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Review

Mechanisms of Connectome Development

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At the centenary of D'Arcy Thompson's seminal work 'On Growth and Form', pioneering the description of principles of morphological changes during development and evolution, recent experimental advances allow us to study change in anatomical brain networks. Here, we outline potential principles for connectome development. We will describe recent results on how spatial and temporal factors shape connectome development in health and disease. Understanding the developmental origins of brain diseases in individuals will be crucial for deciding on personalized treatment options. We argue that longitudinal studies, experimentally derived parameters for connection formation, and biologically realistic computational models are needed to better understand the link between brain network development, network structure, and network function.

Trends

Recent results on the development of structural connectomes allow us to evaluate how different factors shape the topological and spatial organization observed at the adult stage.

Temporal factors, in terms of the birth time of neurons and their formation of connections, as well as spatial factors, in terms of the distance between neurons, influence the extent of bidirectional or long-distance connections, network modules, and network hubs.

Observing connectome development at different stages and through computational models at the neuronal and fiber tract level can uncover the origins of healthy and pathological brain network development.

The Developing Connectome

Human brain development is characterized by a protracted trajectory that extends into adulthood [1–3]. Cognitive abilities improve but, in some cases, developmental brain diseases also arise over time. We are starting to observe how changes in cognition and behavior are linked to changes in the network organization of the brain in health and disease. However, which underlying factors lead to these changes? Based on experimental observations and computational modelling, we describe some potential mechanisms that shape connectome development.

Observing the development of a connectome poses many challenges as it cannot be observed directly. While one may look at the growth of an individual axon under the microscope, the growth of all cells cannot be observed simultaneously. Our views of connectomes are only snapshots at different stages of development and, except for the Developing Connectome project in humans[i] [4], usually only involve the adult stage. In addition, observing the growth of axons is an invasive procedure that either involves *ex vivo* cell cultures of neurons or resected brain tissue. Despite these limitations, there are several types of evidence that might elucidate how neuronal networks originated during development even though we cannot directly observe what happened [5,6]. In this review, we will focus on recent results on the role of space and time in shaping brain connectivity. That is, we will observe factors that are neither internal (genetic) nor external (environmental) but that are given by basic considerations of the formation of neural systems.

The indications that we use for understanding developmental factors are temporal and spatial [7]. Time courses of development concern the formation of synapses (synaptogenesis) and of neurons (birth time and cell lineage). Spatial factors include the direction of axon growth, the distance between neurons, and physical interaction between axonal growth cones and the environment (Figure 1, Key Figure). Note that the growth of dendritic trees and axonal branching will not be covered here but are described in detail in another review [8] and in [9–11]. Spatial

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Key Figure

Overview

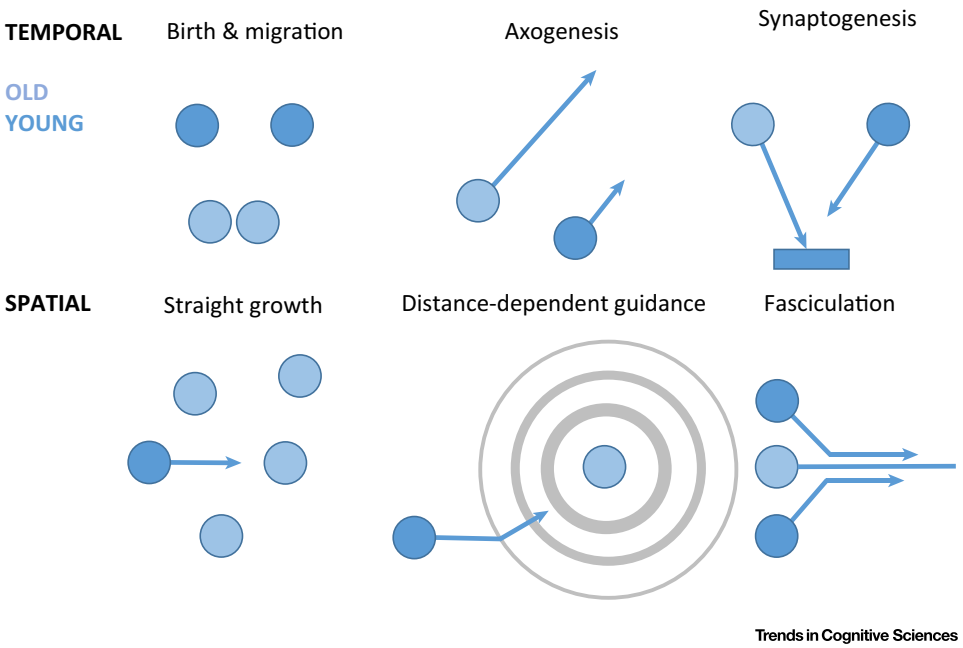

Figure 1. Schematic overview of mechanisms relating to time and space. The temporal sequence of events, such as the birth time of neurons, the time after which axon growth starts, and competition for space on the target neuron at the time of synapse formation can influence network features. Concerning the development in three-dimensional space, growth in a straight line, the local concentration of growth factors at the axonal growth cone, and axon growth along previously established fibers (fasciculation) can also shape network topology.

and temporal factors influence the formation of connections between pairs of neurons and the degree of bidirectional connections between neurons or populations of neurons. However, these factors also influence the spatial and topological organization of the whole network. Features that are crucial at the network level are the formation of long-distance connections, of imbalanced connections, of modules, and of highly connected nodes or hubs and rich-clubs (Box 1). An overview of mechanisms that lead to these network features is provided in Box 2.

Formation of Long-Distance Connections

Axons tend to grow in a straight line [12] while extensions of the axonal growth cone, filopodia, search the space in front of the growth cone for potential neurons with which to connect. The direction of axon growth might change due to physical obstacles (neurons or other tissue) and adhesion [13]. It might also change due to chemical factors, molecules that either attract or repulse the growth cone [14]. On average, axons tend to connect to nearby targets with the probability that two neurons are connected exponentially decreasing with the distance between them [14]. Such an exponential decay of the axon length probability can be observed both at the local level of axonal connectivity between pyramidal cells within rat layers II and III of the primary visual area [15,16] (cf. Figure 2A) as well as at the global level of structural and functional connectivity between brain regions [17–20]. But why is growing in a straight line the preferred mode of forming axons and how does this influence how long axons grow before establishing a synapse?

Box 1. Network Properties

Brain networks, ranging from neuronal networks between neurons or fiber tracts between brain regions, show distinct spatial and topological characteristics (Figure I). While most fiber tracts only reach adjacent or nearby regions along the cortical surface [101], some connections are long-distance. However, more than 95% of excitatory connections within a brain region still originate from the same region [101]. This preference for nearby targets is also true for axons within a region where only few connections are longer than 1 mm [16]. Despite the low number of long-distance connections, these links are important short-cuts that help to lower the characteristic path length [51] (the average number of connections to cross to go from one node to any other node in the network).

Also, most connections are imbalanced with a stronger connection in one direction and a weaker or absent connection in the opposite direction. For fiber tracts between cortical regions in the macaque, 15% of connections are unidirectional [62]. Such asymmetric connectivity was also seen at the level of links between neurons in the fruit fly [102].

Moving towards groups of network nodes, a modular architecture emerges where nodes within a module are well connected whereas there are fewer connections between modules [37,103]. This organization can be described through the modularity Q where larger values represent a more modular organization [104]. The limited amount of connections between modules thereby prevents interference between different processing streams [105–110]. Within the visual cortex, for example, there are two submodules corresponding to the ventral and dorsal pathway [111]. Recently, a modular organization with potential functional specialization has also been found within brain regions using high-resolution human structural connectivity, strongly suggesting that specialized motor tasks, e.g., arm versus leg movement, also have a structural modular correlate [112].

Nodes that are connected to more other nodes than would be expected are called highly-connected nodes or hubs. Hubs can have stronger connections to other hubs than would be expected. Such a 'rich-club' organization [113], with many links between hub nodes, facilitates synchronization and information integration at the global level in neural systems [114–117]. Consequently, removal of these nodes has a relatively severe effect on behavioral performance, consistent with their involvement in many brain diseases, including Alzheimer's disease [118] and schizophrenia [119].

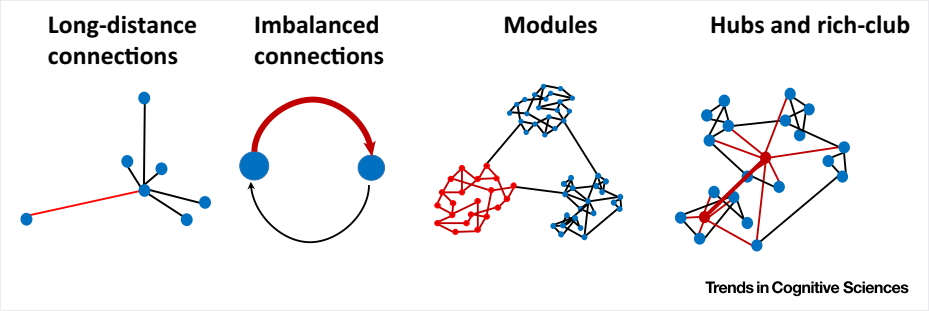

Figure I. Spatial and Topological Features of Brain Networks.

There are (at least) two factors that influence how long it takes an axon to reach another neuron. The first factor is the neuronal density, as a higher number of neurons per volume make it more likely to hit a potential target neuron. Say that for each volume element (e.g., 1 μm^3) there is a probability p that the space contains a neuron and a probability $q = 1 - p$ that the space is empty. Hitting another neuron three volume elements away from the starting point given a (certain) direction means two times passing through empty volume elements and one time (the last growth step) entering a volume element that contains a neuron (Figure 2B): the probability to hit another neuron after n steps or passed volume elements is $P(X = n) = q^{n-1} * p$. The exponential decay of the probability to encounter another neuron as a function of distance between two neurons (or n steps) means that it is more likely to hit a nearby neuron than hitting a neuron that is far away after failing to encounter many nearby neurons. Imagine going through a crowded room in a straight line. You are more likely to bump into someone early on than only passing through an empty space and reaching a person who is farther away. Therefore, basic considerations for axon growth can already account for the observed exponential decay of connection probability with distance [18].

Box 2. Developmental Mechanisms

Accelerated network growth: see nonlinear growth.

Dispersion: a measure whether fibers from one region target many other regions or only few distant other regions. Fasciculation reduces the spreading of fibers and leads to lower dispersion.

Nonlinear growth: the number of nodes that is added at each step is changing over time. Exponential growth where the number of new nodes increases over time can lead to hub and rich-club organization.

Old-gets-richer: nodes that are established early on can receive connections from all later forming nodes leading to a higher ratio of incoming connections and a higher total number of connections. Nodes that are formed late will receive fewer incoming connections as most nodes have already matured leading to a lower overall number of connections.

Parallel growth: extreme case where all nodes start to form connections at the same time. This leads to more bidirectional connections and fewer long-distance connections.

Scale: here, scale is described in terms of the spatial extent of the nervous system. At early stages of development, neurons are nearby enabling easier formation of connections. At later stages, after the nervous system has expanded, neurons will be further apart with early-formed (short) connections transforming into long-distance connections at the adult stage.

Serial growth: extreme case where nodes form connections one after another (i.e., the next node in the sequence only starts axon growth after the previous node has finished axon growth). This leads to fewer bidirectional connections, more long-distance connections, and nodes that establish connections early on more likely becoming network hubs.

Time windows: nodes that are formed at the same time often come from the same cell linage, are spatially nearby, and inherit the same start and end points for axon and synapse formation. Due to spatial proximity and overlapping times for connection formation, nodes with the same time window form topological modules.

The second factor that influences axon length is the degree of curvature during axon growth. Curvature can range from the extremes of a straight line (without being curved) to a random walk where the axon can arbitrarily change direction at each step (Figure 2C). Interestingly, often changing the direction of axon growth does not increase the chances to reach another neuron. For straight growth, each move of the growth cone enters a space that has not been explored before. For a change in direction, as part of the next step, the growth cone is partially moving into space that has already been explored. The resulting curved axon is both using more time and a longer axon length before reaching another cell. An exemplary simulation of axon growth shows that the average length of an axon between two neurons, directly corresponding to the time it takes to establish that connection, is twice as high compared to straight growth if the growth cone is allowed to change direction up to $\pm 40^{\circ}$ at each step (Figure 2D). Growing axons along a straight trajectory is beneficial in terms of wiring length but also for forming functioning circuits: for example, active turning towards an attractor line is needed to get the correct connectivity in the developing tadpole spinal cord [21].

While axons normally grow in a straight line, their target neurons might often be off-course leading to the need to change the growth trajectory. Causes for changing direction could be physical obstacles that either block the path or lead to adhesion of the axon. Alternatively, concentration gradients can lead an axon towards a target. In this way, axonal growth cones detect the concentration of a molecule and follow a gradient of increasing concentration towards the source of that molecule [22]. However, the concentration of a molecule decays exponentially with the square of the distance between source and growth cone. Given the diffusion constant *in vivo* [23], the estimated maximum distance across which a growth cone can detect molecules emitted from a target neuron is 1 cm [24].

How can fibers be guided to the correct off-course target if the target is more than a cm away? Many fiber tracts between brain regions in humans are longer than 10 cm, not to

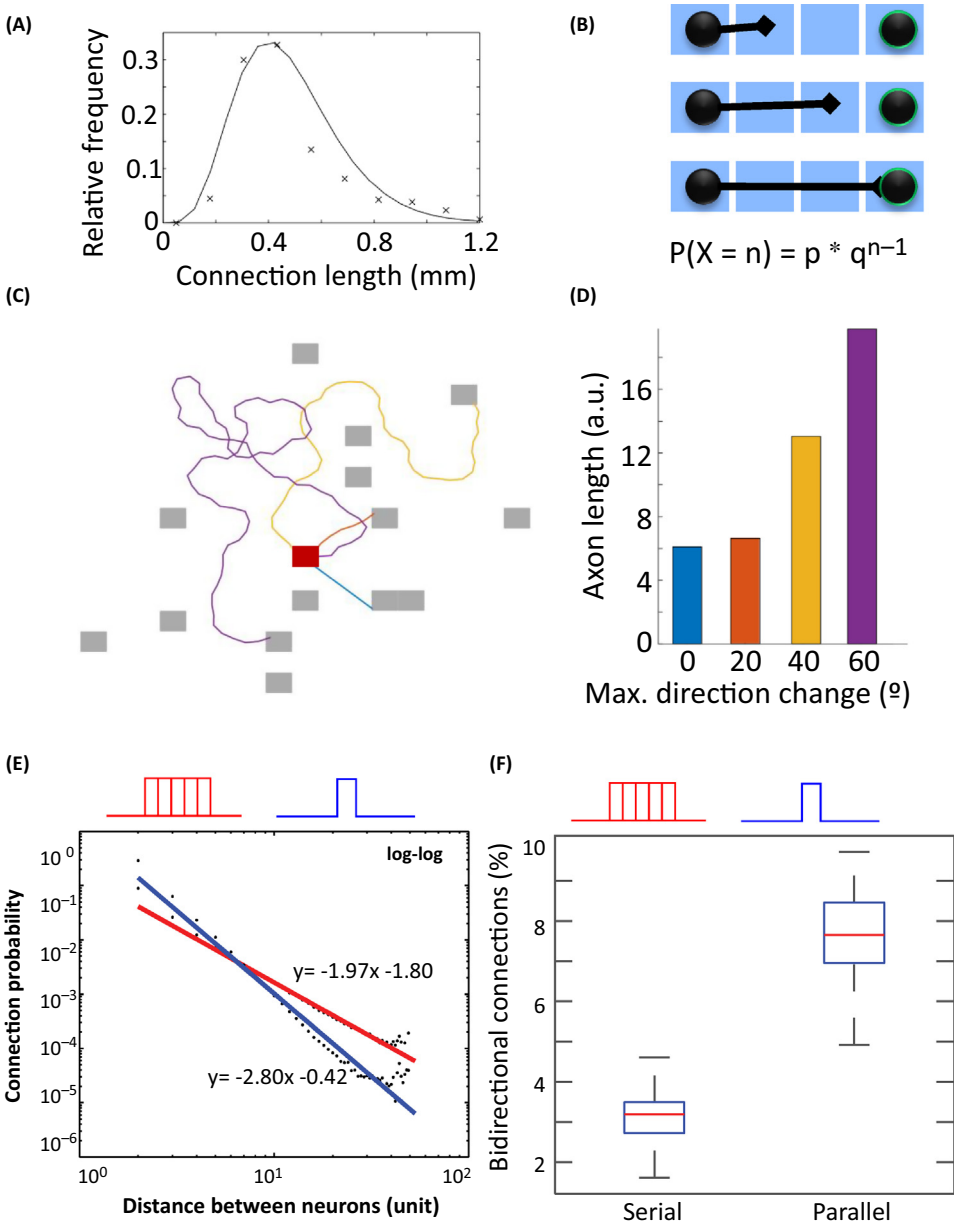

Figure 2. Formation of Long-Distance and Imbalanced Connections. (A) Like the distribution of fiber tract lengths [18,19], most axons within layers 2/3 of the rat primary visual cortex connect nearby neurons and only few go over a longer distance [16,18] (adapted from [19]). (B) This exponential decay with distance can be explained in that the probability to reach another neuron after n steps is the probability to not reach a neuron for $n-1$ steps (q^{n-1}) times the probability to reach a neuron in the final step (p). (C) Often changing direction during axon growth, comparable to a random walk, leads to the growth cone visiting spatial regions that have already been investigated before. (D) This leads, on average, to longer lengths of formed axons. (E) Connection length distribution for simulated sequential (red) and parallel (blue) network growth of 1,400 neurons distributed in three-dimensional space. (F) Boxplot of the percentages of reciprocal connections for serial and parallel growth. Plots E, F adapted from [32]. Abbreviation: a.u., arbitrary units.

mention axons through the spinal cord that can be longer than 1 m. There are two related strategies: axons can follow pathways that were established earlier by pioneer neurons or neurons can connect at an early stage of development when the total size (scale) of a neural system is small.

Fasciculation

Fasciculation is the mechanism where a small number of pioneer neurons form pathways that guide the axons of the following neurons, resulting in a bundle of axon fibers. This might also be the case for the nematode *Caenorhabditis elegans* [25] (Richard M. Durbin, PhD thesis, University of Cambridge, 1987), where some neurons in the ventral cord are formed early on [26], providing a pathway between anterior and posterior parts of the worm. Also, as observed for *Drosophila* [27], neurons of the same clonal lineage often project to other regions through bundled fibers along the same trajectory. A computational model of fasciculation showed that directed random growth along a gradient, with attachment between adjacent fibers, can reproduce observed fiber tract patterns in the olfactory bulb [28].

The reliance on pioneer fibers might prevent more diverse connectivity to other areas located afar. Fasciculation reduces the amount of guidance that is needed during development as only the pioneer fibers need to be guided to the correct location whereas later fibers attach to the existing tract through adhesion and follow it towards the target region.

Scaling

The alternative to fasciculation, and a potential mechanism for the growth of pioneer fibers, is to form connections early on when the brain size is at a smaller scale and potential target neurons are nearby. Studies in *C. elegans* have shown that 70% of long-distance connections exist between pairs of neurons that are both born early before hatching [26]. At this early time, the body size is less than 20% of the adult size, which means that the maximum distance between any two neurons is less than 0.2 mm. This makes axon guidance, as indicated by the increased expression of guidance molecules such as Netrin and Nerfin-1 around this time, feasible.

Based on the maximum gradient distance of 1 cm that axonal growth cones can pick up, scaling (establishing connections while distances are small) will be the preferred mechanism during early connection formation, especially for forming pioneer fibers, while fasciculation (following existing pioneer fibers) will be the main mechanism at later stages of development when source and projection target are further away.

Following axon growth, the resulting position of axons and their overlap with the position of dendrites is often sufficient to explain the pattern of synaptic wiring [21]. The frequency with which nearby axons and dendrites form a synaptic connection, the filling fraction [29], ranges from 50% in the tadpole spinal cord [21] to 12% in macaque visual area V1 [29].

Formation of Imbalanced Connections

Time Windows

The relative difference in birth time between a pair of neurons, independent of whether both neurons are born early or late, can influence connectivity. Two neurons that arise at the same time, through cell division of a common progenitor cell, have several shared features: their genetic mark-up, a nearby spatial location, and a relatively nearby starting time for axo- and synaptogenesis. Pyramidal cells that are part of the same cell lineage are more often connected than cells with a different developmental history [30]. Even if two cells have different direct ancestors, being born at the same time still means that the formation of connections occurs concurrently unless one of the cells is involved in a cell migration process. For pairs of connected neurons in *C. elegans*, most are born within 50 minutes of each other while hatching takes place around 840 minutes [26].

Serial and Parallel Growth

Given the role of timing [31], we can study the extreme cases of network development to investigate the effects of birth times, developmental time windows and competition between

neurons [18] (Figure 2E,F), where all nodes are either starting to form connections at the same time (parallel case: overlapping time windows, blue) or where they form connections sequentially, one node after another (serial growth case: nonoverlapping time windows, red) [32]. Sequential growth leads to a higher proportion of long-distance connections (Figure 2E): as all previously established neurons have finished the connection formation, fewer 'docking spaces' [18] at target neurons are available so that axonal growth cones need to travel further to find a target neuron with free space on the soma or dendritic tree. On the other hand, for parallel growth where connection formation is on-going for most neurons, many free places are still available, leading to shorter axon lengths for established connections. This easier connection formation during parallel growth results in more bidirectional connections between pairs of neurons due to overlapping developmental time windows (Figure 2F).

In conclusion, this suggests that neurons that are born at the same time are more likely to form bidirectional links while unidirectional connections are more likely between neurons born at different times. This organization was indeed confirmed for the connectome of *C. elegans* [32].

Formation of Modules

Multiple Time Windows for Connection Establishment

Similar time windows are due to a comparable cell lineage from common progenitor cells or common formation times of brain regions. As neurons or brain regions arise during division of earlier neurons or regions, they also tend to be spatially nearby. We can therefore think of spatial clusters of nodes with similar time windows (Figure 3A). If two nodes with the same time window for sending and receiving connections are more likely to connect to each other, a network where each node can have one out of three time windows (Figure 3B) results in a network with three network modules (Figure 3C). The size of a module is determined by the width of the time window while the amount of connections between modules is determined by the overlap of the time windows [33,34]. While the number of modules in general corresponds to the number of unique time windows, a large number of time windows leads to a larger overlap between time windows. For this case, connections between modules become so frequent that modules start to merge and the number of detected modules becomes lower than the number of time windows [34].

The role of time windows for module formation has been experimentally observed in *Drosophila* [35]: neurons linking to other neurons in the same module are born around the same time with an early time window corresponding to the locomotor, an intermediate time window corresponding to the visual and olfactory, and a late time window corresponding to the auditory module.

An alternative model for the formation of modules includes neural activity where the system is optimized to reduce wiring length and increase performance, resulting in a number of modules that corresponds to the number of optimized tasks [36]. However, such a mechanism would operate on an already formed network and might not be needed if modules have already been established through the time window mechanism discussed above.

Dispersion: Assessing Connectivity between Regions

A measure to assess the degree to which a node connects to nodes that belong to another group of nodes, nodes in a different region, or nodes in a different module is dispersion. Dispersion does not simply measure the relative number of connections that link to other modules (the measure for this would be the participation coefficient [37]), but to what proportion of other modules the node is connected. If there is a high degree of targeted wiring, nodes within one region of the network should connect to few other regions. That means, instead of randomly following a direction, they should follow existing fibers that lead to an already

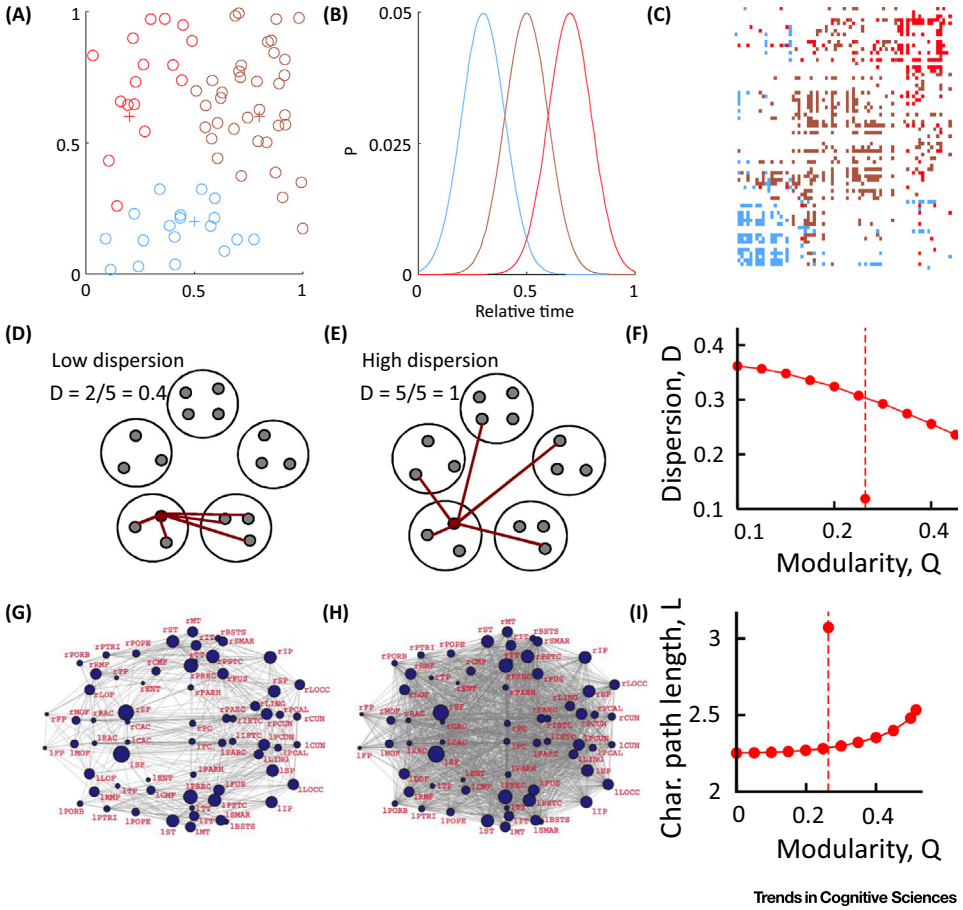

Figure 3. Formation of Modules. (A) Spatial arrangement during development: node time windows are represented by colors, and the two-dimensional positions of initial seed nodes (+) and later developing nodes (o) are shown. The axes show the horizontal (x-axis) and vertical (y-axis) position. (B) Temporal dependence of projection establishment depending on node domain. Relative time on the x-axis was normalized such that '0' stands for the beginning of development and '1' for the end of network growth, while the y-axis represents the probability of establishing a connection at that time. The color represents the time window corresponding to one of the three seed nodes. (C) Clustered adjacency matrix with different time window populations showing three topological modules [33,34] (A–C adapted from [33]). The dispersion *D* of a network measures to how many different regions a node is on average connected to: note that with the same node degree (number of connections), a node could either have low (D) or high (E) dispersion. (F) The dispersion D of human connectivity (data point on the vertical line) is much lower than those of the benchmark networks with the same or different modularity *Q*. The network of modules is shown for (G) human structural connectivity (brain areas; horizontal plane) and for (H) benchmark network with similar modularity *Q*. Each node is a region of the network whose size is proportional to the square root of the number of nodes within. Locations are given by the centers of mass of a region's constituent ROIs. (I) Characteristic path length *L* of human connectivity across 998 ROIs (data point on the dashed vertical line) is much higher than those of the benchmark networks (Plots D–I adapted from [38]).

connected region. For the human connectome, individual nodes could be regions of interest (ROIs) and regions could be cortical or subcortical areas. We then define dispersion as the fraction of regions (brain areas) with which a node (ROI) is connected [21]: the dispersion is low if an ROI is only connected to ROIs within fewer regions (Figure 3D); the dispersion is 1 if the ROI is connected to other ROIs within its own region as well as with ROIs in all other regions (Figure 3E). For human structural connectivity in healthy subjects with 998 ROIs (nodes) and 66 brain areas (regions), the dispersion is 0.12 which means that an ROI within a brain area is, on average, only connected to 12% of all brain areas (i.e., itself and seven other areas). For a rewired network that retains the overall modularity *Q*, the dispersion is much higher, around 30% (Figure 3F) [38]. When we compare the original layout of fiber tracts (Figure 3G)

with the one following rewiring (Figure 3H), the higher dispersion becomes visible as a more diffuse pattern of connections. Each plotted region corresponds to, on average, 10 ROIs. If several ROIs project to another region, a line between both ROIs is plotted. Following rewiring, fewer ROIs project to the same region and thus more lines are visible. The reduced dispersion of connections in the original network of 998 ROIs also influences global efficiency: compared to rewired networks with the same or altered modularity *Q*, the characteristic path length is increased (Figure 3I). This separation in the network could help to reduce interference between different processing pathways and different sensory modalities [38].

Given the relationship between dispersion and other network properties that change in schizophrenia [39], autism [40] or epilepsy [41], a reduced coherence of fiber tracts might be an important component in the path towards developmental diseases. Moreover, the dispersion might be related to changes in diffusion weighted imaging, since a more distributed pattern of connectivity would break apart the fascicular pattern of fiber tracts. Therefore, we would expect that higher values of dispersion will be associated with lower values of fractional anisotropy (FA) and with a shift towards networks with lower characteristic path length. For neural disorders, for example, lowered FA was reported for partial intractable epilepsy [42], autism spectrum disorders [43], and schizophrenia [44,45]. Note, however, that lower FA might not only result from more diffuse fiber tracts within a voxel but also from reduced myelination [46,47].

Formation of Hubs and Rich-Clubs

Previous studies have shown that functional connectivity of the human brain, looking at signal correlations between voxels in fMRI, are scale-free [48]. However, at the gross level of signal correlations between brain regions, it was argued that these functional networks are not scale-free [49]. When comparing structural connectivity between cat and macaque brain regions with random, scale-free [50], and small-world [51] networks, only for scale-free networks was the effect of removing nodes or connections similar to that of brain networks [33]. In addition, as for scale-free networks, brain networks contain highly-connected nodes that are unlikely to occur in randomly connected networks [33]. These hubs might be the underlying reason for robustness toward random lesions [49,52–54]. Changes that target hub nodes, on the other hand, have more severe consequences and are a feature of developmental alterations, for example, in schizophrenia [55,56], preterm birth [57,58], and, to some extent, in autism and attention-deficit/hyperactivity disorder (ADHD) [59].

Old-Gets-Richer

If neuronal networks show more highly-connected nodes than for random benchmark networks, how could such hubs arise? There are several potential developmental mechanisms that would yield brain networks with highly connected nodes. Work in brain evolution suggests that when new functional structures are formed by specialization of phylogenetically older parts, the new structures largely inherit the connectivity pattern of the parent structure [60]. Such inheritance of connectivity by copying modules can lead to scale-free networks [61]. A developmental mechanism for varying the node degree of regions could be the width of the developmental time window for synaptogenesis at different regions [33,34]. We observed these developmental hypotheses using data of fiber tracts between brain regions in the macaque, based on tract tracing following injected dyes (cf. [62] and CoCoMac database [63,64]), and data of axonal connections between neurons in *C. elegans* (Figure 4A). For *C. elegans,* neurons that are generated early during development tend to accumulate more connections and tend to be hubs of the adult network [26]: all hub neurons are born before hatching. For the macaque brain, regions of the archi- and paleo-cortex that mature earlier during brain development receive more incoming fiber tracts from younger brain regions of the neocortex [65]. This effect, even though to a smaller extent, is still visible between the early

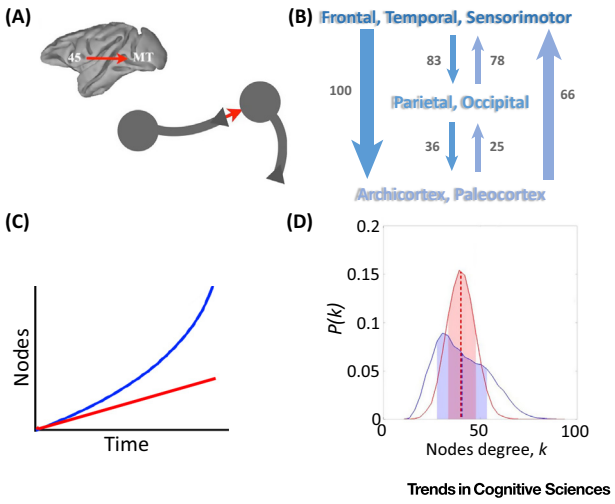

Figure 4. Formation of Hubs. (A) Highly-connected nodes can be observed at the level of fiber tracts between brain regions (here: macaque) and the level of individual neurons (*C. elegans* network). (B) For the macaque, fiber tracts follow the 'old-gets-richer' model where regions that are ontogenetically (and phylogenetically) older (archi- and paleocortex) receive more incoming connections from younger nodes (neocortex) whereas younger nodes receive fewer incoming connections from older nodes (based on [65]). (C) Another mechanism for hub formation is nonlinear (accelerated) growth (blue) which, compared to linear growth (red), leads to a wider degree distribution (D) with more highly-connected nodes but also more nodes with few connections (see higher variability for blue degree distribution [67]) (Plots A and D based on [67]).

developing parietal and occipital lobes compared to the later developing regions of the neocortex (Figure 4B). It means that old nodes can receive incoming connections from all later nodes leading to a higher overall degree. Younger nodes, on the other hand, receive fewer incoming connections from existing nodes as these finish connection establishment earlier, leading to a lower overall degree and a lower proportion of incoming connections.

In addition to this old-gets-richer mechanism for establishing hub nodes, several mechanisms have been proposed that include preferential changes establishing or removing connections. In a rich-gets-richer model of preferential attachment, new nodes are preferentially attaching to existing nodes that already have many connections [50] resulting in the early nodes becoming network hubs. Alternatively, in a poor-gets-poorer model of preferential depletion, connections are sequentially removed from a completely connected network where nodes with fewer connections have a higher chance of another connection being removed from them [66]. While these models generate hubs and also a scale-free degree distribution [50], as found for voxel-level functional connectivity in fMRI [48], they have a crucial disadvantage in terms of biological plausibility: nodes, even though being spatially far away from another node, would need to know how many connections that node has before starting to form a connection.

Accelerating Network Growth

A more realistic model was recently proposed by looking at the effect of accelerating growth [67]. In biological systems, the number of new nodes that are added to a network at each time interval increases exponentially over time (blue curve) rather than only adding the same number of nodes at each step (red curve) (Figure 4C). For bacterial cells, the number of cells per unit volume (c) in the growth phase can be described by an exponential function: $c(n) = c_0 \cdot 2^n$, where c_0 is the initial unit volume of the culture, and n is the number of divisions a cell has undergone [68]. For brain evolution, it was proposed that new neural structures form by separation of already existing areas [69], with the number of brain areas then increasing exponentially. In a similar way, one would expect an exponential growth during the growth of the brain and its parcellation into areas during ontogenetic development.

Such nonlinear growth leads to a wider degree distribution including more highly-connected nodes or hubs as well as more nodes with few connections (blue distribution), compared to

linear growth where the same number of nodes is added at each step (red distribution, Figure 4D). In addition, nonlinear growth resulted in the emergence of rich-club connectivity, i.e., denser than expected connectivity between network hubs [67]. Moreover, the relatively denser rich-club structural connectome architecture in preterm babies [58], despite an overall decrease of white matter resources, could be reproduced by a nonlinear growth model in weighted networks where connections that are established early on have a higher weight [67].

Case Study: Developmental Changes in Schizophrenia

Healthy brains undergo changes in network organization during early childhood and the teenage years, a process that starts earlier for girls than for boys [70]. Moreover, onset times of developmental diseases, ranging from autism spectrum disorders and anxiety disorders to schizophrenia and bipolar depression, range from the first year after birth to (early) adulthood. Indeed, delays in connectome maturation were recently linked to psychiatric diseases [71]. How does timing influence different subtypes of a developmental disease such as schizophrenia?

Early onset schizophrenia (EOS), before the age of 18 years, is characterized by changes in structural and functional hubs and in the default mode network, and by more gray matter in the frontotemporal network [72]. At the same time, long-range callosal fibers between hemispheres are reduced and homotopic regions in both hemispheres show more divergent connectivity patterns [73]. Finally, compared to adult onset schizophrenia, EOS shows reduced local and remote hub connectivity [74].

In light of the mechanisms discussed earlier, a delay in the development of nodes within a hemisphere could explain the reduced connectivity in EOS. Slower nonlinear growth, where fewer nodes form at each step, will reduce the connectivity of network hubs and could explain the reduced connectivity in the default mode network and of structural and functional hubs. Finally, a later start of maturation could also lead to a longer duration of maturation. In that way, longer-lasting tissue growth might partially counteract the effect of pruning and lead to an increased amount of gray matter.

Concluding Remarks and Future Perspectives

Limitations

Connectivity can be studied at the micro-scale of connections between neurons or at the macro-scale of connections between brain regions [75]. We provided examples of how network features could result from developmental mechanisms at either scale. However, this does not mean that mechanisms are necessarily limited to the discussed scale and future studies will be needed to determine the domains within spatial and temporal scales of when these mechanisms apply.

The described models are observing the initial formation of connections, but neuronal networks also undergo a secondary reorganization due to the removal of connections. While functional plasticity describes the changes in synaptic weights between connected neurons, structural plasticity describes the formation or removal of a connection between neurons [76]. The basic idea goes back to Hebbian learning [77] where not only 'what fires together, wires together', but also where connections between nodes with different activity patterns are removed or weakened [78,79]. Pruning of connections during development, initially thought to occur until puberty [80], is now thought to occur well into the third decade [81]. Finally, interactions with the environment play a crucial role in fine-tuning local circuits and in encoding diverse functional tasks [82]. While plasticity is crucial in fine-tuning brain function, it is not always needed to establish basic functionality. A study in the *Xenopus* tadpoles recently showed that simple

Outstanding Questions

Can the onset time and length of a time window be increased or reduced and what are the genetic factors?

Is the sequence of developmental events fixed or are alternative orders possible?

If distance-dependent factors play a role, how much of the variability between brains of different species can be explained by different brain sizes during development?

If time-dependent factors play a role, how much of the interspecies variability can be explained by the longer brain development duration in humans?

To what extent is the modular organization of brain networks driven by structural/physical versus dynamical/activity factors?

Can the onset of psychiatric diseases be explained by changes in developmental time windows, e.g., delays of time window onset or later offset of a time window?

In addition to pharmacological options, can physical forces or neural stimulation be applied to alter brain development, moving from pathological towards healthy trajectories?

growth rules, based on chemical gradients and physical borders, are sufficient to establish swimming behavior during development [83]. Indeed, it is an open question to what extent these mechanisms could also lead to functional circuits in the cortex.

Another approach to understand the role of different factors is to use generative models. These models use single factors or combinations of factors to generate connectivity that is close to the observed connectivity in macaque and *C. elegans* [84], mouse [85], or human [86]. However, one should keep in mind that these studies are based on features of the *adult* network. The contribution of factors might be different during development as brain sizes are smaller, not all brain regions already exist, and the relative spatial position of regions or neurons prior to cortical folding or migration differs. Concerning topological factors, not all connections already exist and some early connections might disappear later during development as was found for transient projection fibers [87–89].

Future Work

Experimental challenges are determining connectivity at early stages of development and obtaining longitudinal data for the same individual [90]. Recent advances in image processing as part of the Developing Connectome Project have led to human *in utero* macroconnectome data [91] and an observation of the rich-club architecture in newborns [92]. Longitudinal studies of the development of the macroconnectome between brain regions are mostly limited to follow-up recordings 1–2 years after the initial measurement. Longer-term studies face challenges in continuous recruitment of the same subjects, in stability of scanning protocols, and in endurance of MRI scanners. More crucially, funders are reluctant to sponsor projects over 10–20 years. For the development of the microconnectome between individual neurons, data is limited to *in vitro* studies where tissue is removed from the brain. For cell cultures, recent studies of hippocampal tissue have shown the emergence of rich-club connectivity and coordinated dynamics [93].

Computational challenges for modelling human connectome development are getting the parameters for detailed simulations of biological systems and the complexity of running large-scale models. Parameters for axon growth, synapse formation, and neural activity could be determined through *in vitro* experiments of resected human tissue [94] or of human cell cultures.

While the Human Brain Project does not model brain network development [95], there are simulators for detailed growth and synapse formation along dendritic trees (NetMorph [96]), and for migration and connection formation in populations of neurons (Cx3D [97,98]). In our lab, we are developing simulators of brain tissue activity[ii] [99] and, together with CERN Openlab and academic collaborators, of brain tissue development[iii] [100].

This review presented several potential mechanisms for the formation of long-distance connections, asymmetric connections, network hubs, and network modules. Yet, there might be more undiscovered mechanisms that can influence developmental features of human structural connectivity. Understanding these mechanisms will inform us about the emergence of architectures that enable higher cognitive functions and the factors that limit these functions for neurodevelopmental diseases. We hope that this contribution will provide a framework for future studies on these mechanisms.

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Resources

[i]www.developingconnectome.org/
[ii]www.vertexsimulator.org/
[iii]https://biodynamo.web.cern.ch/
[iv]www.greenbrainproject.org/

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