of neurodegeneration across Alzheimer's and Parkinson's disease. We will review studies that implicate the dysfunctional interactions amongst distributed brain regions as a side-effect of pathological involvement of the neuromodulatory arousal system in these neurodegenerative disorders. From this perspective, we will argue that future work in clinical neuroscience should attempt to consider the inherent complexity in the brain and employ analytic techniques that do not solely focus on regional functional impairments, but rather captures the brain as an inherently dynamic, distributed, multi-scale system. Through this lens, we hope that we will devise new and improved diagnostic markers and interventional approaches to aid in the treatment of neurodegenerative disorders.

Keywords Parkinson's disease · Alzheimer's disease · Dementia · Systems neuroscience · Neuromodulatory arousal system

Introduction

Clinical neuroscience has a rich history of linking pathological alteration of neuronal regions to abnormal cognitive, affective, motoric and sensory abnormalities. Case studies on lesion-related loss of function have been critical in driving these insights. Indeed, much of modern neuroimaging—which relates functions to the activity of isolated regions of the brain—is based upon a similar logical backbone: namely, that specific functions can be ascribed to individual regions of the brain. There is an inherent advantage in compartmentalising the brain's functional roles into smaller structures: it enables clinicians and researchers more directed focus in experimental and therapeutic treatments.

This approach has led to numerous insightful discoveries; however, it is a perspective that is not without its challenges. For one, the human brain is massively interconnected, such that the loss of neurons in one region is rarely (if ever) confined to a specific region. In addition, in neurodegenerative diseases, accumulation of abnormally folded proteins and atrophy are often identified in regions of the brainstem and forebrain, however, the impact of this pathology is felt at the systems-level—that is, in the projections of pathologically affected regions, which are typically broad and relatively diffuse. Finally, there is emerging evidence that many symptoms of neurodegenerative disorders likely occur due to compensatory (as opposed to primary) effects of pathology, further reinforcing the importance of a systems-level vantage point. Thus, a more parsimonious assumption is that functions emerge from the interactions between brain regions, implying that functional ability should be considered in the context of the rest of the nervous system.

In contrast to the localisation perspective, in which specific functions are attributed to particular regions in the brain, the systems-level approach considers functions as processes that emerge from interactions between brain regions. In other words, the systems-level approach embraces the fact that the brain is a complex system of interacting parts, and further assumes that a satisfying description of function (and

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dysfunction) will only emerge from studying the interactions of the different components that make up the system. In short, the systems-level approach requires interpreting the function of a particular region in the context of its interactions with the rest of the brain. For illustrative purposes, consider a paradigmatic example of localisation in the brain: the sensory 'homunculus'—a thin strip of the postcentral cerebral cortex that is thought to 'represent' sensory inputs to different regions of the body. If untethered from thalamic innervations that arrive via the dorsal column tract, this strip of cortex shows vast reconfiguration [1] that betrays a crucial feature of the brain: the system reconfigures so as to process whatever information to which it now has access. Similarly, if the subcortical projections of primary sensory regions are chemically interrupted in rodents, the animals no longer detect sensory inputs that would otherwise register as perceptual inputs [2]. In other words, the function of this area of the brain is not hidden within the pyramidal neurons of the cerebral cortex, but rather in their connections to the rest of the network: e.g., the thalamus [3], the ascending neuromodulatory system [4] and other areas of the cerebral cortex [5]. This example clearly demonstrates the importance of a systems-level perspective when interrogating how the structure of the brain supports its function.

Tracking the brain from the systems-level perspective

How can we begin to embrace the systems-level approach? Graph theory has been used extensively across several disciplines to interrogate the properties of complex networks, in which the interactions within a network is determined by its structure (topology) and dynamics [6]. Graph theory has been particularly useful in investigating how different regions of the brain interact with one another, rather than examining their behaviour individually. The major advantage of this approach is that it lends itself to a natural understanding of the complexity of the many interacting components of the brain. This approach can lead to insights about the system that are often opaque when the parts are viewed in isolation. For instance, using graph theoretical techniques, the brain has been shown to exhibit the characteristics of either a 'small-world' network, as it has evolved to maximize efficiency and/or minimize cost of processing [7], or a multi-scale, hierarchical network [8], in which interactions between neurons can exist at multiple spatial temporal scales, thus simultaneously improving the resilience and efficiency of neural processing [9]. Graph theory also lends itself well to the representation of the brain using mathematical frameworks in which nodes are represented as parcellated brain regions connected via edges which represent axonal projections [10, 11]. Using these approaches, it has been found that the brain contains a highly interconnected set of highly connected regions—a so-called "rich club" [12] that is distributed across the brain. Importantly, long axonal projections are more energy expensive [13], suggesting that much of the brain's energetic budget is spent setting up and maintaining this organisation [14]. Crucially, these same regions are also common sites of pathology in neurodegenerative disorders [15], suggesting a crucial link between structure and function that is hard to discern from the location-based perspective.

Once viewed from the systems-level, a number of other common features of brain organisation clearly appear. For instance, the functional connections between regions (i.e., their temporal similarities during the 'resting' state) typically cluster into tight-knit communities [16], however, the extent to which an individual region 'participates' in different communities can change substantially over time, and as a function of cognitive challenges [17]. To provide an intuition for this, imagine the interactions you have with other people at your university, hospital or institute (Fig. 1A): the vast majority of connections you make are with people from your

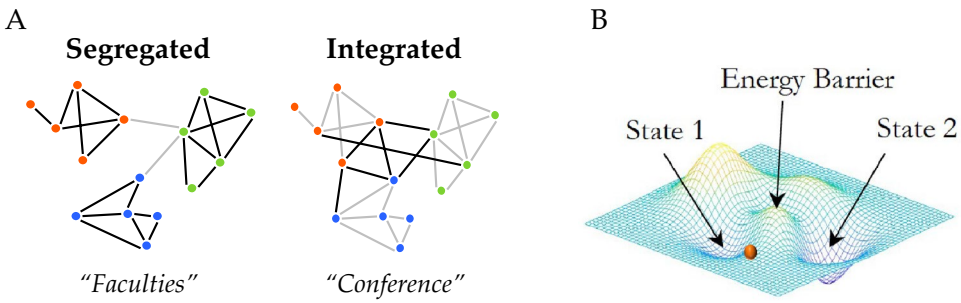

Fig. 1 Systems-level perspective on neural connections. **A** network of connections between regions (either structural or functional) can be conceptualised along a continuum—segregated networks contain tight-knit communities that resemble interactions within faculties of a university, whereas integrated networks dissolve these boundaries, similar to the way that scientists and clinicians interact at academic conferences; **B** brain state trajectories can be conceptualised as landscapes, in which defines the energy required to move between different brain states is linked to the height/depth of the landscape

faculty that you typically interact with—in other words, your interactions are relatively modular (or community-based). This particular mode of interaction is the norm, that is until you attend an inter-faculty conference, in which you connect with people from different fields across a range of different faculties. Viewed from the systems-level, these interactions would be far more integrated—the original communities that were so clear in your normal day-to-day will now be far less obvious (Fig. 1A). These shifts in network topology can be defined by two extremes; segregated states in which regions are strongly connected with other regions within their own modules (e.g., connect with only colleagues in your school) and weakly connected to regions outside of their modules, and integrated states is strong connections between regions of different communities [18]. This is of particular interest, because several studies have shown that the brain's network architecture reconfigures as a function of cognitive performance [14, 16], and these same patterns are often dysfunctional in neurodegenerative disorders [12, 19–21]. Thus, the inherent flexibility of the brain is critically dependent upon shifting between the segregated and integrated states.

Another way to conceptualise the brain from the systems-level is to capture the dynamics of instantaneous brain state changes. Many previous approaches in analysing neuroimaging datasets have focussed predominantly on the average activity across time, neglecting the temporal dynamics of neural activity. A growing body of literature has attempted to focus upon quantifying the temporal dynamics of brain activity. Research has evidenced that time-varying functional connectivity is more sensitive to capturing the discrepancies between healthy and diseased individuals [22]. In particular, conceptualising the state of the brain using low-dimensional approaches (such as principal component analysis) allows neuroimagers to imagine the brain as a proverbial ball that rolls around a topological landscape, which shifts the location of its hills and valleys as a function of need (Fig. 1B). This approach creates a low-dimensional topological representation of changes in the instantaneous brain state shifts by borrowing concepts from chemistry; by computing the likelihood of a brain shifting based upon the energy required to move into a different brain state (Fig. 1B). Hence, the likelihood/probability of shifting into novel brain states is inversely related to the energy required—more frequently occurring brain states would have lower energy barriers to achieve this state (and *v.v.*) [23]. We can represent these results by using a map of the brain states across a landscape, in which brain states that are more difficult to shift from have a larger 'attractor' or well (see Fig. 1B). This novel approach has been useful to capture both temporal and spatial dynamics of the complex activity patterns inherent within the human brain, allowing us privileged access to the patterns when they begin to fail [24, 25].

The ascending arousal system controls systems-level organisation in the brain

Recent advancements in the afore-mentioned techniques have resulted in a growing field of research in network neuroscience. However, there is a clear shortcoming to this approach: namely, our limited understanding of the neurobiological mechanisms responsible for controlling the dynamic shifts between different network topological states. In previous work, we have argued that the ascending neuromodulatory system is well-positioned to orchestrate the brain's ability to both integrate the brain [17, 24] and also to dynamically shift between brain states [23] (Fig. 2). The arousal system is comprised of several autonomous pacemaking nuclei that can dynamically alter both global and local fluctuations in overall cortical and subcortical activity by altering second-messenger cascades within targeted neurons [25, 26]. Ultimately, this leads to large-scale effects at the macroscopic level in which changes in neural dynamics

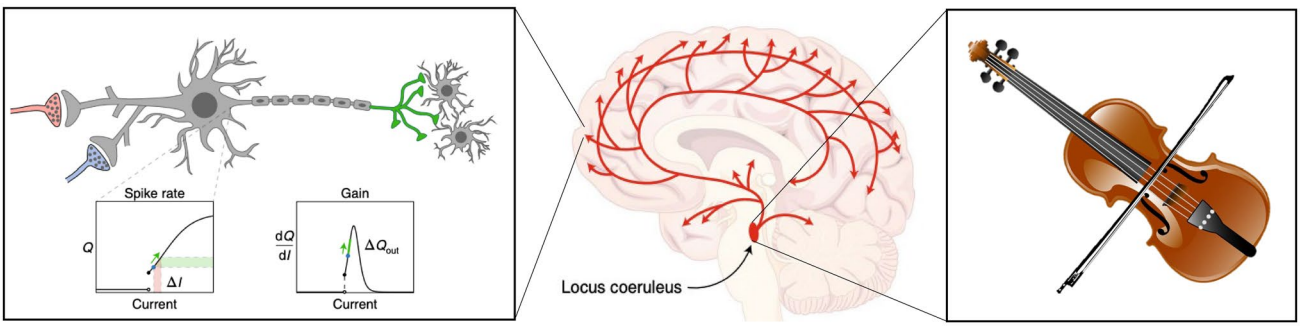

Fig. 2 The ascending arousal system orchestrates systems-level neural activity. Through intrinsic second-messenger cascades, noradrenaline released by the locus coeruleus (middle) changes the gain of individual neurons: i.e., changes the amount that input (current) is translated into firing rate outputs (Q; left). This is analogous to the way in which a bow resonates the strings of a violin, causing changes in the timbre of the sounds emergent in the violin (right)

facilitates the flexible shifts between differing brain states [27–29].

Whilst there are several distinct neuromodulatory systems in the brain, the noradrenergic and cholinergic systems are well-positioned to influence broad-scale dynamic reconfigurations in network topology in strikingly different ways [28]. For instance, these two neuromodulatory systems can facilitate changes in the timescale of neural dynamics in brain networks by altering the oscillatory activity across the brain: typically by decreasing low-frequency synchronous brain activity and increasing high-frequency activity [30–32]. The locus coeruleus is the main noradrenergic input to the brain and has diffuse, non-specific projections to the entire cerebral cortex [27, 33, 28], which we have proposed is important for facilitating shifts into integrated states by diffusely increasing neural gain across multiple regions in the brain, promoting connectivity across different communities [24, 26, 34, 35]. Recently, we proposed that the locus coeruleus works analogous to a bow expressing musical notes on a violin, as different styles of bowing can have distinct musical effects similar to the different modes of locus coeruleus activity can alter brain dynamics (see Fig. 2) [31]. In relation to the attractor landscape analysis, phasic bursts in noradrenergic activity has been shown to push the brain into a 'low-energy' transition by facilitating a lower energy barrier and flattening the landscape for the brain to shift between different states [23]. In contrast, the cholinergic systems has more targeted projections to specific regions of the cerebral cortex, which in turn are crucial for facilitating shifts into segregated states [36] by facilitating an increase in the signal-to-noise ratio in targeted regions [31, 32]. In the context of attractor landscapes, phasic bursts in the cholinergic system causes 'high-energy' transitions, which drives the brain to stay within a particular state [23].

The impact of pathological involvement in the ascending arousal system

How does this systems-level perspective map onto the abnormal brain states characteristic of neurodegenerative disease? In both Alzheimer's disease and Parkinson's disease, abnormal function is often tied to the accumulation of abnormally folded proteins that aggregate in cell-bodies of neurons, ultimately leading to neuronal death [37, 38]. While the symptoms of Alzheimer's disease are typically attributed to the accumulation of tau-pathology within the hippocampus and amygdala, and the symptoms of Parkinson's disease to the degeneration of dopaminergic cells in the substantia nigra pars compacta, it is less-well appreciated that the locus coeruleus is an early and substantial site of pathological involvement in both disorders [39, 40]. Based on the neuroimaging and modelling studies described above, impairments in this system would have a devastating effect on the ability for the brain to integrate specialist networks in the flexible, dynamic ways required to solve challenging cognitive problems. That is, by taking a systems-level perspective, the otherwise inexplicable symptoms of cognitive decline in neurodegenerative disease can begin to unravel.

This perspective could help to provide new explanations for otherwise difficult-to-treat symptoms of neurodegenerative disease. Previous work has attempted to explain all symptoms that manifest in Parkinson's disease as directly related to the loss of dopaminergic neurons, despite the fact that there are several other structures in Parkinson's disease that also degenerate [41]. The warning signs that this may not be the correct framing have been present for a long time. For example, there are several symptoms in Parkinson's disease that are not fully ameliorated by standard dopaminergic replacement therapy. A primary example of this is the symptom of freezing of gait, which presents as paroxysmal episodes of patient's inability to walk, despite an intention to do so [42]. Although freezing of gait was originally presumed to arise due to low levels of dopamine, more recent work suggests that the symptom arises due to abnormal patterns of inter-regional coordination that ultimate overwhelm processing within the basal ganglia [43].

Similarly, visual hallucinations are a common symptom of both Parkinson's disease [44] and dementia with Lewy bodies [45], however, these symptoms are similarly difficult to attribute solely to dopaminergic impairments. In individuals with Parkinson's disease, visual hallucinations likely arise from pathology across several structures across the brainstem [46], thalamus [47] and temporal cortex [48], suggesting that considering the brain from the systems-level may help us to interrogate the complex neurobiological abnormalities responsible for this symptom. By employing this systems-level approach, Zarkali et al. [20] found reduced dopaminergic and serotonergic transmission was associated with a structural–functional decoupling in Parkinson's disease, with more decoupling associated with the serotonergic receptors involved in cognition. Recently, using a systems-level approach to investigate cognitive fluctuations in individuals with dementia with Lewy bodies (who suffer from substantial hallucinatory burden) revealed that cognitive fluctuations are associated with substantial dynamical network impairments, including reduced integration across the brain that overlapped spatially with the expression of subclasses of noradrenergic and cholinergic receptors [24]. These results point towards exciting new avenues for understanding complex disorders of neurodegeneration, while also pointing towards potential novel treatment options.

The presence of pathological involvement within a region of the brain does not imply that abnormalities need be confined within the given region's local network.

Indeed, the brain's ability to adapt to changes in both its functional and structural capacity is critical for normal function. This suggests that the brain's maladaptive response to specific regional impairments may provide crucial clues for understanding the pathophysiology of neurodegenerative disease, especially in the early stages of degeneration in which there is substantial neuronal loss but relatively normal cognitive and behavioural functions [49]. In principle, this is likely occurring because of the complex behaviour of the adaptive brain, in which case compensatory mechanisms to adaptively reconfiguring neural networks is critical for performing normal brain function in the presence of degeneration [50]. For instance, maladaptive compensatory mechanisms may arise when the degenerated brain is incapable of fulfilling a function using the standard approach, and instead needs to rely on other regions to compensate for a potential loss of function using other structures of the brain that would not only typically be involved in elucidating a behaviour. For example, anxiety-induced freezing of gait in Parkinson's disease often occurs in the context of a dopaminergically depleted basal ganglia, but also appears to be due to a maladaptive response from the ascending noradrenergic system activating prior to freezing events [51]. This over-engagement of the arousal system results in a system-level integration across motor, cognitive and limbic regions in the cortex and subcortex, that ultimately impair functional connectivity with the dopaminergically depleted basal ganglia [52]. We expect that many other complex, state-dependent symptoms of neurodegenerative disease will be explicable when viewed through similar compensatory lenses.

Conclusion

In the future, we hope that clinical neuroscience will more readily adopt the techniques and intuitions inherent within systems neuroscience in an effort to better understand—and treat—complex disorders of the brain. If we can better understand the healthy brain by viewing the brain as a complex system, then we have a great opportunity to re-invigorate our perspective on diseased brains, helping us to interpret their complex pathophysiological basis in a way that naturally lends itself to novel interventions. To date, determining the distinct causes and progression of neurodegeneration has been inherently challenging, due to the long timescale of degeneration and the pre-existing theories of specific cites of pathology contributing to all manifestations of symptoms. We propose that by incorporating the afore-mentioned systems-level approaches that place the complexity of the brain front and centre will give greater insight into how the brain works, and further establishes the complex nature of degeneration.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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