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Current perspectives on the brain connectome

The description by Jules Joseph Dejerine and Augusta Dejerine-Klumpke of the fiber connections uniting diverse brain areas have become, in modern times, association fibers. These were proposed as a biological basis for corroborating or refuting medical hypotheses derived from the clinical consequences of brain injury – often interpreted considering such theoretical perspectives as localizationism, holism, or associationism. Given the 3D nature of these association networks, however, anatomical dissections are somewhat arbitrary with respect to what one is trying to find. More recently, new structural and functional techniques have been developed with the hope of objectively untangling the useful reality suggested by these association networks. These past years, there has been much interest in mapping the connectome – the complete map of neural connections in a nervous system of a given species – to understand how brain structure gives rise to brain function, and ultimately, how it generates behaviour.

The connectome approach has now infiltrated multiple disciplines in a broader context, one in which network thinking permeates technology, infrastructure and social life. In the neurosciences, it has become the dominant metaphor of contemporary brain research. How the connectome constrains global properties of large-scale networks, across multiple brain regions or the entire brain, however, remains incompletely understood. As the likelihood of partial or complete connectomes expands to more systems and species it becomes critical to understand how this exhaustive anatomical information can inform our understanding of large-scale circuit function.

In this perspective, we are dedicating a special volume to highlight some of the challenges and current progress in mapping the connectome. The topics of interest include the healthy human brain, investigating rewiring during development, learning and experience-dependent plasticity, and individual differences. The functional and structural disorders of the connectome are also considered as they relate to pain, Alzheimer's disease and dementia, among others.

The brain connectome refers to the complex network of synaptic connections between neurons. These connections are responsible for transmitting information and coordinating the different functions of the brain. The connectome is made up of both structural and functional connections. The study of the brain connectome has seen a rapidly growing expansion in cognitive neuroscience; an understanding of these connections can help us better appreciate how the brain processes information and controls behavior.

The study of the brain connectome has been sparked by advances in neuroimaging technologies, which have allowed researchers to visualize the brain's structural and functional connections in exceptional detail. Ever since Ramón y Cajal S (1906) developed the staining techniques which allowed him to see the cell bodies of neurons and the branching patterns of individual neurons, there has been a constant progression towards finer imaging of brain structure and function. Ramon y Cajal was ahead of his time in suggesting that connections in the central nervous system (CNS) were not static, but rather dynamic and in some cases, plastic (1991). The modern ideas about the functional specification of brain regions, and the importance of communication between regions, however, predate these technical developments. This knowledge can be attributed to the work of Franz J. Gall (1758–1828), who not only identified the functions of different areas of gray matter in the brain, but also recognized the importance of white matter connectivity between these regions (Zola-Morgan, 1995). Carl Wernicke (1848–1905), known as the father of disconnection theory, further emphasized the significance of connectivity in brain function (Catani & Ffytche, 2005). Wernicke believed that functions were not solely localized within specific brain regions, except for primary sensory and motor functions. Building upon this idea, Geschwind (1965) proposed that higher cognitive and emotional processes involve a combination of functional specialization and connectivity between different brain areas. This suggests that the brain is composed of complex anatomical networks that support these processes. More recently, diffusion tensor imaging (DTI) has enabled the mapping of the white matter tracts that connect different regions of the brain (Hasan et al., 2011), while functional magnetic resonance imaging (fMRI) has revealed the patterns of neural activity or communication between those regions (e.g., Ogawa et al., 1992).

Also, recent advances in connectomics, a field of neuroscience that involves the mapping and analysis of neural connection in the brain, makes use of brain imaging data to extract the relevant information (e.g., Xia & He, 2023). Computational algorithms help identify and segment the different regions of the brain and map the connections between them. Further analyses consist in quantifying the strength and directionality of the connections between different regions of the brain, and in identifying patterns of connectivity that are associated with specific cognitive functions. The final step, usually, is characterizing the key features of the connectome that are relevant to the specific cognitive processes and studying the underlying neural mechanisms that support these processes. The future of connectomics promises to yield a more inclusive understanding of brain structure and function (Laird, 2021).

Several networks have been involved in the study of the connectome. The structural network is a key component of the brain connectome and refers to the physical connections between different regions of the brain. This network provides the basic framework for the brain's functional connectivity (e.g., Zhang et al., 2019). This information can be used to better understand how the brain processes information, re-

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sponds to stimuli, and generates behavior, as well as to identify abnormalities or disruptions in brain connectivity that may be associated with neurological and psychiatric disorders. Overall, the structural network is a foundational element of the brain connectome, providing the physical basis for the complex network of connections that underlies cognitive function and behavior.

The functional network exemplifies the patterns of neural activity between different regions of the brain, as usually measured by fMRI techniques. Although functional brain networks are shaped and constrained by the underlying structural network, they are not merely a one-to-one reflection of the underlying structural system. The functional network is dynamic and can vary over time since brain activity and communication are constantly changing as we engage in cognitive or motor activities, or as we experience different sensory stimuli. This network involves multiple regions widely distributed throughout the brain that are coordinated to perform diverse functions. Despite its distributed nature, the network can also be organized in clusters of regions working together to perform specific tasks or functions (e.g., Duffau, 2021). This functional network is also plastic as it can be shaped by development, experience and learning, disease, and the environment.

Following the work of Vinod Menon, neuroimaging and functional connectivity studies have identified a few functional networks. The default mode network (DMN), salience network (SN), and central executive network form a tri-network system that is postulated to explain much of cognition and behaviour (Menon, 2011). The default mode network (DMN) is active when the brain is at rest and not focused on any specific task; it is associated with self-referential thinking and processing of internal information. A set of midline structures including the medial prefrontal cortex, posterior cingulate cortex and precuneus are principally involved. The DMN is anti-correlated with task-positive networks: when one is active, the other is less active. It is, however, highly connected to other functional networks, such as the salience and frontoparietal networks. Various neurological and psychiatric disorders have been found to impact the DMN, resulting with changes in cognitive and social functioning.

The salience network including the dorsolateral prefrontal cortex, the anterior cingulate cortex, and insula is also involved in detecting and filtering important stimuli in the environment, such as pain or social cues, and then shifting attention, both internally and externally, towards them. It is highly integrated with the DMN and frontoparietal network, allowing for dynamically switching between different networks within the brain. These regions are densely interconnected and concerned in facilitating communication between other brain networks in the coordinated processing and regulation of attention, emotion, and cognitive control. This switching mechanism enables the brain to flexibly transition between internally focused and externally oriented cognitive states. The salience network also plays a role in decision making reward processing, and is affected by neurologic and psychiatric disorders, such as Alzheimer's disease (e.g., Nishida, 2013), or autism.

The central executive network, or executive control network (ECN) is associated with higher-level cognitive functions such as problem solving, task switching, and working memory. Neuroimaging and functional connectivity studies have shown that the prefrontal and anterior cingulate cortex, the parietal cortex, and the temporo-parietal junction are strongly related to each other in the coordination of multiple brain regions allowing the integration and coordination of information across cognitive domains. The ECN is particularly important for goal-directed behavior, allowing us to plan and execute complex actions, inhibit inappropriate responses, and flexibly adapt to changing environments. Studies have also shown that the ECN is critical for normal cognitive functioning and can be disrupted in psychiatric illness (e.g., Doucet & Frangou, 2021; Zhang et al., 2011).

The sensorimotor network (SMN) is also a key component of the brain's connectome and is responsible for processing and integrating sensory information from the environment as well as generating motor commands. The SMN is hierarchically organized, distributed over multiple regions, and is highly adaptable with the ability to reorganize and rewire in response to injury or to changes in the environment (e.g., Hegarty et al., 2020). DTI studies on the brain connectome in humans have revealed that the motor cortex (M1) is highly connected to other regions involved in motor control, including the primary motor area, SMA, cerebellum, and the basal ganglia.

The primary motor area (M1) is a key region in the study of the brain connectome, as it is responsible for generating and controlling voluntary movements and action. It is also highly interconnected with other regions playing a critical role in sensorimotor integration and control integration (Battaglia-Mayer & Caminiti, 2019). In a study examining the role of the motor cortex in stroke patients, the researchers found that after stroke, the motor cortex undergoes extensive reorganization, with new connections forming between the motor cortex and other regions of the brain (Hallett, 2001). This reorganization may play a critical role in recovery of motor function after stroke. Using fMRI to examine motor cortex activity during movement execution and observation, it was found that the same regions of the motor cortex were active during both tasks, suggesting that this region may be involved in both action execution and action observation. Overall, the primary motor area plays a critical role in the brain connectome, serving as a hub for sensorimotor integration and control.

The brain undergoes significant structural and functional changes during development, including the formation and pruning of neural connections, the myelination of white matter tracts, and the specialization of different brain regions for specific functions (Bassett et al., 2011; Bennett et al., 2018). One approach to studying the developmental processes of the brain connectome is through longitudinal studies, which follow individuals from infancy to adulthood and track changes in brain structure and function over time. These studies can reveal how different brain regions become functionally connected and how the size and strength of these connections change over time (Jolles et al., 2016). They can also help identify critical periods of development when the brain is particularly susceptible to environmental influences and when disruptions to normal development may have lasting effects on brain function and behavior.

The brain's connectome continually rewires throughout the life of an organism, with different patterns of connectivity emerging at different stages of development. Aging is known to have significant effects on the brain connectome. As people age, they experience changes in brain structure and function, including the loss of neurons and synapses, as well as changes in the connectivity between different brain regions (Bookheimer et al., 2019). One of the most consistent findings in research on aging and the brain connectome is a decline in white matter integrity, leading to disruptions in communication between brain regions. Studies have shown that older adults have decreased white matter integrity, which is associated with declines in cognitive function and increased risk of neurodegenerative diseases (e.g., Petkovski, Ritter & Jirsa, 2023). Additionally, aging is associated with changes in the functional connectivity of the brain. For example, older adults have been found to have decreased connectivity within certain brain networks, such as the default mode network, which is involved in self-referential processing and memory. However, they also have increased connectivity between certain regions, such as those involved in attention and cognitive control. Overall, aging has complex effects on the brain connectome, but the decline in white matter integrity and changes in functional connectivity are thought to play important roles in age-related declines in cognitive function and the development of neurodegenerative diseases.

Environmental influences can also impact on the brain connectome, particularly during critical periods of development. For example, exposure to stress, trauma, or toxins during early childhood can lead to changes in brain structure and function, including alterations in the brain connectome. Studies have shown that children who experience early adversity, such as neglect or abuse, have altered white matter connectivity in regions involved in emotion regulation and cognitive control (Herzberg & Gunnard, 2020). Similarly, exposure to toxins such as lead or alcohol during early development can lead to changes in white matter integrity and functional connectivity. Environmental factors can also have positive effects on the brain connectome. For example, physical exercise has been found to increase white matter integrity and functional connectivity in regions involved in cognitive control and memory. Cognitive training and learning new skills have also been found to increase connectivity within certain brain networks.

In this special issue on the brain connectome and cognitive function, we re-examine some of the papers submitted to the journal within these past three years. We also include more recent submissions addressing aspects of cognitive function that are now discussed when considering connectivity patterns between the functional networks in the brain. Among others, for example, procrastination refers to the tendency to delay or postpone tasks, often leading to negative outcomes and reduced productivity. Research has shown that procrastination is coupled with reduced connectivity between the prefrontal cortex and regions related to reward processing, emotion regulation, and memory. For example, the paper by Chen and Feng (2022) showed that individuals who chronically procrastinate have differences in the strength and efficiency of connections within their brain connectome compared to non-procrastinators. These differences can manifest in weakening cognitive control, inhibitory processes, and self-awareness. See also earlier contributions from Wang, Zhang, and Feng (2021).

Equally, mindfulness training has been shown to have an impact on the brain connectome, specifically in terms of strengthening connections between different regions of the brain. In a study with older subjects, Sevinc et al. (2021), found that mindfulness training led to strengthened connectivity between the hippocampus and posteromedial cortex. Improved connectivity between networks is thought to enhance cognitive functioning and emotional regulation. Mindfulness training also impacts positively on the connectivity between the DMN, involved in self-referential thinking and wandering, and the ECN, involved in attentional control and cognitive flexibility. Here, Kim et al. (2023) looked at trait mindfulness and functional connection patterns.

Environmental factors of a social nature appear to also play a role in shaping the connectome. Research has shown that socio-economic status (SES) and education can affect the network of connections between different regions of the brain. One study found that individuals from lower SES backgrounds had weaker connections in brain regions involved in language processing, memory, and executive function, compared to those from higher SES backgrounds (Ursache & Noble, 2016). Similarly, individuals with higher levels of education had stronger connections between brain regions involved in attention and cognitive control, compared to those with lower levels of education. It is important to note that these findings do not imply that individuals from lower SES backgrounds or with lower levels of education have inherently weaker or less capable brains. Rather, these differences may be due to a variety of factors, such as differences in environmental factors, access to resources, and opportunities for cognitive stimulation and development. Also, creativity and its underlying neural mechanisms reflect the changing nature of the functional connections throughout the lifespan, as shown by Kruse et al. (2023).

Multiple sources of evidence have substantiated models of abnormal neural connectivity in autism spectrum disorder, revealing differences in the brain connectivity of individuals with autism compared to typically developing individuals. Such investigations have led to characterization of autism as a distributed neural systems disorder with widespread cortical underconnectivity, particularly in regions involved in social communication and language processing, and in the DMN, and differences in the connectivity between the amygdala and the prefrontal cortex (see Di Martino et al., 2017). Also, local overconnectivity and mixed results suggest disrupted brain connectivity as a potential neural signature of autism. However, more research is needed to fully understand the relationship between brain connectivity and autism.

Physical exercise and training have also been shown to impact on the connectome, with numerous studies demonstrating changes in brain structure, function, and connectivity in response to exercise. For example, exercise has been shown to increase gray matter volume in several brain regions, including the hippocampus, prefrontal cortex, and motor cortex. It can also increase white matter integrity, suggesting that exercise may facilitate the growth of new neural connections. Functional changes have also been observed following exercise in the form of increased activity and connectivity in several brain regions, including the prefrontal cortex and hippocampus. Exercise may also enhance brain plasticity, allowing the brain to adapt and change in response to new experiences. The study by Chen et al. (2023) on skilled baseball batters, add new evidence of topological reorganization in brain networks associated with sensorimotor experience in sports. Physical exercise and training thus exert profound effects on the brain connectome, leading to structural, functional, and connectivity changes that may improve cognitive function and overall brain health (Foster, 2015; Dhamala, 2021).

An interesting notion that has emerged from studies on social interaction and communication between people is that of an interbrain connectome. In other words, there is a complex network of connections not just within an individual's brain, but also between the brains of different individuals. The interbrain connectome includes brain regions involved in social cognition, such as the prefrontal cortex, the amygdala, and the insula. These regions are thought to be involved in processes such as empathy, theory of mind, and emotional regulation. The strength and patterns of connections within the interbrain connectome can vary depending on factors such as social context, relationship type, and individual differences in social skills. For example, studies have shown that the interbrain connectome between romantic partners is different from that between strangers, and that individuals with higher levels of social skills have stronger and more synchronized interbrain connectivity during social interactions. In this perspective, see the study by Sun et al. (2021) looking at cooperation with partners differing in social experience, using fNIRS-based hyperscanning methods. Overall, the notion of an interbrain connectome highlights the importance of social interactions and relationships in shaping brain function and development.

The relationship between functional and structural connectivity with cognitive scores was recently examined in a study integrating neuroimaging, connectomics and machine learning approaches. The authors found that functional connectivity is more predictive of cognitive scores, that integrating the two modalities did not enhance explained variance, and that gray matter parcellation can impact on the quality of cognitive prediction (Dhamala, 2021). White matter pathways and neural coactivation patterns in the brain produce complex cognitive functions.

Studies on the brain connectome have changed our perspective on brain and cognitive function by revealing that the brain is not simply a collection of discrete regions performing specific functions in isolation, but rather a highly interconnected and dynamic network of neural circuits that work together to support a wide range of cognitive processes. This understanding has led to a shift away from the traditional localizationist view of brain function and towards a more distributed, network-based perspective, which emphasizes the importance of connections between brain regions in shaping behavior and cognition. Additionally, research on the brain connectome has highlighted the importance of individual differences in brain connectivity and how they relate to cognitive abilities and disorders, suggesting new avenues for personalized approaches to diagnosis and treatment.

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Victor Frak
Département des sciences de l'activité physique, UQAM, Canada
Henri Cohen
Département de psychologie, UQAM and Paris Descartes, Canada