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Review

Injured Brains and Adaptive Networks: The Benefits and Costs of Hyperconnectivity

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A common finding in human functional brain-imaging studies is that damage to neural systems paradoxically results in enhanced functional connectivity between network regions, a phenomenon commonly referred to as 'hyperconnectivity'. Here, we describe the various ways that hyperconnectivity operates to benefit a neural network following injury while simultaneously negotiating the trade-off between metabolic cost and communication efficiency. Hyperconnectivity may be optimally expressed by increasing connections through the most central and metabolically efficient regions (i.e., hubs). While adaptive in the short term, we propose that chronic hyperconnectivity may leave network hubs vulnerable to secondary pathological processes over the life span due to chronically elevated metabolic stress. We conclude by offering novel, testable hypotheses for advancing our understanding of the role of hyperconnectivity in systems-level brain plasticity in neurological disorders.

Trends

Brain-imaging methods coupled with network neuroscience now provide previously unavailable opportunities to examine large-scale network changes after injury.

One common response to neurological disruption of neural networks is increased brain connectivity between residual network regions, referred to as 'hyperconnectivity'.

Network hubs are centralized nodes in brain networks, are disproportionately represented as sites of pathology, and may also have an important role in reintegration of function during recovery.

There is converging evidence that increased brain metabolism, through local activity and increased network burden, is associated with neurodegeneration.

Understanding Brain Disorders in an Era of Network Neuroscience

Now firmly rooted in the era of the human connectome, novel mathematical applications are commonly paired with established functional brain-imaging methods [e.g., **functionalMRI** (see Glossary) magnetoencephalography] to model the consequences of brain injury and disease in humans [1,2]. Here, we review a literature leveraging the powerful framework of **networkneuroscience** to understand the macroscale, or system-level, modifications occurring in neural networks after neurological disruption. Our discussion is focused on one common finding in brain disorders: physical disruption of neural networks secondary to injury or disease may paradoxically result in a regional increase in functional connectivity (i.e., **hyperconnectivity**) between some parts of the disrupted neural network. We argue that the optimal expression of network change after injury, or network plasticity, is centered around network **hubs**, or the most highly connected and efficient network nodes. Over the course of this review, we integrate findings from the brain-imaging literature to explore the time line for expression of hyperconnectivity after neurological disruption and its role in clinical outcome in chronic brain disorders. Ultimately, we anticipate that large-scale network plasticity is guided by principles that optimize network efficiency, requiring integration of principal network nodes to maintain efficient communication across a distributed, dynamic neural network.

Connections and Hyperconnections

In network neuroscience, a 'connection' can be defined as the temporal covariance in the signal produced by two spatially distinct brain regions [3]. For the purposes of this discussion, 'hyperconnectivity' represents enhanced functional connectivity in terms of the number or strength of connections in a clinical sample compared with a control sample, and we focus our

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review on increased connectivity after injury as opposed to connectivity loss for two reasons. First, hyperconnectivity represents an observable brain response to neural network disruption as opposed to the absence of a response or functional deficit that has been historically a central focus in the clinical neurosciences. While this tradition of linking structural brain damage to behavioral and functional loss provides evidence of the local consequence of injury, the recent focus on hyperconnectivity provides a window into how dynamic neural systems respond to insult, which is essential for understanding the recovery of function and neuroplasticity. Second, we aim to reframe the conceptualization of hyperconnectivity, with particular attention given to cost and efficiency as important influences on network response. Any modifications to network connectivity in response to injury are obliged to comply with the natural limits of a spatially embedded, metabolically expensive, neural network [4,5]. We propose that adaptive hyperconnectivity (not all increased connectivity will be adaptive) operates to retain a network topology that maintains communication while minimizing the costs of network connection and maximizing network efficiency (**cost-efficiency**). Here, we explore the evidence for hyperconnectivity, the time line for its expression, and its implications for long-term clinical outcome.

As a final introductory caveat, we focus our discussion on the coherent brain signals that are observable via functional brain-imaging methods, but patterns of oscillatory brain activity are reliably constrained by brain structure [6–8]. Therefore, a functional hyperconnectivity hypothesis is best understood in the context of large-scale changes in brain structure occurring after brain injury. Importantly, there is relative consistency in the structural connectome with respect to white matter connections and network hubs across individuals and the life span [9–11], and an overlapping hub structure is evident in functional data [12], which serves as a foundation for our discussion regarding hubs as centers of neural network plasticity.

Network Science and Resilience in Brain Networks

Network science draws on ideas and methods from mathematics, physics, and statistics to study network representations of physical, biological, and social phenomena. In abstraction, these network representations are mathematical objects called **graphs**, the centerpiece of graph theory, which is a subdomain of discrete mathematics [13]. Individual agents operating in the network are represented as vertices (or commonly, **nodes**), a meaningful relationship between pairs of nodes is represented by **edges** (links or connections) between them, which may be **weighted** to capture the strength of the relationship between any two nodes, and the **degree** of any node quantifies the number of connections incident to that node. The definitions and practical usage for several key graph metrics are provided in Box 1.

Box 1. Graph Theory Metrics

The following provides a list of common graph theoretical terms relevant for the current paper. These terms are illustrated in Figure I using a simple graph example for illustration.

Clustering: measure of the local density of connections, calculated as the number of triangles over the number of connected triples ('how many of my friends are friends with each other'). For Figure IA. the clustering coefficient is 1, whereas for Figure IB, it is 0.

Degree (of a node): number of edges incident to that node.

Density: the density of a graph is the ratio of the number of observable connections in the network to the number of possible connections in the network.

Edges: (pairwise) connections between nodes.

Hub: a node with high degree or high betweenness centrality. Node *c* (Figure ID; in red) has high degree and betweenness centrality, while node *b* (Figure IA,B; in blue) has high degree centrality within the network. The

Glossary

Alzheimer's disease (AD): a neurodegenerative disease usually occurring in older age; characterized behaviorally by dense memory impairments in new learning and progressive global cognitive decline.

Apolipoprotein E (ApoE): a protein encoding by the *APOE* gene. *APOE* is polymorphic, with three forms (ε2, ε3, and ε4) and has been linked to cholesterol and lipid transfer, as well as to a broader role in neural tissue repair and synaptogenesis. The APOE ε4 allele is a predictor of increased risk for neurodegeneration later in life [135].

Beta-amyloid (Aβ): a peptide found in the brain that, when elevated, forms amyloid plaques, which are a marker for AD, although it remains unclear whether this relationship is causal.

Cost-efficiency: connections in biological networks have metabolic, time, and wiring costs. With regard to metabolism, cost-efficiency can be defined as the trade-off between the metabolic demand of a network and the effectiveness of information transfer.

Default mode network (DMN): brain network originally observed to be anticorrelated with task-related functioning. It has been linked to nongoal-directed cognition, memory, and semantic processing, and has a critical role in the ongoing or intrinsic activity of the brain [136].

Functional MRI: non-invasive technique using strong magnetic fields to examine blood flow changes in the brain to infer brain functioning.

Hyperconnectivity: enhanced network connectivity observed in clinical samples compared with control sample; measured as an increase in the number or strength of connections in the network.

Mild cognitive impairment (MCI): considered an intermediate stage between normal aging and the onset of a formal neurodegenerative process, such as AD.

Network neuroscience: positioned at the intersection of brain and network science, a group of methods that capitalizes upon mathematical and computational modeling to study brain network organization and function.

Preferential attachment: a hypothesized principle for network development, whereby those nodes betweenness centrality of a node reflects the frequency with which it sits along the shortest path between any two other nodes in the graph.

Modules/communities: clusters of nodes densely linked among themselves and more sparsely linked to nodes outside the cluster. Three communities are circled in red in Figure ID.

Node: brain region of interest.

Path length: we use path length here to indicate the shortest path length, or the shortest distance (in number of edges) separating two nodes, e.g., in Figure ID from node *a* to node *d*, the path length is 5.

Weight (of an edge): relationship strength between corresponding pair of nodes (e.g., correlation). In Figure IA,B, the network is unweighted, while in Figure IC, it is weighted.

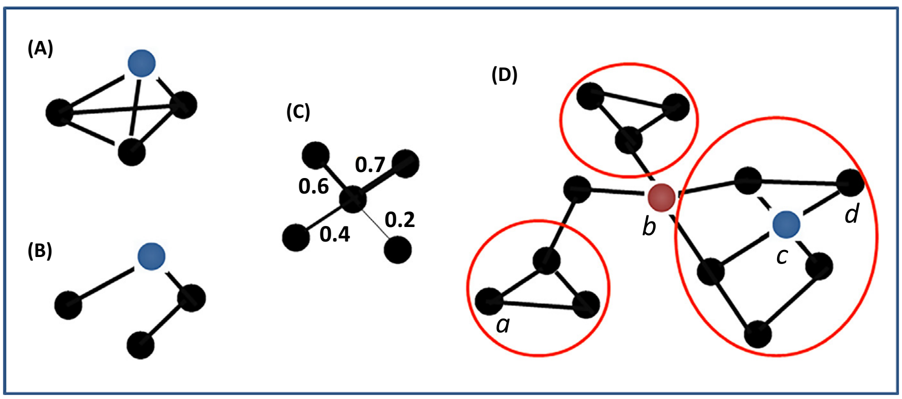

Figure I. Computational Attacks and the Resilience of Structural Brain Networks.

having more connections are disproportionately more likely to gain new connections as the network grows (i.e., the 'rich get richer' principle).
Tau/tauopathy: brain protein primarily distributed in axons that has a role in microtubule functioning; aggregation of tau results in intracellular fibrillary deposits in neurons and glia (tauopathy). Tauopathy has been linked to neurodegenerative conditions, such as AD.

Graphs can be characterized using global metrics that describe the nature of network organization or its topology. First in a study of *Caenorhabditis elegans* two decades ago [14] and more recently in humans [15–17], neural networks have been described by a small-world topology characterized by a high **density** of links locally (**clustering**) and a few long-distance connections shortening pathways between far ends of the network (short average **path length**) [7]. The power of a small-world organization is this co-presence of clustering and short average path length, which serves to maximize regional communication and retain efficient communication globally. While a small-world topology has appeal in describing brain functioning, the exact network structure characterizing neural systems is an active area of investigation. For example, several investigators have argued that other topologies may more accurately capture the important advantages afforded by the **modularity,** or the presence of densely linked subgroups of nodes, evident in neural networks (e.g., 'large-world' organization [18]). What has been reliably demonstrated is that human neural networks not only reveal relatively high clustering and short average path length consistent with a small-world topology, but also exhibit a modular community organization with relatively few highly connected nodes [18,19] (i.e., hubs) that operate at the center of information transfer. These network characteristics likely evolved to afford efficient and sustainable encoding and communication while adhering to selection pressures of signaling time and metabolic costs [20–22] (see Box 1 for examples of network metrics).

The modularity evident in human neural systems and the presence of a select number of highly connected network hubs indicate that neural systems may be well represented by a specific type of small-world network, namely a 'scale-free' network. The presence of network hubs in scale-free networks is central to our discussion of network plasticity, and this topological organization may have evolved as a consequence of **preferential attachment** dynamics during network development [23]. The principle of preferential attachment refers to the greater probability for highly connected nodes to be sites where additional connections are added during periods of network growth [23]. In practice, this means that the nodes with a higher degree of connectivity gain disproportionately more connections, or 'the rich-get-richer', resulting in the formation of network hubs. We return to preferential attachment in the context of neuroplasticity in greater detail below. Importantly, the scale-free topology is robust to disruption, with particular resilience to random removal (e.g., injury or failure) of individual nodes or edges [24]. The resilience may be attributable to the low-probability selection of high degree nodes and connection redundancy [24], which is intriguing and has important implications for neural network response to injury.

Figure 1 provides a plot of 'random' and 'targeted' attack scenarios for connection deletion in the structural connectome derived from human diffusion MRI data [25]. A targeted attack is represented as the selective deletion of high-degree nodes from the network. These data are relevant to our discussion of functional hyperconnectivity in several important ways. First, Figure 1 indicates that neural networks are robust to random insult (i.e., edge or node deletion chosen at random), which is consistent with a long history in clinical neurology and neuropsychology, where not all brain lesions have observable behavioral consequences (e.g., 'silent' lesions). Second, targeted attack on networks, or attack initiated by the deletion of highest-degree nodes, has significant consequences for network efficiency and, therefore, behavioral functioning. We argue that a primary goal of hyperconnectivity is to sustain communication through network hubs, thus maximizing information transfer and minimizing behavioral deficit.

The structural resource thresholds for network efficiency outlined in Figure 1 dovetail conceptually with cognitive reserve theory, namely that the emergence of behavioral deficit after injury can be predicted by an interaction between the magnitude of the injury and *a priori* intellectual status [26,27]. Enhanced cognitive reserve arising from environmental enrichment has been shown to predict connectivity in neural network hubs in healthy adults (e.g., anterior cingulate cortex [28]). Similarly, in **mild cognitive impairment** (MCI), considered an intermediate phase between normal aging and **Alzheimer's disease** (AD), higher cognitive reserve is associated with increased connectivity in cognitive control regions [29]. Cognitive reserve may afford resilience to targeted attack in network hubs (e.g., mesial temporal and posterior regions in AD) presumably due to increased edge density [30] and ultimately set thresholds for resilience to edge deletion and degenerative network changes [31,32]. Therefore, the behavioral consequences of neurological disruption are dependent upon network organization and connection redundancy, which together determine the ceiling for symptom-free edge deletion across individuals. Uncovering the interactive relationships between cognitive reserve and genetics in determining network resilience may hold important clues for the timing of hyperconnectivity and the onset and course of brain pathology. Figure 2A,B illustrates the functional connectivity in response to random (or nonhub) structural damage as well as a physical resource gradient for the expression of hyperconnectivity.

What Is the Evidence for the Hyperconnectivity Response?

The finding that physical disruption of a network following injury (i.e., local node removal) results in functional hyperconnectivity may appear counterintuitive, but this effect has been observed in multiple studies, including Parkinson's disease [33–40], multiple sclerosis [41–51], traumatic brain injury (TBI) [52–59], cerebrovascular accident [60], and epilepsy [61–63]. We suggest that

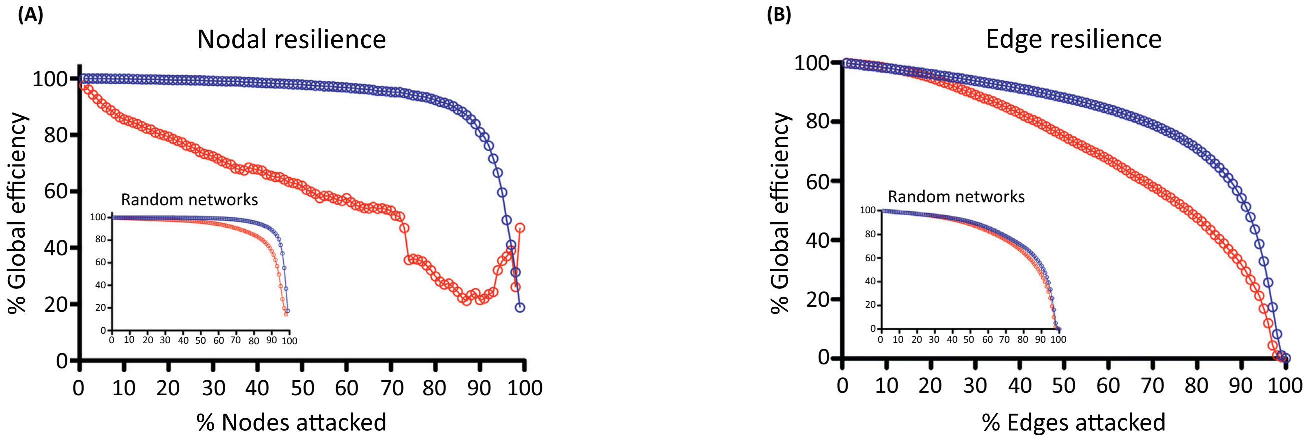

Figure 1. Structural Connectivity and Simulated Response to Random (Blue Lines) and Targeted (Red Lines) Network Attack. Data based upon a human structural connectome informed using diffusion tensor imaging to generate responses to simulated random and targeted deletion of nodes (A) and edges (B). Compared with random network disruption, targeted attack results in diminished global efficiency for node and degree deletion, with the greatest loss of network efficiency with the removal of high-degree nodes. Figure reprinted with permission from [25]

a plausible goal of hyperconnectivity is to re-establish network communication through network hubs; if this is the case, then the functional hyperconnectivity response should be most prominent following 'random' edge deletion, which (probabilistically) leaves network hubs functionally exploitable. There is an established literature demonstrating a resource temporal gradient (i.e., a loss of neural resources over time) influencing the network response, with hyperconnectivity representing an early phase response to many neurodegenerative disease processes that diminishes as the network succumbs to late-stage cortical atrophy, which directly affects network hubs, making connectivity sporadic or even impossible. This pattern of regionally increased functional connectivity early after disease diagnosis or after brain injury has been documented in Parkinson's disease [33–35], multiple sclerosis [41,42,66,67], TBI [53,56–58], and MCI [68,69], followed by connectivity decline as symptoms and disease burden progress [70–73].

In fact, enhanced brain resource utilization may precede disease states or be indicative of risk for pathology. For example, young healthy carriers of the **Apolipoprotein E** (APOE) ε4 allele, a genetic risk factor for later-life neurodegeneration, including AD, demonstrate enhanced response of the **default mode network** (DMN) [136] during rest and hyperactivation when engaged by an episodic memory task (i.e., increased local fMRI signal) [74,75], followed by diminishing connectivity during the advanced expression of the disease [72,76–79]. Recent longitudinal work shows similar trajectories with healthy older Apoe ε4 carriers exhibiting increasing frontal to hippocampal connectivity over a 35-month time frame compared with an Apoe ε2 (lower risk) group [72]. The hyperconnectivity response has become so common in the clinical neural network literature that the term 'compensation' now represents an accepted, albeit nonspecific, explanation of the phenomenon [80,81]. What will be important to determine moving forward are the factors that influence the onset and persistence of hyperconnectivity and the long-term consequences for chronic engagement of additional neural resources. For example, TBI has been increasingly recognized as a risk factor for AD [82,83], where posterior connection loss is widely observed in connectivity studies [64,65], but what remains unknown is the transition between hyper- and hypoconnected states and the vulnerabilities associated with chronically elevated resource use, given evidence of hyperconnectivity in much younger brain-injured samples. Figure 3 (Key Figure) schematically represents this graded connectivity

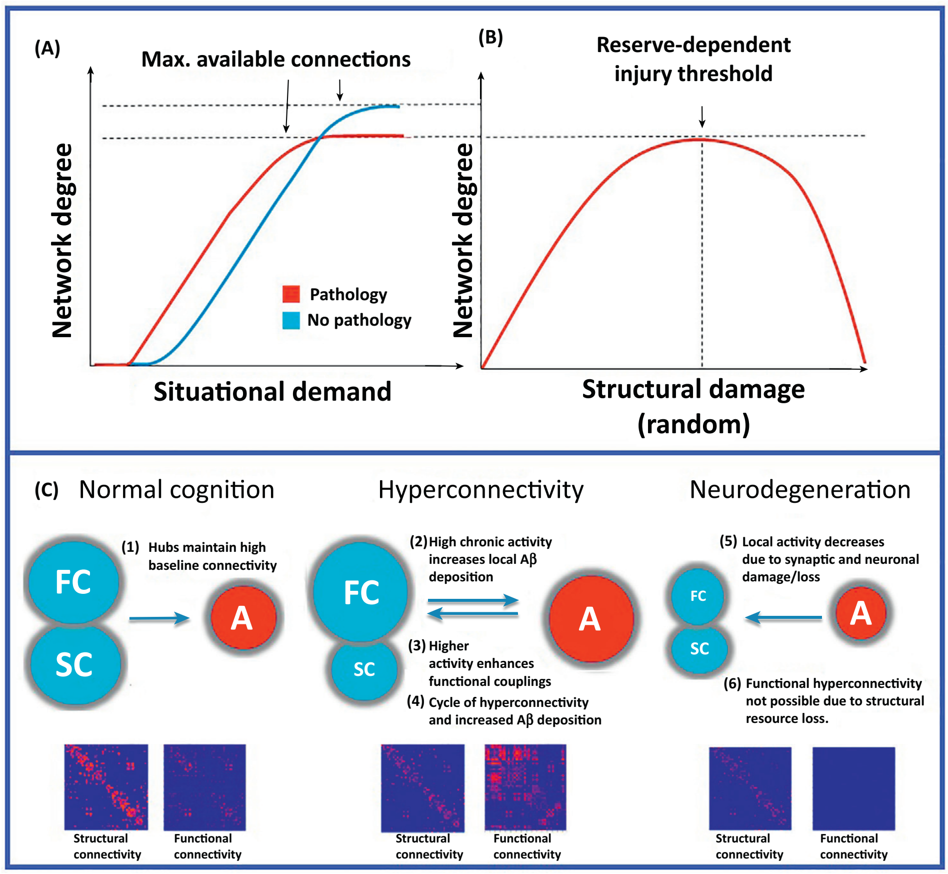

Figure 2. Schematic Representation of the Interaction between Structural and Functional Connectivity after Neurological Disruption. In (A), the red slope represents earlier connectivity recruitment based upon situational demand (e.g., task load or fatigue). Increased connectivity occurs at a lower situational demand after neurological insult and reaches asymptote levels at a lower resource threshold compared with the non-injured system (blue). In (B), increased connectivity rises to some critical injury threshold (determined by genetics and environmental enrichment) after which widespread disconnection occurs. (C) Proposed relationship between increased metabolism in hubs and beta-amyloid (Aβ) deposition. Hubs have higher intrinsic activity, making them most susceptible to pathology. In stage two, hyperconnectivity results from higher local activity initiating a cycle of Aβ deposition and enhanced activity and/or connectivity. In stage three, hyperconnectivity gives way to connectivity loss at a critical resource threshold, resulting in neurodegeneration. Abbreviations: A, activity; FC, functional connectivity; PIB, ^{11}C-PIB; SC, structural connectivity. Panels (A),(B) adapted from [80] and Panel (C) adapted with consultation with lead author [123].

response in network hubs (Figure 3A), highlighted by data from several important findings in the literature (Figure 3B).

How Is Hyperconnectivity Expressed?

The literature points to both regional and centralized scenarios for increased connectivity in response to injury. With regard to the former, mapping brain structure to function has provided some insight into the regional resources that could be leveraged to bolster connectivity and, therefore, function after injury. Using structural connectomics and diffusion tensor imaging, investigators have demonstrated that information transfer times are dependent upon not only the most direct path between nodes, but also the utilization of available alternative or detour paths [84]. One possibility for local hyperconnectivity is that neurological disruption requires ongoing recruitment of available detour paths (Figure 4). There is evidence for the increased use of regional resources in traditional task-based fMRI activation studies in clinical samples where a primary finding is a more spatially diffuse BOLD response in task-related regions compared with areas more circumscribed in healthy control (HC) samples [85–89]. Moreover, one common finding in graph theoretical studies of neurological disruption is an increased clustering coefficient [90–92], which may represent the exploitation of regional 'detour' pathways to amplify signal through additional inputs and enhance alternative means of information processing. Thus, in the region of the lesion, one intuitive explanation for hyperconnectivity is the leveraging of available detour paths either transiently during recovery (Figure 4B) or more permanently as depleted networks work to maintain communication with critical network hubs (Figure 4C).

A separate scenario for enhanced connectivity in response to disruption is a centralized response within critical network hubs irrespective of the nature or location of pathology. There has been much recent attention given to the role of the most highly integrated network hubs of the brain [e.g., precuneus, posterior cingulate cortex (PCC), medial/lateral frontal cortex, and thalamus; commonly termed the 'rich-club'] in directing global brain dynamics and information transfer [93–96]. A centralized hyperconnectivity response expressed through network hubs, irrespective of the pathophysiology, may achieve two important goals for network communication following neurological disruption. First, rich club nodes demonstrate the highest stability in functional connectivity mapping [8] and are optimally positioned to coordinate novel communication between available resources as network plasticity occurs [95]. For example, recent simulations based on cortical networks in the cat demonstrate that rich-club network hubs galvanize network dynamics and facilitate synchronization moving network activity from decentralized to centralized cortical synchronization [96]. It may not be too surprising then that these same vital network hubs are the sites of hyperconnectivity across brain disorders (e.g., multiple sclerosis [41–44,46], TBI [52–58], and Parkinson's Disease [33–35]). Functionally, rich-club hyperconnectivity could work to amplify the signal to overcome increased neural noise (as observed in aging [97]) and signal dampening due to the regional effects of injury. Second, from a neural dynamics perspective, rich-club nodes may have an important role in achieving states of 'criticality', a concept from physics describing behavior in complex dynamic systems where activity at a 'critical point' resides at phase transition points (e.g., water at the liquid–vapor transition point). Criticality is controversial in the neurosciences (reviewed in [98]), but remains an intriguing possibility to account for how complex behaviors, such as cognition, can emerge from the apparent cacophony of billions of time-varying neural signals [99,100]. Neural systems are required to process several inputs on a moment-to-moment basis and, by operating at a critical point, the system maintains enough 'order' to ensure coherent representations of sensory inputs, reinforcing reliable responses while simultaneously retaining a measure of 'disorder', giving it flexibility to adapt. Criticality may provide neural systems with a wide dynamic range for processing various environmental inputs and may maximize the opportunity for information transfer and storage [101], while hubs may have a particularly important role in maintaining these nonlinear dynamics [102]. Although extending these latest findings to states of injury and plasticity is speculative, the link is intriguing, given the central role of hubs in guiding information transfer and the growing evidence for enhanced network involvement of centralized hubs after neurological disruption.

We have argued that a common response post injury is increased connectivity and that this enhancement in neural networks is resource dependent, maintains a resource gradient based upon disease progression, and leverages network hubs to restore network communication. However, alternative explanations are possible. From a physiological perspective, hyperconnectivity could be explained as a 'release' of neural signaling from inhibitory control. From a mathematical perspective, one might argue that hyperconnectivity is an inevitable outcome of node removal (e.g., network failures in the US power grid [103]). If accurate, these alternative explanations pose two distinct problems for the current argument. First, hyperconnectivity is

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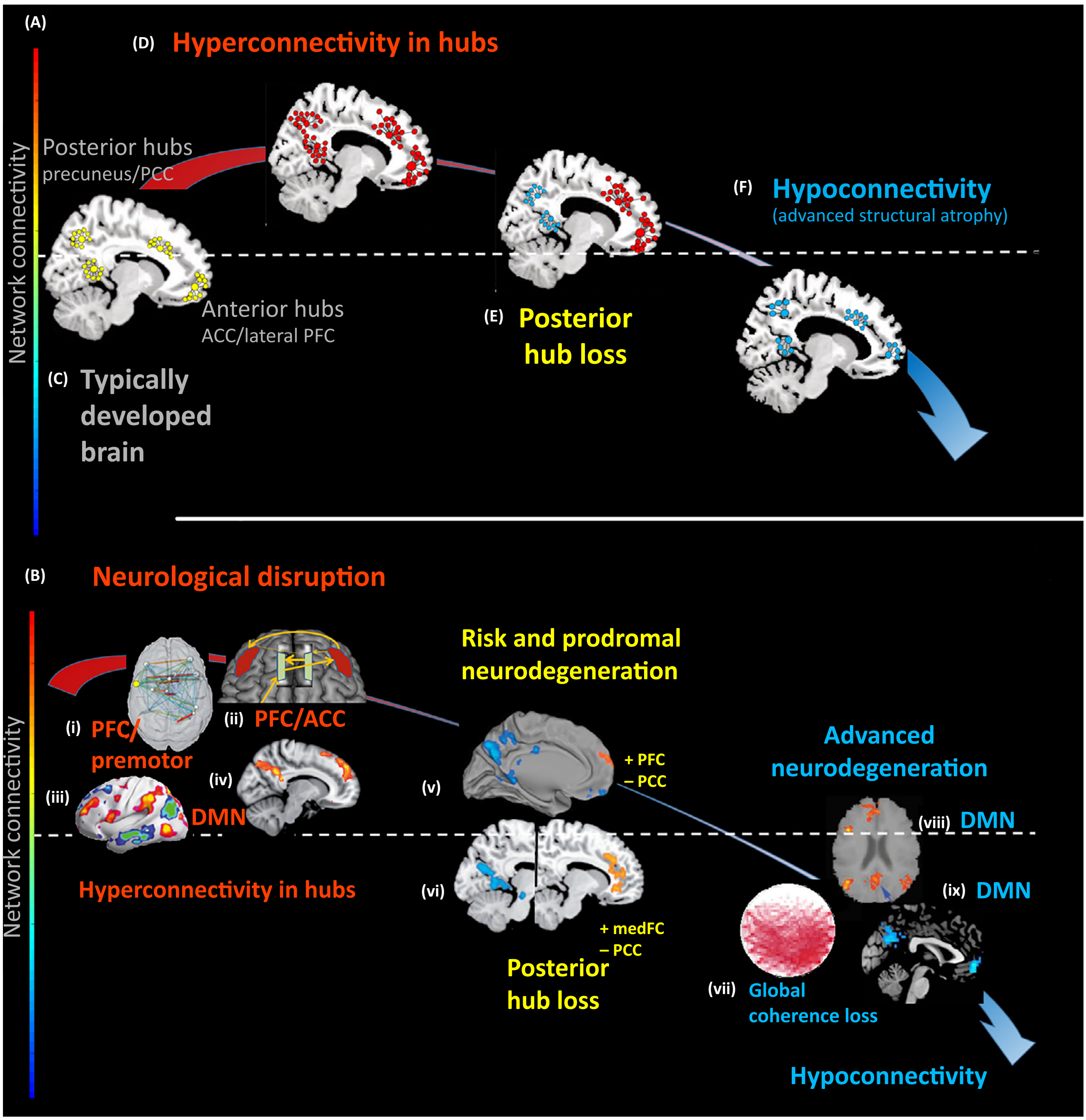
Key Figure

Centralized Hyperconnectivity Response and Resource Gradients



Trends in Cognitive Sciences

Figure 3. (A) Schematic representation of the hubs commonly demonstrating hyperconnectivity in injury and disease (i, ii) and the structural resource-dependent trajectory from hyper- to hypoconnectivity. (iii, iv) (B) Mirrors the schematic in (A) with evidence from seminal studies in the literature. Findings in (B): (i) brain injury results in increased prefrontal and motor connectivity [137]; (ii) increased frontal connectivity during task engagement in brain injury [54], (iii) increased connectivity in default

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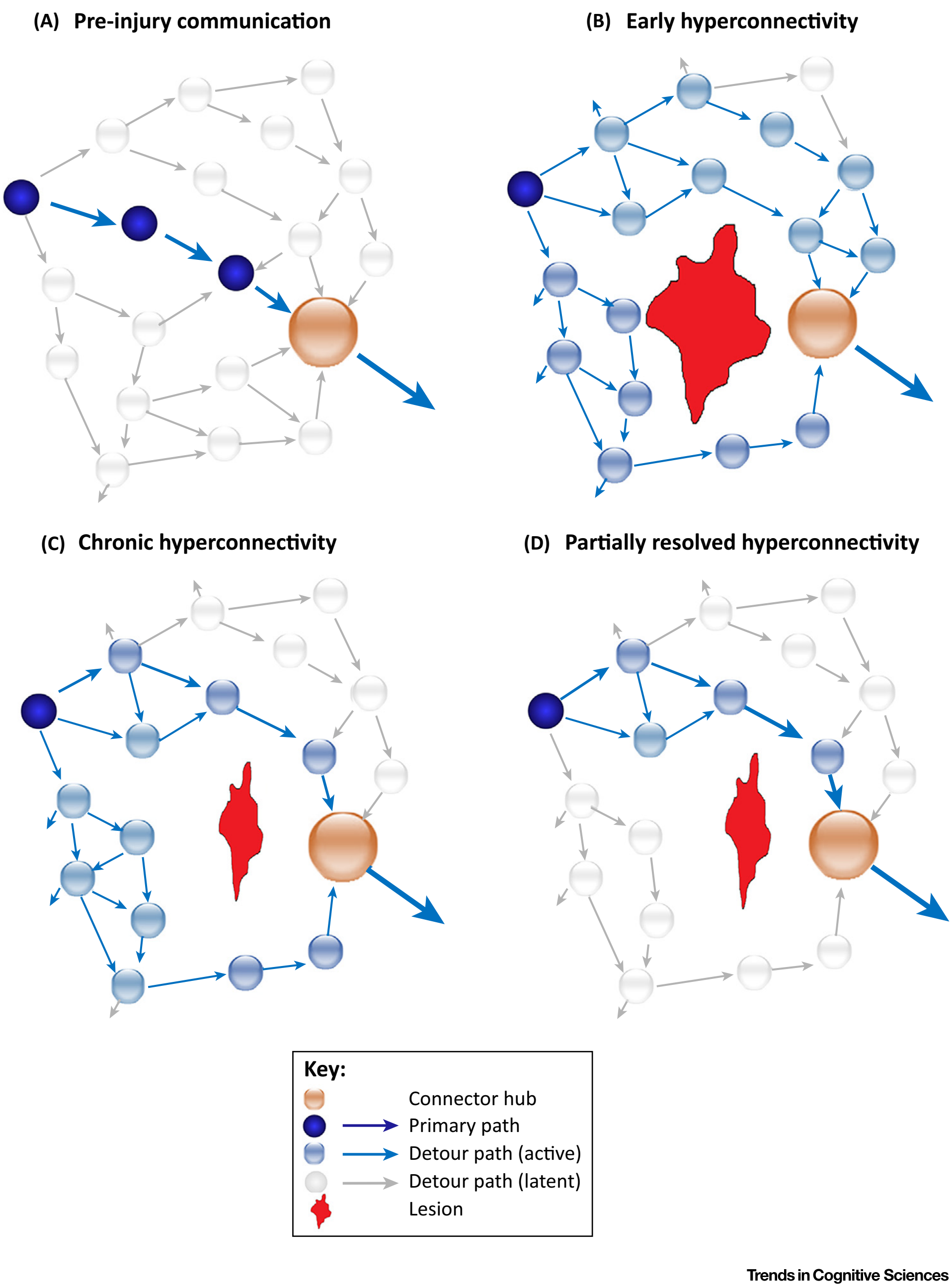

Figure 4. Regional Hyperconnectivity Expressed through Local Detour Paths. Schematic example inspired conceptually by Goni *et al.* [84] to demonstrate the inclusion of detour paths during adaptation to the local effects of brain lesion. (A) Pre-injury communication within the local network to community hub. (B) A lesion (in red) disrupts the primary pathway to the local hub, resulting in the spread of the signal via detour pathways to accumulate enough signal necessary for signal propagation using less-established inputs. Connections to hubs, clustering, and path length all increase locally to amplify the signal using less-established routes. (C) Partial resolution of hyperconnectivity as signaling using detour paths becomes more permanent and/or refined secondary to increased use, but still requiring additional input signals, (D) Near-complete resolution of hyperconnectivity with relatively longer path length.

mode network (DMN) hubs in multiple sclerosis [44]; (iv) increased connectivity in posterior cingulate cortex (PCC) and medial frontal regions of the DMN in traumatic brain injury (TBI) [52]; (v) increased beta-amyloid (Aβ) deposition predicts increased frontal connectivity in context of posterior connectivity in healthy aging [138]; (vi) increased medial frontal connectivity with loss in PCC connectivity in Alzheimer's disease (AD) [139], (vii) global interhemispheric connectivity loss in AD [140], (viii) connection loss in PCC connectivity in AD [141] and (ix) anterior and posterior connectivity loss in AD [142]. Images in Panel (B) reproduced with permission (see [44,52,54,137–142]).

not purposeful. Second, hyperconnectivity is an artefactual outcome of its measurement. In response, we turn to three sources of evidence that show that hyperconnectivity is purposeful and neurologically meaningful. First, support for the hypothesis that hyperconnectivity largely occurs in network hubs is not consistent with the possibility that connection changes are random, represent widespread disinhibition, or are the result of mathematical artifact. The sites for hyperconnectivity reported across multiple studies show higher consistency than one would expect if the network response to node removal were random. Second, in the majority of the studies cited, the magnitude of the altered connectivity was consistently linked to behavioral outcome (i.e., task performance or clinical outcome), indicating a purposeful network response. Third, hyperconnectivity has been observed across several distinct pathophysiological disorders and, in a recent meta-analysis, local lesions were not strong predictors of network response unless they were isolated to hubs [104]. This evidence reduces the likelihood that hyperconnectivity is aberrant signaling due to pathology-induced disinhibition.

The Trouble with Increasing Connectivity

So far, we have presented a literature where complex neural networks adapt to significant disruption through adjustments in connectivity, with the primary goal of enhancing network communication to maintain meaningful responses to environmental demands. However, communication has a metabolic cost in neural systems, so any adjustment to network connectivity after injury must be balanced against the natural tensions between **network cost and efficiency**. Neural networks maintain an intricate balance between metabolic and structural cost and communication efficiency [19–21,105], and, therefore, functional recovery is likely optimized by network modification that negotiates these constraints. As connection density increases, so does routing efficiency [19]; thus, the greatest efficiency would be achieved if all possible neural connections were expressed. However, to adhere to the budgetary constraints of the brain in space (physical material), energy (metabolism), and time (signaling latencies over long distances), the evolutionary solution is a sparse network of strategically placed connections [21,22].

One important assumption in network neuroscience is that the relationships between nodes modeled statistically translate to scalable metabolically demanding brain connections. That is, if the nodal degree established via correlational analysis is capturing meaningful biological communication between any two network nodes, it should also be a reliable indicator of metabolic cost. In seminal work examining these relationships, nodal degree established via rsfMRI and PET methods has been shown to maintain a strong association with glucose uptake [21] (Figure 5). The coupling between network links established using resting-state functional connectivity and neurometabolism has been observed elsewhere [106,107] and, importantly, these relationships appear to hold even in cases of catastrophic brain injury resulting in persistent vegetative state [108]. Examining the number and Euclidean distance of network connections, researchers described the evidence for this cost-efficiency negotiation in TBI, where network cost was greatest at 3 months post injury, but was partially equilibrated by 6–12 months post injury, because the network arguably accommodates cost-efficiency demands [109]. This time line maps nicely onto clinical recovery trajectories reported in the TBI literature, which has traditionally documented the largest clinical gains during the first year after injury [110]. If we can assume that connections established via fMRI methods have real metabolic cost, then re-establishing network communication after disruption via available but commonly dormant pathways (depicted in Figure 4) must be accompanied by a parallel increase in metabolic cost and possibly even in transmission time and wiring costs. Therefore, we propose that any response to injury must negotiate the same cost–efficiency trade-offs, and one way for doing so is to organize plasticity through hubs. Thus, adjustments post injury may be a recapitulation of the principle of preferential attachment, where those centralized nodes with the greatest connectivity are the regional focus of network plasticity.

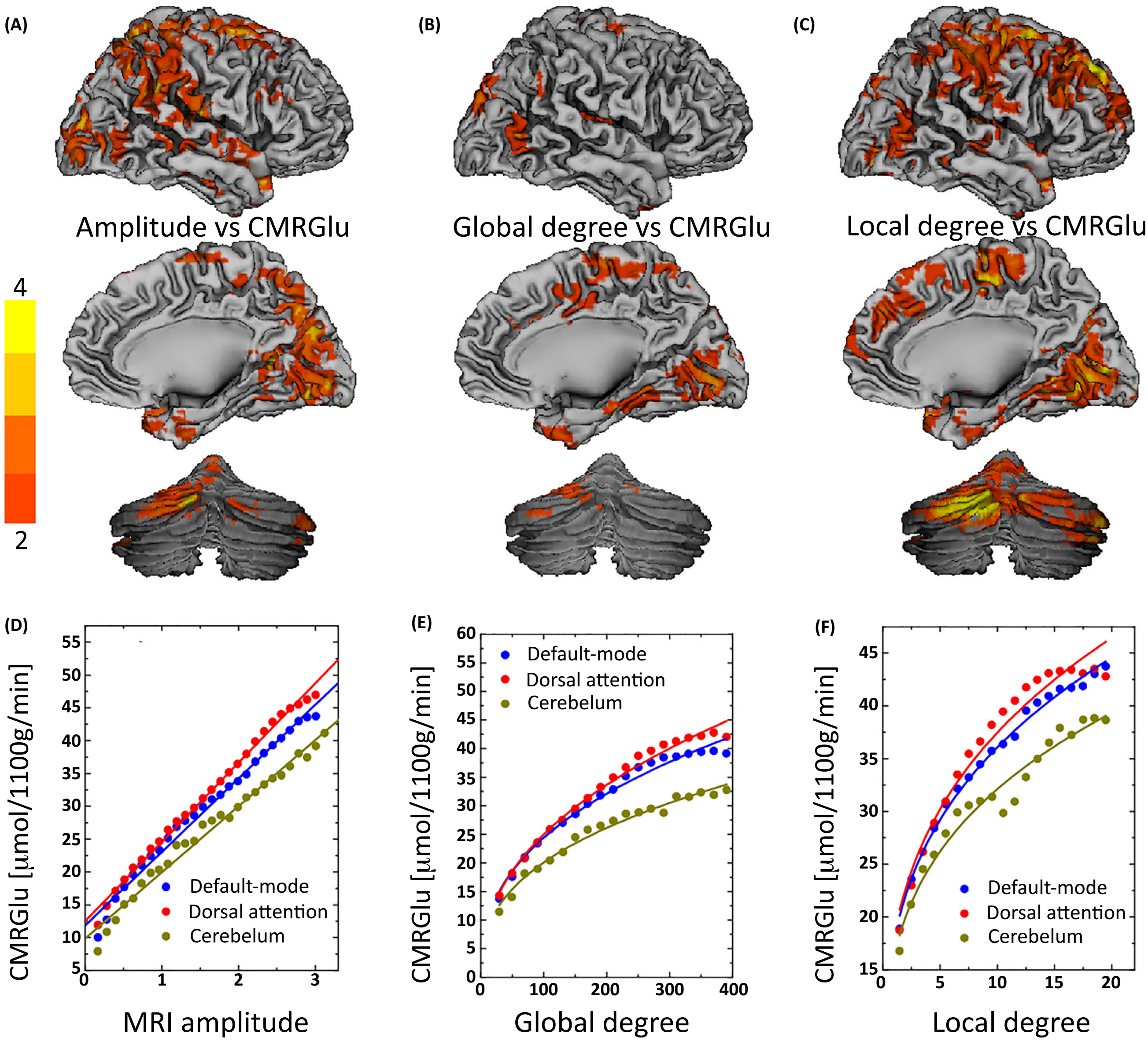

Figure 5. Statistical maps of the voxelwise correlations between cerebral metabolic rate of glucose (CMRglu) and (A) resting-state (R)-fMRI signal amplitude, (B) global degree, and (C) local degree in 54 healthy subjects. The color bars indicate t-score values. Scatter plots exemplifying the linear association between CMRGlu and R-fMRI signal amplitudes (D) and the power scaling of CMRGlu and degree (E,F) across 54 healthy subjects for three different networks. The color lines are reduced-major axis regression fits to the data (0.96 <R2 <0.99). Reprinted, with permission, from [21].

Reconfiguration through Hubs to Balance Network Cost-Efficiency

Network modeling based upon mouse data demonstrated that the scale-free nature of neural networks in sensory and auditory cortex is achieved by preferential attachment [111], and this is consistent with *in vitro* work examining 'hub neurons' in mouse hippocampus during the first month of development [112]. The appearance of network hubs has been identified as an important developmental trajectory point in preterm human infants [113]; thus, the formation of hub connectivity may be an essential goal of early neurodevelopment. Again, given that network hubs are common sites of enhanced connectivity after neurological disruption, a mechanism such as preferential attachment focused on network hub plasticity may serve to preserve global information transfer and network stability. Until critical thresholds are reached and functioning within network hubs is lost due to injury or disease process, these centralized nodes may remain the focal point of network plasticity and, in fact, may become more centralized, operating as a magnet for adaptive collateral connections during recovery [44]. By the same reasoning, when hubs are lost to injury or disease, the consequences are devastating (e.g., advanced AD or cases of catastrophic TBI).

If hyperconnectivity after disruption poses a potential metabolic crisis, neural systems require a strategic response for connectivity enhancements. Investigators have demonstrated that the same regions commonly identified as network hubs are also the most metabolically efficient regions in the brain with respect to glucose uptake [21], and this design has been shown to be highly heritable in twin studies, with a small group of hubs showing the highest cost-efficiency [114]. Consistent with this, demonstrations using network control theory reveal that rich-club regions facilitate low-energy dynamics and, when hubs are removed, network cost increases during state transitions [115].

Therefore, capitalizing upon hub efficiency may mitigate cost-efficiency problems associated with hyperconnectivity. One possibility is that preferential attachment or related neurodevelopmental processes that evolved to segregate the brain into distinct modules may also guide neuroplasticity throughout the life span and could have a crucial role during recovery after neurological insult. Through enhanced connectivity via established network hubs either in prodromal phases of disease (e.g., MCI) or after formal disruption of the system (e.g., TBI or multiple sclerosis), neural networks can flexibly restore encoding and communication while maximizing metabolic efficiency. One possible concern for this blue print for network plasticity is that it disproportionately shifts network load onto hubs.

Possible Consequences of Chronic Hyperconnectivity

Findings revealing that elevated brain metabolism is associated with unwanted consequences have been intensifying across separate literatures for some time. There was strong circumstantial evidence a decade ago that the most highly connected networks (e.g., posterior DMN) contained nodes with a disproportionately higher deposition of **amyloid beta** (Aβ) [116], a marker of AD. Research in animals [117–119] and humans [120–122] more directly demonstrated that regions with the highest metabolism during normal brain functioning show enhanced Aβ deposition. A meta-analysis of brain lesion studies implicated hubs as the common site for pathology irrespective of disease [60], and recent network simulations using a neural mass model revealed that transient increases in activity preceded gradual declines and these effects were disproportionately evident in hub regions [123]. Emerging from these data is the perspective that elevated metabolic demand in rich-club nodes places these hubs at risk for the development of pathophysiology in abnormal aging [124] and that hub 'overload' may be a marker of pathology [1].

In the context of this growing awareness of the relationship between elevated metabolism and neurodegeneration, chronic hyperconnectivity should not be viewed solely as an adaptive 'compensatory' mechanism [81]. While the causal link between elevated activity and Aβ deposition remains a point of debate, one clear possibility is that the relationship is reciprocal. That is, increased connectivity and genetic risk for Aβ deposition results in continued neural recruitment and chronic elevations in metabolism [122]. According to this 'acceleration hypothesis', once initiated, Aβ deposition may be hastened by abnormally increased brain metabolism, particularly in vulnerable regions (e.g., posterior regions within the DMN). There is compelling evidence using metabolic imaging in humans that elevated metabolism is not solely a reaction to Aβ deposition [68] and this finding is consistent with interstitial fluid measurements of Aβ and metabolism, including diminished Aβ in regions of depressed neuronal function, providing support for the proposition that that persistently and abnormally elevated neuronal activity modulates Aβ concentration [125]. It has also been demonstrated that communities of neurons enduring greater oxidative stress are susceptible to degenerative processes [126,127] and, again, this distress exacerbates Aβ deposition [127].

If it is the case that increased brain metabolism secondary to local hyperconnectivity is a predictor of Aβ deposition and eventually sites of neurodegeneration, then the long-term influences of hyperconnectivity in all neurological disorders must be examined with a critical eye as a possible indicator of the risk for degeneration later in life (Figure 3C). This risk is perhaps accentuated by genetic vulnerability and less-developed cognitive reserve. What remains uncertain is whether the metabolic vulnerability that has been repeatedly linked to posterior network hubs, such as the PCC and hippocampus, is reserved to those systems, or if hyperconnectivity following injury and disease could also drive similar metabolic crisis in other hubs. Important recent work has begun to answer this question by examining a large sample of individuals (N = 128) representing distinct stages of the AD disease process. Connectivity data demonstrated that hub overload may be initiated in posterior regions but then spread across network hubs, resulting in a 'cascade' of network failure [81]. These findings implicate frontal system failure later in the AD process; thus, it remains to be determined whether the timeline and hub chronology for these cascading affects is mirrored in other injury/and/or disease processes (e.g., TBI, or multiple sclerosis). Research efforts are needed to examine connectivity changes in late-life brain disorders decades after diagnosis to determine whether disorder-specific markers of hub overload exist.

For now, the link between hyperconnectivity, elevated metabolism, and neurodegenerative risk requires additional clarification, in particular given the complicated relationship between Aβ and **tauopathy**, where the latter has been demonstrated to be more clearly linked with neurobehavioral impairment than has the former [128,129]. As one example, persistent challenges to cognitive reserve may occur during repetitive closed TBI, which shows a stronger link with eventual tauopathy rather than with Aβ pathology [130]. With the advent of PET-tau tracers [131–133], recent work has begun to map these relationships in the healthy older brain [134]. In the Outstanding Questions, we offer several direct approaches and testable hypotheses for advancing our understanding of hyperconnectivity in the context of cost–efficiency and risk and resilience.

Concluding Remarks

We have made the argument that hyperconnectivity is a fundamental response to neuropathology and may be an important signal for system-level plasticity. We have focused on regional hubs as the most likely candidates for its expression, but the role and permanence of enhanced network signaling may be context dependent. For example, we anticipate that increased hub connectivity may precede disease onset, may be directly linked to the disorder (regional), or may be a nonspecific response designed to enhance whole-brain signaling (centralized). The specificity of the hyperconnectivity response remains an open question and work is needed to determine whether resources galvanized to adapt to insidious disease processes differ mechanistically from what is observed in acute injury and chronic disease states (see Outstanding Questions). While hyperconnectivity may have a role in system-level dynamics, there is also evidence of specific lesion-connection adaptations and not all responses may be equally efficacious. Given the implications that hyperconnectivity has for network cost-efficiency and risk of neurodegeneration, future detailed analyses determining its spatiotemporal dynamics are essential to understand the robustness of any heightened connectivity response over time (e.g., [12]). In sum, future models of neurological disruption should conceptualize the

Outstanding Questions

What is the chronicity for hyperconnectivity after neurological disruption and determinants for resolution? The transience of hyperconnectivity and its consequences for behavior require examination over longer windows of time, including early after recovery and decades after diagnosis.

What are the strategic network regions and optimal physical distances for increased connectivity post injury? What is the consequence for strategic increases in network response with regard to network efficiency and cost?

Is hyperconnectivity differentially effective (or indicative of different processes) at distinct oscillatory frequencies? It will be important to uncover the underlying coherent oscillatory behavior in large neuronal assemblies observable as hyperconnectivity in network modeling.

What are the relationships between sustained hyperconnectivity, cognitive reserve, and structural resource loss? Hyperconnectivity must be examined in the context of resource availability while considering factors of risk (genetics) and resilience (cognitive reserve).

Is hyperconnectivity a driver for abnormal neurometabolism? While there is strong evidence that network hubs are sites for Aβ deposition, what is less clear is whether hyperconnectivity contributes to these effects both within and outside hubs.

effects of injury beyond the tradition of lesion-to-connection loss pairing and formally integrate the proactive network response observed as hyperconnectivity.

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References

1. Stam, C.J. (2014) Modern network science of neurological disorders. *Nat. Rev. Neurosci.* 15, 683–695
2. Fornito, A. *et al.* (2017) Opportunities and challenges for psychiatry in the connectomic era: psychiatry in the connectomic era. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 2, 9–19
3. Friston, K.J. *et al.* (1993) Functional connectivity: the principal-component analysis of large (PET) data sets. *J. Cereb. Blood Flow Metab.* 13, 5–14
4. Bullmore, E. and Sporns, O. (2012) The economy of brain network organization. *Nat. Rev. Neurosci.* 13, 336–349
5. Raichle, M.E. and Gusnard, D. (2002) Appraising the brain's energy budget. *Proc. Natl. Acad. Sci. U. S. A.* 99, 10237–10239
6. van den Heuvel, M.P. (2009) Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Hum. Brain Mapp.* 30, 3127–3314
7. Hagmann, P. *et al.* (2008) Mapping the structural core of human cerebral cortex. *PLoS Biol.* 6, e159
8. Shen, K. *et al.* (2015) Network structure shapes spontaneous functional connectivity dynamics. *J. Neurosci.* 35, 5579–5588
9. Betzel, R.F. *et al.* (2014) Changes in structural and functional connectivity among resting-state networks across the human lifespan. *Neuroimage* 102, 345–357
10. Perry, A. *et al.* (2015) The organisation of the elderly connectome. *Neuroimage* 114, 414–426
11. Contreras, J.A. *et al.* (2015) The structural and functional connectome and prediction of risk for cognitive impairment in older adults. *Curr. Behav. Neurosci. Rep.* 2, 234–245
12. Shine, J.M. *et al.* (2016) Temporal metastates are associated with differential patterns of time-resolved connectivity, network topology, and attention. *Proc. Natl. Acad. Sci. U. S. A.* 113, 9888–9891
13. Newman, M.E.J. (2003) The structure and function of complex networks. *SIAM Review* 45, 167–256
14. Watts, D.J. and Strogatz, S.H. (1998) Collective dynamics of 'small-world' networks. *Nature* 393, 440–442
15. Salvador, R. *et al.* (2005) Neurophysiological architecture of functional magnetic resonance images of human brain. *Cereb. Cortex* 15, 1332–1342
16. Stam, C.J. (2004) Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? *Neurosci. Lett.* 355, 25–28
17. Bassett, D.S. *et al.* (2006) Adaptive reconfiguration of fractal small-world human brain functional networks. *Proc. Natl. Acad. Sci. U. S. A.* 103, 19518–19523
18. Hilgetag, C.C. and Goulas, A. (2016) Is the brain really a small-world network? *Brain Struct. Funct.* 221, 2361–2366
19. Gallos, L.K. *et al.* (2012) A small world of weak ties provides optimal global integration of self-similar modules in functional brain networks. *Proc. Natl. Acad. Sci. U. S. A.* 109, 2825–2830
20. Bassett, D.S. *et al.* (2009) Cognitive fitness of cost-efficient brain functional networks. *Proc. Natl. Acad. Sci. U. S. A.* 106, 11747–11752
21. Tomasi, D. *et al.* (2013) Energetic cost of brain functional connectivity. *Proc. Natl. Acad. Sci. U. S. A.* 110, 13642–13647
22. Chen, Y. *et al.* (2013) Trade-off between multiple constraints enables simultaneous formation of modules and hubs in neural systems. *PLoS Comput. Biol.* 9, e1002937
23. Barabási, A.-L. and Albert, R. (1999) Emergence of scaling in random networks. *Science* 286, 509–512
24. Albert, R., Jeong, H. & Barabasi. (2000) A. Error and attack tolerance of complex networks. *Nature* 406, 378–382
25. Crossley, N.A. *et al.* (2014) The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain* 137, 2382–2395
26. Barulli, D. and Stern, Y. (2013) Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn. Sci.* 17, 502–509
27. Stern, Y. (2012) Cognitive reserve in ageing and 'disease. *Lancet Neurol.* 11, 1006–1012
28. Arenaza-Urquijo, E.M. *et al.* (2013) Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. *Neuroimage* 83, 450–457
29. Franzmeier, N. *et al.* (2016) Alzheimer's Disease Neuroimaging Initiative. Resting-state global functional connectivity as a biomarker of cognitive reserve in mild cognitive impairment. *Brain Imaging Behav.* Published online October 05, 2016. http://dx.doi.org/10.1007/s11682-016-9599-1
30. Santarnecchi, E. *et al.* (2014) The smarter, the stronger: intelligence level correlates with brain resilience to systematic insults. *Cortex* 64C, 293–309
31. Premi, E. *et al.* (2013) Cognitive reserve in granulin-related frontotemporal dementia: from preclinical to clinical stages. *PLoS One* 8, 1–8
32. Sumowski, J.F. *et al.* (2010) Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: functional magnetic resonance imaging evidence for cognitive reserve. *Brain* 133, 362–374
33. Gorges, M. *et al.* (2014) To rise and to fall: functional connectivity in cognitively normal and cognitively impaired patients with Parkinson's disease. *Neurobiol. Aging* 36, 1727–1735
34. Fernández-Seara, M.A. (2015) Resting state functional connectivity of the subthalamic nucleus in Parkinson's disease assessed using arterial spin-labeled perfusion fMRI. *Hum. Brain Mapp.* 36, 1937–1950
35. Stoffers, D. *et al.* (2008) Increased cortico-cortical functional connectivity in early-stage Parkinson's. *Neuroimage* 41, 212–222
36. Yu, R. *et al.* (2013) Enhanced functional connectivity between putamen and supplementary motor area in Parkinson's disease patients. *PLoS One* 8, e59717
37. Helmich, R.C. *et al.* (2010) Spatial remapping of cortico-striatal connectivity in Parkinson's disease. *Cereb Cortex.* 20, 1175–1186
38. Simioni, A.C. *et al.* (2015) Compensatory striatal-cerebellar connectivity in mild-moderate Parkinson's disease. *Neuroimage Clin.* 10, 54–62
39. Kwak, Y. *et al.* (2010) Altered resting state cortico-striatal connectivity in mild to moderate stage Parkinson's disease. *Front. Syst. Neurosci.* 4, 143
40. Vervoort, G. *et al.* (2016) Functional connectivity alterations in the motor and fronto-parietal network relate to behavioral heterogeneity in Parkinson's disease. *Parkinsonism Relat. Disord.* 24, 48–55
41. Roosendaal, S.D. *et al.* (2010) Resting state networks change in clinically isolated syndrome. *Brain* 133 (Pt 6), 1612–1621

42. Faivre, A. *et al.* (2012) Assessing brain connectivity at rest is clinically relevant in early multiple sclerosis. *Mult. Scler. J.* 18, 1251–1258
43. Bonavita, S. *et al.* (2011) Distributed changes in default-mode resting-state connectivity in multiple sclerosis. *Mult. Scler. J.* 17, 411–422
44. Hawellek, D.J. *et al.* (2011) Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis. *Proc. Natl. Acad. Sci. U. S. A.* 108, 19066–19071
45. Leavitt, V.M. *et al.* (2012) Warmer outdoor temperature is associated with worse cognitive status in multiple sclerosis. *Neurology* 78, 964–968
46. Faivre, A. *et al.* (2015) Brain functional plasticity at rest and during action in multiple sclerosis patients. *J. Clin. Neurosci.* 22, 1438–1443
47. Schoonheim, M.M. *et al.* (2015) Thalamus structure and function determine severity of cognitive impairment in multiple sclerosis. *Neurology* 84, 776–783
48. Rocca, M.A. *et al.* (2010) Functional and structural connectivity of the motor network in pediatric and adult-onset relapsing-remitting multiple sclerosis. *Radiology* 254, 541–550
49. Dogonowski, A.M. *et al.* (2013) Expanded functional coupling of subcortical nuclei with the motor resting-state network in multiple sclerosis. *Mult. Scler.* 19, 559–566
50. Loitfelder, M. *et al.* (2012) Abnormalities of resting state functional connectivity are related to sustained attention deficits in MS. *PLoS One* 7, e42862
51. Valsasina, P. *et al.* (2011) A multicentre study of motor functional connectivity changes in patients with multiple sclerosis. *Eur. J. Neurosci.* 33, 1256–1263
52. Sharp, D.J. *et al.* (2011) Default mode network functional and structural connectivity after traumatic brain injury. *Brain* 134, 2233–2247
53. Hillary, F.G. *et al.* (2014) The rich get richer: brain injury elicits hyperconnectivity in core subnetworks. *PLoS One* 9, e104021
54. Hillary, F.G. *et al.* (2011) Examining working memory task acquisition in a disrupted neural network. *Brain* 134, 1555–1570
55. Hillary, F.G. *et al.* (2011) Changes in resting connectivity during recovery from severe traumatic brain injury. *Int. J. Psychophysiol.* 82, 115–123
56. Iraji, A. *et al.* (2016) Resting state functional connectivity in mild traumatic brain injury at the acute stage: independent component and seed-based analyses. *J. Neurotrauma* 32, 1031–1045
57. Bharath, R.D. *et al.* (2015) Recovery of resting brain connectivity ensuing mild traumatic brain injury. *Front. Hum. Neurosci.* 9, 1–13
58. Johnson, B. *et al.* (2012) Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. *Neuroimage* 59, 511–518
59. Mayer, A.R. *et al.* (2011) Functional connectivity in mild traumatic brain injury. *Hum. Brain Mapp.* 32, 1825–1835
60. Nicolo, P. *et al.* (2015) Coherent neural oscillations predict future motor and language improvement after stroke. *Brain* 138 (Pt 10), 3048–3060
61. Caeyenberghs, K. *et al.* (2014) Hyperconnectivity in juvenile myoclonic epilepsy: a network analysis. *Neuroimage Clin.* 7, 98–104
62. O'Muircheartaigh, J. *et al.* (2012) Abnormal thalamocortical structural and functional connectivity in juvenile myoclonic epilepsy. *Brain* 135 (Pt 12), 3635–3644
63. Vollmar, C. *et al.* (2011) Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study. *Brain* 134 (Pt 6), 1710–1719
64. Sheline, Y.I. and Raichle, M.E. (2013) Resting state functional connectivity in preclinical Alzheimer's disease. *Biol. Psychiatry* 74, 340–347
65. Tijms, B.M. *et al.* (2013) Alzheimer's disease: connecting findings from graph theoretical studies of brain networks. *Neurobiol. Aging* 34, 2023–2036
66. Tona, F. *et al.* (2014) Multiple sclerosis: altered thalamic resting-state functional connectivity and its effect on cognitive function. *Radiology* 271, 814–821
67. Duong, M.V.A. *et al.* (2005) Modulation of effective connectivity inside the working memory network in patients at the earliest stage of multiple sclerosis. *Neuroimage* 24, 533–538
68. Cohen, A.D. *et al.* (2009) Basal cerebral metabolism may modulate the cognitive effects of Aβ in mild cognitive impairment: an example of brain reserve. *J. Neurosci.* 29, 14770–14778
69. Gour, N. *et al.* (2011) Basal functional connectivity within the anterior temporal network is associated with performance on declarative memory tasks. *Neuroimage* 58, 687–697
70. Olde Dubbelink, K.T. *et al.* (2014) Functional connectivity and cognitive decline over 3 years in Parkinson disease. *Neurology* 83, 2046–2053
71. Hacker, C.D. *et al.* (2012) Resting state functional connectivity of the striatum in Parkinson's disease. *Brain* 135 (Pt 12), 3699–3711
72. Ye, Q. *et al.* (2016) The apolipoprotein E gene affects the three-year trajectories of compensatory neural processes in the left-lateralized hippocampal network. *Brain Imaging Behav.* Published online October 12, 2016. http://dx.doi.org/10.1007/s11682-016-9623-5
73. Tewarie, P. *et al.* (2015) Functional brain networks: linking thalamic atrophy to clinical disability in multiple sclerosis, a multimodal fMRI and MEG study. *Hum. Brain Mapp.* 36, 603–618
74. Bookheimer, S.Y. *et al.* (2000) Patterns of brain activation in people at risk for Alzheimer's disease. *N. Engl. J. Med.* 343, 450–456
75. Filippini, N. *et al.* (2009) Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc. Natl. Acad. Sci. U. S. A.* 106, 7209–7214
76. Bondi, M.W. *et al.* (2005) fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology* 64, 501–508
77. O'Brien, J.L. *et al.* (2010) Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. *Neurology* 74, 1969–1976
78. Brown, J.A. *et al.* (2011) Brain network local interconnectivity loss in aging APOE-4 allele carriers. *Proc. Natl. Acad. Sci. U. S. A.* 108, 20760–20765
79. Machulda, M.M. *et al.* (2011) Effect of APOE ε4 status on intrinsic network connectivity in cognitively normal elderly subjects. *Arch. Neurol.* 68, 1131–1136
80. Hillary, F.G. *et al.* (2015) Hyperconnectivity is a fundamental response to neurological disruption. *Neuropsychology* 29, 59–75
81. Jones, D.T. *et al.* (2016) Alzheimer's Disease Neuroimaging Initiative. Cascading network failure across the Alzheimer's disease spectrum. *Brain* 139 (Pt 2), 547–562
82. Mortimer, J.A. *et al.* (1991) Head trauma as a risk factor for Alzheimer's disease: a collaborative reanalysis of case-control studies. EURODEM Risk Factors Research Group. *Int. J. Epidemiol.* 20 (Suppl 2), S28–S35
83. Nemetz, P.N. *et al.* (1999) Traumatic brain injury and time to onset of Alzheimer's disease: a population-based study. *Am. J. Epidemiol.* 149, 32–40
84. Goñi, J. *et al.* (2014) Resting-brain functional connectivity predicted by analytic measures of network communication. *Proc. Natl. Acad. Sci. U. S. A.* 111, 833–838
85. Christodoulou, C. (2001) Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. *J. Neurol. Neurosurg. Psychiatry* 71, 161–168
86. Ernst, T. *et al.* (2002) Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. *Neurology* 59, 1343–1349
87. Forn, C. *et al.* (2012) Functional magnetic resonance imaging correlates of cognitive performance in patients with a clinically isolated syndrome suggestive of multiple sclerosis at presentation: an activation and connectivity study. *Mult. Scler. J.* 18, 153–163
88. McAllister, T.W. *et al.* (2001) Differential working memory load effects after mild traumatic brain injury. *Neuroimage* 14, 1004–1012

89. Chiaravalloti, N. (2005) Cerebral activation patterns during working memory performance in multiple sclerosis using FMRI. *J. Clin. Exp. Neuropsychol.* 27, 33–54
90. Nakamura, T. *et al.* (2009) Resting network plasticity following brain injury. *PLoS One* 4, e8220
91. Gamboa, O.L. *et al.* (2014) Working memory performance of early MS patients correlates inversely with modularity increases in resting state functional connectivity networks. *Neuroimage* 94, 385–395
92. Pederson, M. *et al.* (2015) Increased segregation of brain networks in focal epilepsy: an fMRI graph theory finding. *Neuroimage Clin.* 8, 536–542
93. Zamora-López, G. *et al.* (2010) Cortical hubs form a module for multisensory integration on top of the hierarchy of cortical networks. *Front. Neuroinform.* 4, 1
94. van den Heuvel, M.P. and Sporns, O. (2011) Rich-club organization of the human connectome. *J. Neurosci.* 31, 15775–15786
95. van den Heuvel, M.P. *et al.* (2012) High-cost, high capacity backbone for global brain communication. *Proc. Natl. Acad. Sci. U. S. A.* 109, 11372–11377
96. Gómez-Gardeñes, J. *et al.* (2010) From modular to centralized organization of synchronization in functional areas of the cat cerebral cortex. *PLoS One* 5, e12313
97. Hong, S.L. and Rebec, G.V. (2012) A new perspective on behavioral inconsistency and neural noise in aging: compensatory speeding of neural communication. *Front. Aging Neurosci.* 4, 27
98. Beggs, J.M. and Timme, N. (2012) Being critical of criticality in the brain. *Front. Physiol.* 3, 163
99. Chialvo, D.R. (2010) Emergent complex neural dynamics. *Nat. Phys.* 6, 744–750
100. Moretti, P. and Muñoz, M.A. (2013) Griffiths phases and the stretching of criticality in brain networks. *Nat. Commun.* 4, 2521
101. Petermann, T. *et al.* (2009) Spontaneous cortical activity in awake monkeys composed of neuronal avalanches. *Proc. Natl. Acad. Sci. U. S. A* 106, 15921–15926
102. Minati, L. *et al.* (2015) Synchronization, non-linear dynamics and low-frequency fluctuations: analogy between spontaneous brain activity and networked single-transistor chaotic oscillators. *Chaos* 25, 033107
103. Crucitti, P. *et al.* (2004) Model for cascading failures in complex networks. *Phys. Rev. E* 69, 045104
104. Aerts, H. *et al.* (2016) Brain networks under attack: robustness properties and the impact of lesions. *Brain* 139 (Pt 12), 3063–3083
105. Achard, S. and Bullmore, E. (2007) Efficiency and cost of economical brain functional networks. *PLoS Comput. Biol.* 3, 0174–0183
106. Wagner, G. *et al.* (2016) Resting state functional connectivity of the hippocampus along the anterior-posterior axis and its association with glutamatergic metabolism. *Cortex* 81, 104–117
107. Passow, S. *et al.* (2015) Default-mode network functional connectivity is closely related to metabolic activity. *Hum. Brain Mapp.* 36, 2027–2038
108. Soddu, A. *et al.* (2015) Correlation between resting state fMRI total neuronal activity and PET metabolism in healthy controls and patients with disorders of consciousness. *Brain Behav*. 6, e00424
109. Roy, A *et al.* The evolution of cost-efficiency in neural networks during recovery from traumatic brain injury. *PLoS One*. (in press)
110. Novack, T.A. *et al.* (2001) Outcome after traumatic brain injury: pathway analysis of contributions from premorbid, injury severity, and recovery variables. *Arch. Phys. Med. Rehabil.* 82, 300–305
111. Sadovsky, A.J. and MacLean, J.N. (2013) Scaling of topologically similar functional modules defines mouse primary auditory and somatosensory microcircuitry. *J. Neurosci.* 33, 14048–14060
112. Schroeter, M.S. *et al.* (2015) Emergence of rich-club topology and coordinated dynamics in development of hippocampal functional networks *in vitro*. *J. Neurosci.* 35, 5459–5470
113. Cao, M. *et al.* (2016) Early development of functional network segregation revealed by connectomic analysis of the preterm human brain. *Cereb. Cortex* Published online March 3, 2016. http://dx.doi.org/10.1093/cercor/bhw038
114. Fornito, A. *et al.* (2011) Genetic influences on cost-efficient organization of human cortical functional networks. *J. Neurosci.* 31, 3261–3270
115. Betzel, R.F. *et al.* (2016) Optimally controlling the human connectome: the role of network topology. *Sci Rep.* 6, 30770
116. Buckner, R.L. *et al.* (2005) Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J. Neurosci.* 25, 7709–7717
117. Busche, M.A. *et al.* (2012) Critical role of soluble amyloid-beta for early hippocampal hyperactivity in a mouse model of Alzheimer's disease. *Proc. Natl. Acad Sci. U. S. A.* 109, 8740–8745
118. Cirrito, J.R. *et al.* (2005) Synaptic activity regulates interstitial fluid amyloid-beta levels *in vivo*. *Neuron* 48, 913–922
119. Bero, A.W. *et al.* (2012) Bidirectional relationship between functional connectivity and amyloidb deposition in mouse brain. *J. Neurosci.* 32, 4334–4340
120. Buckner, R.L. *et al.* (2009) Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J. Neurosci.* 29, 1860–1873
121. Vlassenko, A.G. *et al.* (2010) Spatial correlation between brain aerobic glycolysis and amyloid-β (Aβ) deposition. *Proc. Natl. Acad Sci. U. S. A.* 107, 17763
122. Myers, N. *et al.* (2012) Within-patient correspondence of amyloid-β and intrinsic network connectivity in Alzheimer's disease. *Brain* 137 (Pt 7), 2052–2064
123. de Haan, W. *et al.* (2012) Activity dependent degeneration explains hub vulnerability in Alzheimer's disease. *PLoS Comput. Biol.* 8, e1002582
124. Fornito, A. *et al.* (2015) The connectomics of brain disorders. *Nat. Rev. Neurosci.* 16, 159–172
125. Brody, D.L. *et al.* (2008) Amyloid-beta dynamics correlate with neurological status in the injured human brain. *Science* 321, 1221–1224
126. Dumont, M. *et al.* (2009) Reduction of oxidative stress, amyloid deposition, and memory deficit by manganese superoxide dismutase overexpression in a transgenic mouse model of Alzheimer's disease. *FASEB J.* 23, 2459–2466
127. Lin, M.T. and Beal, M.F. (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443, 787–795
128. Arriagada, P.V. *et al.* (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 42, 631–639
129. Nelson, P.T. *et al.* (2012) Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J. Neuropathol. Exp. Neurol.* 71, 362–381
130. McKee, A.C. *et al.* (2009) Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J. Neuropathol. Exp. Neurol.* 68, 709–735
131. Maruyama, M. *et al.* (2013) Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron* 79, 1094–1108
132. Harada, R. *et al.* (2013) Comparison of the binding characteristics of [18F]THK-523 and other amyloid imaging tracers to Alzheimer's disease pathology. *Eur. J. Nucl. Med. Mol. Imaging* 40, 125–132
133. Okamura, N. *et al.* (2013) Novel 18F-labeled arylquinoline derivatives for noninvasive imaging of tau pathology in Alzheimer disease. *J. Nucl. Med.* 54, 1420–1427
134. Sepulcre, J. *et al.* (2016) *In vivo* tau, amyloid, and gray matter profiles in the aging brain. *J Neurosci.* 36 (28), 7364–7374
135. Corder, E.H. *et al.* (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 261, 921–923
136. Raichle, M.E. and Snyder, A.Z. (2007) A default mode of brain function: a brief history of an evolving idea. *Neuroimage* 37, 1083–1090 discussion 1097–1099

137. Caeyenberghs, K. *et al.* (2012) Graph analysis of functional brain networks for cognitive control of action in traumatic brain injury. *Brain* 135 (Pt 4), 1293–1307

138. Mormino, E.C. *et al.* (2011) Relationships between β-amyloid and functional connectivity in different components of the default mode network in aging. *Cereb. Cortex* 21, 2399–2407

139. Zhou, J. *et al.* (2010) Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain* 133 (Pt 5), 1352–1367

140. Stam, C.J. *et al.* (2009) Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease. *Brain* 132 (Pt 1), 213–224

141. Greicius, M.D. *et al.* (2004) Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc. Natl. Acad. Sci. U. S. A.* 101, 4637–4642

142. Agosta, F. *et al.* (2012) Resting state fMRI in Alzheimer's disease: beyond the default mode network. *Neurobiol. Aging* 33, 1564–1578