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Review

Human Connectomics across the Life Span

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Connectomics has enhanced our understanding of neurocognitive development and decline by the integration of network sciences into studies across different stages of the human life span. However, these studies commonly occurred independently, missing the opportunity to test integrated models of the dynamical brain organization across the entire life span. In this review article, we survey empirical findings in life-span connectomics and propose a generative framework for computationally modeling the connectome over the human life span. This framework highlights initial findings that across the life span, the human connectome gradually shifts from an 'anatomically driven' organization to one that is more 'topological'. Finally, we consider recent advances that are promising to provide an integrative and systems perspective of human brain plasticity as well as underscore the pitfalls and challenges.

Trends

Changes of the structural connectome appear to precede those observed in functional connectomics. Charting trajectories and atlases of these changes across the life span are becoming available.

Disparities of observations across life-span studies likely reflect differences in study design and analytic approaches. Both open big-data sharing and standardized connectomics warrant successes of reconciling such differences.

Potential sources of artifact must be addressed before visions of comprehensively mapping the connectome across the life span can be realized.

Network neuroscience demonstrates the value of modeling spatial proximity and topological homophily in generative connectome models across the life span.

Neuromodulation connectome approaches hold great potential for deciphering changes in causal relations, as well as probing and altering plasticity across the life span.

A Connectome's Life Span

The **connectome** (see Glossary), commonly defined as the wiring diagram of the brain and its functional interactions in their entirety, is an invaluable tool for cognitive neuroscience to catalog the rich phenotypic variation amongst individuals and clinical populations [1–4]. Age and maturational status are the most basic and arguably robust sources of neurobiological variation in the connectome, motivating the need for life-span perspectives [5]. In this regard, **connectomics** studies have mapped the developing brain to inform models of neurodevelopment [6,7], adulthood plasticity [8], as well as the aging brain to enhance our understanding of neurocognitive decline [9,10]. The integration of **complex network analysis** into the study of each of these stages of the life span has helped to advance a systems-level understanding of organizational changes in these periods [11–14]. However, at both the levels of individual brain regions and the network as a whole, great inconsistencies on the age-related changes of the human connectome exist in the literature [13,15,16]. In part, this is attributable to the fact that these studies of distinct periods of the life span tend to occur disconnected from one another, missing the opportunity to test integrated models of brain organization across the entire life span [17]. How does the human connectome change across the life span? To answer this scientific question, we will discuss the importance of life-span human connectomics, propose a computational modeling framework for investigating changes in connectome organization over the life span by systematically surveying previous studies, and highlight the challenges and promises in mapping the life-span changes of the human connectome.

Why Life-Span Connectomics?

A number of motivations exist for mapping the human connectome and its functional interactions across the life span. First, the comprehensive characterization of development, maturation, and aging processes will allow researchers to identify similarities and differences among processes observed at different times in the life cycle. Already, a number of studies have suggested that

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development and aging bring about opposing changes in brain organization, with development characterized by increasing long-range connectivity [18] and hemispheric specialization [19], and aging characterized by opposite trends [15]. Although intriguing, such findings raise a range of questions regarding whether healthy aging is merely an 'undoing' of brain maturation processes, or a complex interaction of multiple distinct processes [e.g., a loss of integrity in the white matter (WM) architecture, decreased neuronal cell size, decreases in neuronal firing strength, reduction in key neurotransmitters such as dopamine, reductions in neuroplasticity] [20]. Related question is a range of queries about pathologic aging and the unique impacts disease processes have on the declining architecture [21], as well as the interventions aimed at slowing aging processes [22].

An arguably more complex, though an essential goal of life-span connectomics, is the mapping of neural systems underlying cognition and behavior across the life span. Numerous studies have demonstrated age-related changes in the neural correlates of cognition and behavior (e.g., intelligence quotient, working memory, anxiety) [23–25]. Any effort aiming to account for interindividual variations in these domains must take into account the developmental status of the individuals being assessed to meaningfully understand the differences observed [26]. It is important to note that the 'uniqueness' observed for an individual at any given point in his/her life cycle represents the outcome of an entire personal history of biological and environmental experiences [6].

Finally, from the perspective of attempting to achieve clinically useful applications for neuroscience, a key goal of the medical community is to create neurobiologically sound growth curves for the brain that are akin to well-established height and weight curves used to monitor physical development [27]. Such brain-based curves can be used to characterize phenomenological changes associated with the onset of varying forms of mental health and learning disorders [28], as well as to predict the developmental status (i.e., age-expected values) of an individual brain's structure [29] or function [30]. The fact that 75% of mental illnesses have their origins prior to age 24 provides a strong motivation to map brain growth in early life [31]. However, phenomena such as depression can occur throughout the life span (i.e., pediatric depression, adult depression, geriatric depression) [32]. Life-span perspectives can help reveal commonalities and differences among pathophysiologic processes that manifest similar symptom profiles at different stages in life. From a neurological perspective, brain maturation and aging curves may prove useful for identifying factors that can mitigate neurocognitive decline (e.g., cardiovascular fitness) and potentially identify optimal periods for intervention [33].

What Are the Essential Components of a Life-Span Study?

By surveying relevant studies conducted during past 10 years (2007–2016) based upon large samples ($N \geq 100$) of human brain MRI images spanning a minimum segment of 35 years of the life cycle (not limited to studies that included a measure of connectivity), we summarize key aspects of life-span studies to date in Figure 1. First and foremost, the experimental design of a study, especially the age span and sampling (i.e., cross sectional vs. longitudinal) strategy, determines its utility for life-span analyses. Most life-span studies cover a specific age interval using a cross-sectional design. This is primarily due to the time requirements of a true longitudinal design attempting to map the entire life span. Structured **multicohort designs** [34], which leverage the strengths of both cross-sectional and longitudinal designs, are emerging as practical and powerful approaches to examine life-span changes. One of the most important factors in the examination of life-span connectome changes is the choice of metrics for assessing brain organization. This issue is particularly challenging for connectomics given that the test–retest reliability, reproducibility, and validity of some of the most frequently employed connectomics measures are yet to be fully investigated and well established [35,36]. These issues are attracting increasing attention (Box 1).

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Box 1. Reliability and Validity in Connectomics

Why Is the Establishment of Test–Retest Reliability Critical?

Test–retest reliability is commonly defined as the variation in measurements taken by a single person or instrument on the same item, under the same conditions, and in the same period. The quantification of test–retest reliability is critical in the selection and optimizations of measurements because it places an upper bound on their utility in detecting both interindividual differences (e.g., for biomarker discovery) and intraindividual changes (e.g., for longitudinal examinations). For any attempt to map connectome trajectories across the life span in a way that can capture meaningful differences among individuals, the establishment of reliable indices of the connectome is a rate-limiting step.

Current Perspectives of Reliability for Human Connectomics

The reliability can be sensitive to the specific networks/connections and the factors related to scan duration, sampling rate, and analytic methodology (see [36] for a review), hindering the development of consensus standards. To address this challenge, the Consortium for Reliability and Reproducibility was launched in early 2014 [133] and provided invaluable open resources to generate rich estimates of reliability and reproducibility by including a variety of data-acquisition procedures and experimental designs.

Looking Beyond Test–Retest Reliability for Connectomics

Reliabilities across imaging scanners, protocols, preprocessing steps, and analytic strategies are rarely explored in brain connectomics. Recent initiatives such as the Brain Genomics Superstruct have demonstrated the ability to minimize variation across imaging sites [134]. However, such coordination is not always feasible and, if not accounted for, can compromise the reliability of findings when different scanners are used to assess the same participants. Even on the same scanner, a number of factors can change over time (e.g., implementation of a data-acquisition protocol, software version, hardware replacements), potentially compromising reliability. Fortunately, large-scale multimodal imaging initiatives and heterogeneous data-sharing efforts (Box 3) are helping to motivate approaches to minimize or correct for such differences.

Balancing Reliability with Validity

Potential confounding signals in brain imaging data can differ as a function of age across the life span (Box 4), and researchers must balance reliability with validity. The varying controversies surrounding motion, and its potential ability to drive age-related connectome differences, motivate the need to consider the validity of a measure. To facilitate this process, a growing array of noise correction methodologies is emerging; additionally, machine learning-based frameworks, such as NPAIRS [135], are highly informative.

Once sample metrics are derived from the data, statistical methods to model trajectories are required to quantitatively characterize life-span changes of the metrics. To date, the literature has largely relied on a relatively simplistic set of parametric methods (e.g., polynomial curve fitting, *t* tests, and analysis of variance) to model differences across the life span. However, recent work has introduced more complex methods capable of accurately characterizing local changes (i.e., within a very small age interval) in life-span trajectories [37,38]. Box 2 provides more details on these nonparametric/semiparametric methods and guidance on their use.

Empirical Observations from MRI-Based Life-Span Studies

Initial insights into changes in brain structure and organization associated with development, maturation, and aging came from the mapping of relatively nonspecific measures, such as total brain weight and intracranial volume [33,39]. Each of these indices shows dramatic increases over the first 6 years of life, by which time they reach 90–95% of adult values. While the next 6 years are characterized by continued increases, though at a slower rate, late adolescence shows the beginning of a reversal, with progressive decreases that continue throughout the life span. As more fine-grained regional analyses focused on gray matter (GM) emerged, the inverted U-shape trajectories were observed throughout much of the brain, though with higher-order regions (e.g., prefrontal cortices) showing slower increases during development and more rapid losses during aging, relative to sensorimotor cortices [40,41]. Of particular relevance to our discussion of the connectome, studies attempting to differentiate WM from GM found stark differences in their life-span trajectories [42,43]. In contrast to GM, WM volumes increased into the third and fourth year of life, before exhibiting decreases – a finding that is commonly interpreted to reflect the prolonged process of myelination [44]. Importantly, at each end of the life span, factors capable of modifying the timing of trajectories have begun to be

Glossary

Complex network analysis: characterization of real-world networks with nontrivial properties using tools from graph theory and statistical physics (among others).
Connectome/Connectomics: a complete set of neural elements (e.g., neurons, brain regions) and their interconnections (e.g., synapses, fiber pathways, functional connections).
Functional homotopy: the high degree of synchrony in spontaneous activity between geometrically corresponding interhemispheric (i.e., homotopic) regions is a fundamental characteristic of the intrinsic functional architecture of the brain.
GAMLSS: a class of statistical models to extend the simpler generalized linear models and generalized additive models (GAMs) by allowing the values of a dependent variable to be related to explanatory variables with a probability distribution characterized by three parameters of location, scale, and shape (LSS), namely, GAMLSS.
Generative network model: a general framework that involves the use of simple wiring rules to construct synthetic networks whose properties are similar to those of real-world networks.
Graph theory: a branch of mathematics that deals with systems of elements (i.e., nodes, vertices) and their dyadic interactions with one another (i.e., edges, connections).
Hub/Rich club: a hub is a highly central node that occupies an influential position within a network. A rich club is a set of hubs that are more densely interconnected to one another than expected by chance.
Long-term potentiation (LTP)/ Long-term depression (LTD): terms used to describe lasting activity-dependent changes in neuronal synaptic efficacy. LTP refers to changes that increase synaptic efficacy, while LTD refers to changes that decrease synaptic efficiency. LTP and LTD occur throughout the brain, and are key factors in neural plasticity.
Modularity/Efficiency: modularity refers to the propensity for a network to be divisible into internally dense, externally sparse subnetworks known as modules. Efficiency measures the ease with which network nodes can exchange along shortest paths.

Box 2. Advanced Methods for Charting Developmental Trajectories

An array of advanced methods has been developed to model growth curves in the fields of pediatric care and public health. However, as indicated in Figure 1, a survey of the connectomics literature from 2007 to date shows a heavy reliance on more simplistic parametric or semiparametric trajectory models to infer or reconstruct the life-span development trajectory. Recent work has signaled the need to move beyond these approaches in efforts to map the life-span trajectories. Several have explored the potential utility of machine-learning techniques (e.g., support vector regression, relevance vector regression), which can provide estimates of an individual's brain age relative to the chronological age approaches focused on the prediction of an individual's 'brain age'; the two values can be combined to form a 'maturation index' [29,30,67]. Although insightful, these approaches do not provide a true equivalent of pediatric growth charts for weight or height. Following the model of the World Health Organization in the development of their Child Growth Standards, two recent studies highlighted the use of generalized additive models for location, scale, and shape (**GAMLSS**) [37,38], in which a linear predictor is the sum of smooth functions of covariates, rather than simply covariates. This representative framework allows for the estimation of an entire distribution of a measure at each age. The GAMLSS-derived charts are akin to physical pediatric growth charts and thus, for any given brain measure, can yield a quantile rank or percentile for an individual, and can also be generalized to allow for comparing groups based on their rank maps. These more sophisticated approaches have shown promise to become neuroscientifically and clinically useful tools over time, as necessary data are amassed.

identified (e.g., poverty and mental illness during development; aerobic fitness and degenerative processes during aging) [45–47], providing initial insights into interindividual variation. As a broader range of methodologies have emerged for mapping GM/WM organization across the life span, a more refined picture has begun to emerge [48,49]. Anatomical geometry and morphology serve as the basis of the brain connectivity [50], and thus their changes over the life span motivate investigations on the age-related changes of the brain connectivity across the human life span.

Diffusion MRI-based methodologies, which provide more specific measures of WM connectivity organization [e.g., fractional anisotropy, mean/radial diffusivity, longitudinal relaxation rate (R1)], have largely confirmed the findings of the inverted-U trajectories for WM development [51–53], though they have also provided greater differences into differential timing patterns across tracts (e.g., [52,54,55]). In particular, phylogenetically primitive sensorimotor brain structures were found to exhibit the most rapid development and greatest preservation, while more phylogenetically advanced structures (e.g., prefrontal cortex) showed slower development and faster declines, suggesting a first-in-last-out pattern of development across the life span [52]. Questions remain about the biological significance of the changes observed. For R1, which appears to be associated with measurable changes of macromolecule tissue volume across the life span, developmental findings appear to directly suggest that differences in timing among tracts are directly attributable to growth and loss of tissue [55].

Complementing structural perspectives of life-span development for the connectome are those emerging from the burgeoning functional connectivity literature. While early fMRI efforts struggled with the challenges of designing task activation paradigms that could appropriately probe brain function across a range of developmental levels, the emergence of **resting-state fMRI (rfMRI)** removed such barriers [16,56]. Early work tended to focus on development and aging in isolation [57,58]. Pediatric studies consistently revealed age-related increases in long-range connectivity and decreases in both short-range and interhemispheric connectivity [19,59,60], even after accounting for head motion artifacts [61]. By contrast, aging studies revealed consistent patterns of decreases in long-range connectivity [15,62], although these did not converge into consistent patterns at the network level [63–66]. Inspired by the seeming parallels with findings from the structural literature, an initial study of the life span demonstrated quadratic U-shaped life-span trajectories for **functional homotopy** [20]; later work expanded these efforts to characterize inter-regional functional connectivity [67], as well as spontaneous activity amplitude [37]. Compared with the age-related changes of both morphology and structure

Resting-state fMRI: a method of functional brain imaging that can be used to evaluate spontaneous neural activity that occurs when an individual is not performing an explicit task.
Single-cohort/Multicohort design: a cohort design is commonly used for a longitudinal study where one (called single-cohort design) or more (called multicohort design) groups of people are followed up.
Small world/Scale free: 'small world' networks balance attributes of segregation and integration (i.e., high clustering and short path length), facilitating both localized information processing and network-wide integration of information. Scale-free networks exhibit a power-law degree distribution (most nodes make a small number of connections; a small number of nodes make disproportionately more connections).
Wiring cost: anatomical connections require material and energy for their formation, maintenance, and usage in signaling. Assuming that such costs increase monotonically with length (longer connections are more costly), the wiring cost of brain can be approximated by the sum of its connections' lengths.

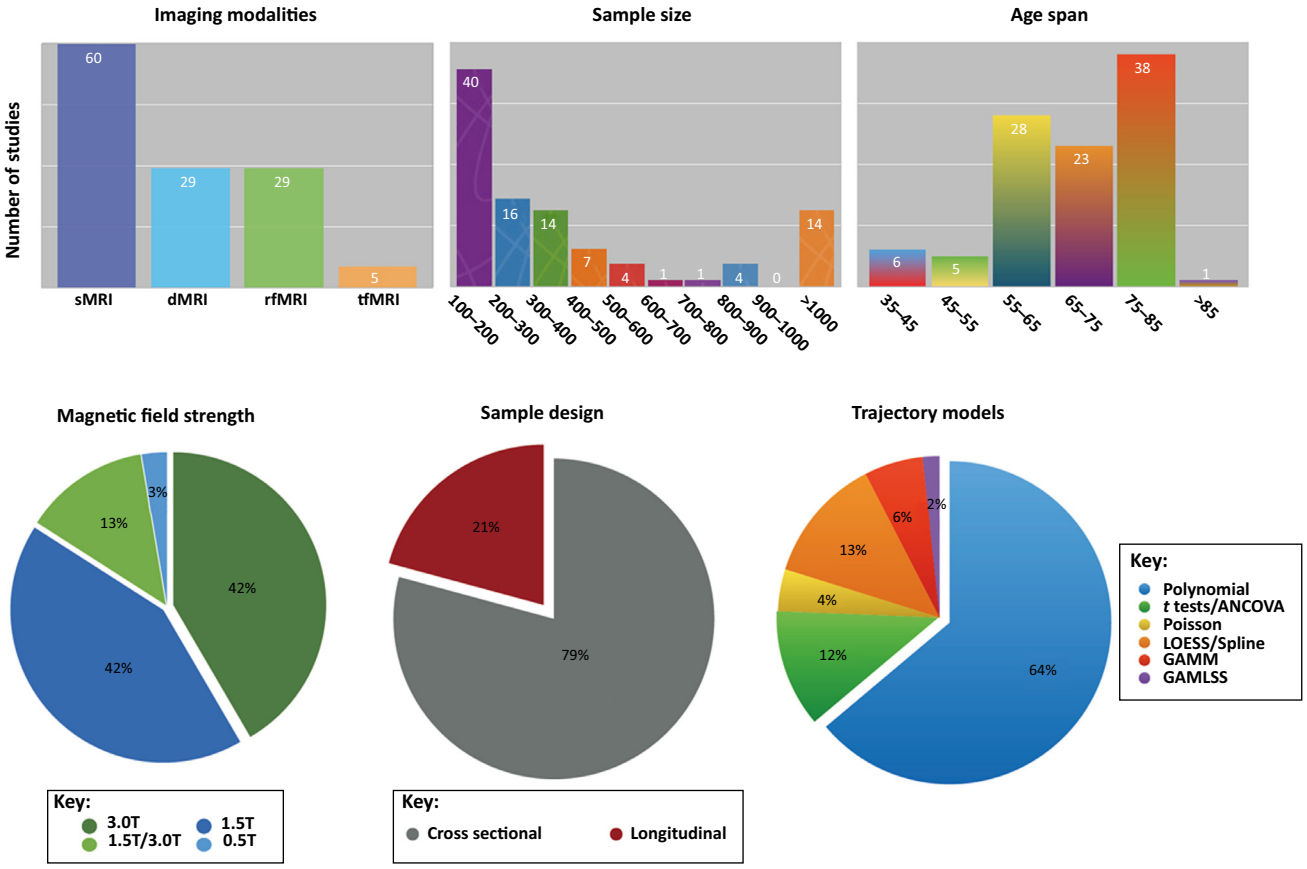

Figure 1. Visual Summary of 10-Year Large-Scale Empirical Life-Span Brain Studies. A total of 101 large-scale ($N \geq 100$) studies published between 2007 and 2016 are summarized as distribution histograms of the publications according to their imaging modality, sample size, age span (i.e., min age minus max age), as well as pie charts of publications regarding magnetic field strength, sample design, and trajectory models. ANCOVA, analysis of covariance; dMRI, diffusion MRI; GAMM, generalized additive mixed model; LOESS, local regression; rfMRI, resting-state fMRI; sMRI, structural magnetic resonance imaging; tfMRI, task fMRI.

across the life span, functional connectivity changes demonstrated greater richness of regional differences of their life-span developmental trajectories [20,67]. Similar to the structural literature, connection-specific differences in U or inverted U trajectories were observed, with some showing differences in timing.

While relatively few efforts have attempted to directly link age-related increases in functional connectivity to structural connectivity, a few patterns are readily discernible from the literature. First, the trajectories of functional connectivity are more in line with the timing of WM changes than GM, with a reversal taking place well past the first two decades of life. Second, declines in functional connectivity appear to occur notably later in life than what is reported in the structural connectivity [20], which may suggest that the brain actively maintains patterns of functional interactions for as long as possible, despite changes in the underlying structural integrity of the underlying connectome.

Recent work has shifted focus onto the properties of the network as a whole by characterizing its organization using tools from network science and **graph theory** [68–70]. The connectome's modular organization, in particular, has generated much interest, in part due to the

important role it is believed to play in shaping communication patterns both within and between functional systems. Interestingly, the extent to which modules are segregated with one another appears to fluctuate over the course of the human life span. The presence of aging-related decreases in **modularity** was first demonstrated in connectivity networks derived from cortical thickness; the work highlighted decreases in the intramodule connectivity and increases in the intermodule connectivity [71] – essentially, a pattern suggestive of dedifferentiation. Interestingly, these findings are mirrored in the task-based aging literature where, compared with younger adults, older adults show reduced differentiation in the hemisphere recruited to perform a task (a finding also reported in children [72]). For example, in a nonverbal task probing inhibitory control and attention, younger adults showed right-lateralized frontal recruitment, while older adults showed recruitment of both hemispheres [73]. However, the interpretation of this pattern of results is contentious, with some suggesting that this pattern represents a compensatory process in older adults [74], while others posit that it reflects dedifferentiation [73]. Functional connectomics have also attempted to address the question of how modularity changes during development and aging [63,64,75]. However, findings regarding modularity have proven to be variable across studies of developing brains. The observation that within-module connectivity decreases for long-range networks such as the default network was consistent across development and aging [58,70], while increases and decreases of within-module functional connectivity (FC) were observed for same networks as well as those of between-module FC for same pairs of networks [63,64]. A recent study also argued that the default network remained relatively stable to a parietal memory network, which is spatially overlapped and temporally correlated with the default network but demonstrated significantly reduced FC profile [66].

Some recent studies have attempted to directly probe changes in network **efficiency** across the life span. Such work builds on the study of small world characteristics of the connectome, engendering high efficiency at both the local and global scales. Both structural [76] and functional [75] connectomics studies have reported linear decreases in local efficiency from adulthood into old age, while global efficiency appears to remain unchanged. When focusing on development, a somewhat inconsistent pattern of results emerges, with local and global efficiency exhibiting both age-related increases [77] and decreases [78].

Overall, it is fair to say that while there are converging themes emerging across studies, the life-span connectomics literature is marked by a number of discrepancies in findings and interpretations. Multiple factors contribute to these discrepancies. First, there are methodological differences in the definition of network nodes (i.e., cortical areas) and edges (i.e., connections between areas) [36,79,80] (e.g., large-scale anatomical/structural parcellation applied to functional data with failure of capturing the rich regional variation in functional specialization [81]). Second, it is inherently difficult to compare and relate findings across different imaging modalities (e.g., connectomes derived with diffusion MRI and rfMRI). Functional connectivity matrices tend to be dense due to reliance on correlation scores that allow for 'indirect' connections, which do not exist in structural connectivity; as such, functional and structural perspectives of the connectome are inherently distinct. Finally, there has been a lack of studies designed to comprehensively capture neurodevelopment, maturation, and aging using the same scanner and acquisition protocol. Efforts such as the Nathan Kline Institute-Rockland Sample (NKI-RS; ages 6–85 years), the upcoming Human Connectome Lifespan Project, and the Chinese Color Nest Project are offering hope in this regard (Box 3). Initial studies using the NKI-RS have suggested the presence of linearly decreasing trajectories for both modularity and efficiency, as well as an inverted U-shaped trajectory of intramodule connectivity and U-shaped trajectory of intermodule connectivity [63–66]. The life-span changes of both functional segregation (decreased within-module connectivity) and integration (increased between-module connectivity) have also been replicated [65].

Box 3. Open Resources for Human Life-Span Connectomics

A large sample of the human brain acquired with high-resolution MRI techniques is essential for a life-span connectome study. A big data framework that builds on such open resources may rapidly accelerate the progress of discovery science of human life-span connectomics and yield better understanding of the underlying brain mechanisms. This need is increasingly addressed through several promising open resources for human life-span connectomics studies, which are documented in detail below.

(i) Nathan Kline Institute-Rockland Sample (NKI-RS): This is an ongoing, institutionally centered endeavor aimed at creating a large-scale ($N > 1000$) community sample of participants across the life span. Measures include a wide array of physiological and psychological assessments, genetic information, and advanced neuroimaging data obtained from a single scanner with multiple modalities. Anonymized data are publicly shared and updated on a quarterly basis at http://fcon_1000.projects.nitrc.org/indi/enhanced/index.html

(ii) Human Connectome Project (HCP) Life Span Sample: The WU-Minn HCP consortium is acquiring and sharing pilot multimodal imaging data acquired across the life span, in six age groups (4–6, 8–9, 14–15, 25–35, 45–55, and 65–75 years) using scanners that differ in field strength (3T and 7T) and maximum gradient strength (70–100 mT/m). The scanning protocols are similar to those for the WU-Minn Young Adult HCP, except shorter in duration. The objectives are to enable estimates of effect sizes for identifying group differences across the life span, and to enable comparisons across scanner platforms, including data from the MGH Lifespan Pilot Project. Both the initial data including unprocessed image data and the minimally preprocessed data have been shared with the public since early 2015 at http://lifespan.humanconnectome.org.

(iii) CCNP Life Span Sample: This ongoing project is supported by Chinese Academy of Sciences, Natural Science Foundation of China, and the Ministry of Science and Technology of the People's Republic of China. The CCNP aims at collecting large-scale life-span data of the human brain and behavior (1200 participants) via a cross-sectional and longitudinal mixed sampling design over a span of 10 years (2013–2022). Each participant visits three high-field (two 3T and one 7T) MRI scanners located at the Institute of Psychology and the Institute of Biophysics, Chinese Academy of Sciences, generating five scans including 2-week test–retest data at the two 3T scanners. As a trial sample using the CCNP design, devCCNP includes three waves of multimodal neuroimaging data from 198 developing patients (6–18 years) across 5 years (2013–2017). The data from devCCNP will be released to the public in early 2017 (http://zuolab.psych.ac.cn/colornest.html).

Computational Models of Life-Span Connectomics

Empirical studies of life-span changes in the human connectome have described the evolution of highly connected **hubs** and **rich clubs**, along with characteristic age-dependent patterns of segregation and integration among functional modules or resting-state networks. Such findings, while informative, are fundamentally descriptive in nature. A more mechanistic understanding of how these properties develop and evolve would be highly desirable and holds promise for early intervention in neurodevelopmental disorders, for example, by predicting which individuals are susceptible to deviations from normal trajectories and when. Complementing these descriptive accounts are theoretical studies that have proposed a range of mechanistic **generative network models** for explaining the growth and evolution of connectome topology. In the context of complex networks, generative modeling refers to a set of mathematically and algorithmically defined approaches in which simple wiring rules are used to create synthetic networks with the same features as those encountered in real-world networks. For example, the Watts–Strogatz and Barabási–Albert models explain the origin of **small world** [82,83] and **scale-free** [83] networks, respectively.

Brain networks, however, are not well described by either of these canonical models. Rather, the majority of generative models for brain networks have addressed the important role played by the network's spatial embedding and cost conservation, for example, a model of the macaque cortico-cortical network that penalizes the formation of long-distance connections [84,85]. Other generative models have combined spatial (cost preserving) with topological (performance enhancing) factors. In such models [86,87], rules that promote links among nodes with matching topological properties have been shown to add significant precision to the match between synthetic and empirical networks.

Recently, an extensive set of generative models on data collected from individual human participants was tested across three different data sets [88]. The best-fitting models combined spatial and nonspatial factors based on the overlap of two node's connection patterns – stable

links were more likely to form between nodes with greater similarity in terms of the list of their connection partners, a form of 'homophily'. Model fitting to individual human data yielded a highly compressed account of the relative balance of spatial and topological factors (expressed by two key parameters). Applying this generative model to the human life span demonstrated significant trends in the relative power of spatial and nonspatial factors to account for connectome topology. With age, the degree to which spatial separation in the brain imposed a penalty or cost on structural connections weakened, and networks become progressively more difficult to fit. This finding suggests that changes in the topology of the structural connectome across the life span exhibit characteristic patterns and indicate a gradual shift from a more 'spatial brain' to one where a trade-off between spatial and nonspatial generative rules increasingly favors the latter over the former (Figure 2).

Finally, as with any modeling framework, it is essential to avoid overinterpreting generative models. Multiple models (i.e., distinct wiring rules) might offer equally good explanations of the observed network data. Alternatively, the best-fitting solution may be at odds with some known neurobiology. Future work is needed to add more detail to this emerging picture. More refined geometric or anatomical rules and generative mechanisms could be employed and tested against nonspatial factors [89,90]. More accurate connectome reconstruction methods should provide more sensitive and reproducible structural network data sets. More biologically based generative models that involve rules governing connection growth and plasticity should be applied to life-span data (e.g., [31,78]). Jointly, descriptive and generative lines of research are beginning to provide a unified framework for understanding the progression of individual differences in the brain network organization, as well as their linkage to variations in behavior across different periods of the life span.

Toward an Understanding of Plasticity across the Life Span

As mentioned earlier, a key goal of life-span studies is to identify modifiable targets for interventions aiming to alter pathologic trajectories. Central to this notion is the idea of plasticity, or the 'intrinsic property of the nervous system enabling rapid adaptation in response to changes in an organism's internal and external environment' [91]. Central nervous system (CNS) plasticity decreases across the life span [92,93], and may contribute to cognitive decline [92]. Variability in brain plasticity can provide both a potent biomarker of CNS development and decline across the life span [91] and a target for interventions (e.g., cardiovascular exercise [94], brain stimulation [95,96]). Plasticity is yet to be carefully examined within a life-span sample.

CNS plasticity is classically associated with changes in **long-term potentiation** and **long-term depression** at the cellular level [96]. From an intervention perspective, one of the most effective approaches to modifying brain plasticity in nonpathologic populations to date remains cardiovascular fitness or cognitive training [45]. Cardiovascular fitness training has been shown to be able to increase plasticity in non-human models [97], and is inferred to be responsible for beneficial changes in older human models, such as increased GM and WM volumes [98], improved frontal lobe function, frontoparietal cortical recruitment, and functional connectivity [99–101].

In recent decades, the emergence of brain stimulation methodologies such as theta-burst repetitive transcranial magnetic stimulation [100] have provided a mechanism for probing brain plasticity in a manner of minutes, as well as attempting to modify it over repeated sessions. In addition, single-pulse transcranial magnetic stimulation probes have begun to demonstrate their value in establishing and/or testing causal models of interactions within the connectome [102]. Arguably, while the past and present eras of connectomics have focused largely on the mapping of the human connectome in common settings, the next generation of studies will work to shift the focus to experimentally probing and establishing causality within the connectome. In addition

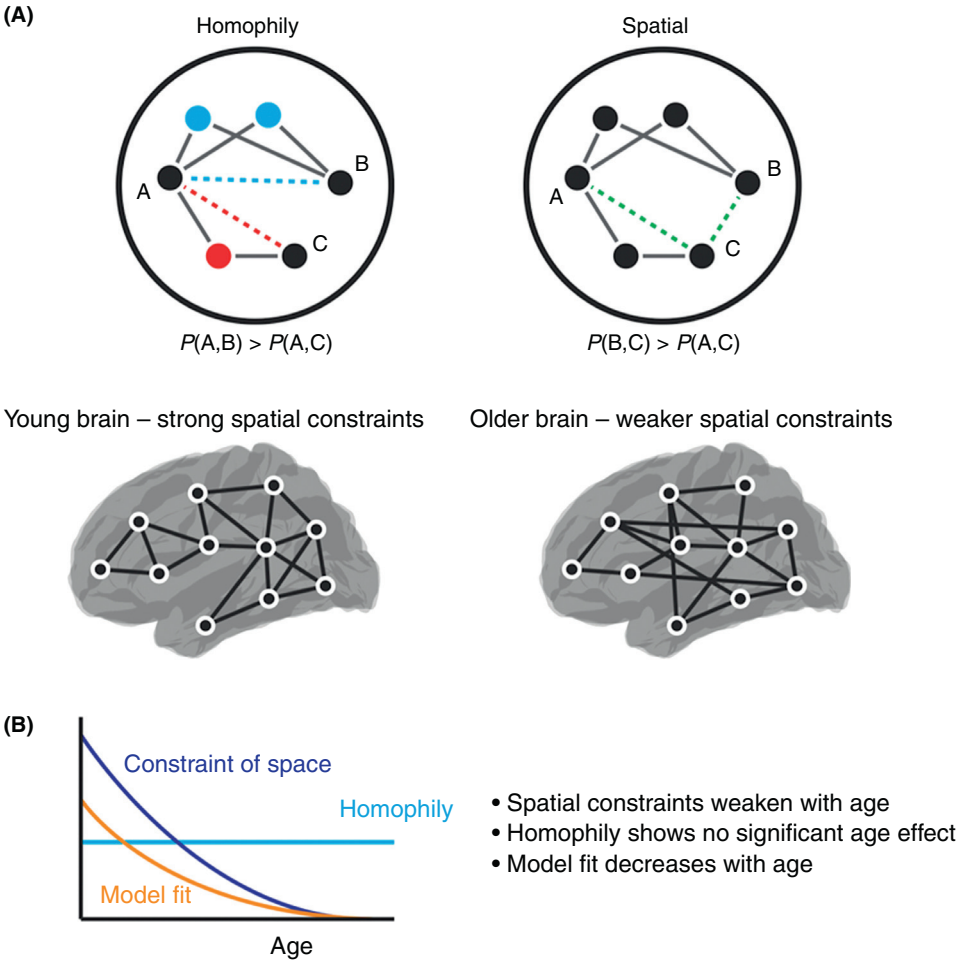

Figure 2. Generative Models of Life-Span Connectomes. With a simple wiring rule [88], synthetic connectomes can be generated that embodied many of the same properties as observed connectomes. (A) The wiring rule was based on two countervailing forces: homophilic attraction and a spatial penalty. Homophily implies that brain regions with many common neighbors are more likely to connect to one another. In this example (top left), regions A and B have two common neighbors (blue), while A and C have only one (red). Under a homophilic attraction mechanism, it would be more likely for a connection to form between nodes A and B than between nodes A and C. The spatial penalty (top right) embodies the brain's drive to reduce its wiring cost by favoring the formation of short-range connections. Here, because B and C are separated by a shorter distance than A and C, it would be more likely for a connection to form between nodes B and C than between nodes A and C. When applied to life-span data, the authors observed that the effect of the spatial constraint was stronger in younger brains than in older brains. (B) The results of this study indicated that, with age, spatial constraints and the ability for the generative model to fit the observed data decreased monotonically. The homophily exhibited no statistically significant age effect.

to brain stimulation methodologies, the recent emergence of powerful genetic techniques capable of providing researchers with tight control of specific circuits or cell lines (e.g., optogenetics and chemogenetics) is promising to expand the experimental reach of studies focused on life-span causality.

Pitfalls and Challenges

The expected merits of life-span connectomics research are made clear by the growing number of studies and increasing investments (e.g., NIH Human Connectome Lifespan Project [103]). However, a number of methodological caveats, assumptions, and obstacles must be addressed for the field to reach its full potential. As previously discussed (Box 4), the potential for artifactual

Box 4. Piecing Together Life-Span Data across States and Artifacts

Initial life-span studies have attempted to examine human brain function and structure from childhood through the older adult/elder years, an endeavor that has required consideration of a number of potential confounds and logistical challenges along the way (Table I). One issue arises due to age-related changes in motion [106,107], which can impact image quality and registration for brain imaging [104]. The head motion in scanner contains individual states (i.e., short-time scale), which induce artifactual findings for functional imaging [108], while its trait (i.e., long-term) components bring challenges of neurobiological interpretation regarding its links to individual differences in connectomics [105,109]. Other factors, such as age-related differences in cardiovascular health and neurovascular coupling properties also present challenges in the interpretation of findings [136]. However, the ultimate goal of life-span studies is to examine the brain from its fetal origins to old age. This goal raises even greater concerns due to the need to carry out imaging across differing states – some of which inherently differ with respect to levels of arousal/consciousness (i.e., fetal, sleep) and motion (i.e., fetal). Fortunately, a number of recent innovations and insights are providing hope for our ability to overcome these challenges. First, for structural imaging, prospective motion assessment and correction strategies are evolving; examples include navigator-based imaging. Second, researchers are working to develop age-specific templates to guide anatomical registration, as well as strategies for combining images from different developmental periods in a common stereotactic space. Third, researchers are working to demonstrate the reproducibility of findings for functional imaging across fetal, sleep, and awake states, as well as devising strategies for optimizing the between-state reliability of assessments for the same individual. In addition, for those interested in examining the brain's responses to external stimulation, alternative paradigms, such as naturalistic stimulus (e.g., movie) viewing, are emerging, which can be applied to individuals of any age range.

Table I. Potential Confounds of the Human Connectome across Life Span

Developmental period	Imaging state	Motion	Brain size (% total postnatal growth)	Anatomical stability	Heart rate, beats/min	Respiratory rate, breaths/min
Fetal	Fetal	Severe	NA	Low	110–180	35–45
Infant	Sleep	Low–Moderate	10–40	Low	80–160	20–50
Toddler	Sleep	Low–Moderate	40–70	Low	80–120	20–30
Early childhood	Awake	Severe	70–90	Moderate	70–110	20–30
Late childhood	Awake	Low–Moderate	90–100	High	60–100	20–30
Adolescence	Awake	Low	100	High	60–100	12–30
Young adult	Awake	Low	100	High	50–80	12–30
Middle adult	Awake	Low	100	Moderate–high	50–80	16–20
Aging adult	Awake	Low–Moderate	100	Low	50–80	16–20

findings to arise from age-related differences in non-neural signals (e.g., head motion [104–109], physiological parameters [110]) or image-processing parameters (e.g., anatomical template definitions [79,81], denoising strategies [111–113]) remains a continuing concern. In addition, constructs such as the global signal, which remains highly controversial due to questions about whether its origins are neural [114–116], become even more challenging when one considers the possibility of age-related differences across the life span [117,118]. A growing number of strategies are emerging to overcome the various artifacts (e.g., independent component analysis-based denoising strategies, statistical standardization) [119–121], allowing researchers to continue to move forward. However, it may be equally important to pursue lines of translational research in non-human models that allow for a more direct understanding of the origins of the signals captured by neuroimaging.

In addition to concerns about artifacts, the imaging community remains divided on what the most promising MRI-based modality is for the study of life-span connectomics. This likely reflects the reality that no single perspective of human brain development will suffice to capture entirety of developmental, maturational, and aging phenomena. Our previous discussion of computational connectomics attempted to introduce a novel methodology for integrating functional and

structural perspectives of the human connectome and its changes across the life span. Future work will not only need to expand and mature such integrational methodologies, but also increase consideration of additional modalities such as arterial spin labeling [122], which are increasingly being used to capture developmental processes [123].

Beyond imaging methodologies, a number of considerations remain, especially questions regarding the sampling strategies optimal to moving life-span connectomics forward – both in the short term and in the long term. Cross-sectional studies can provide insights into the age-related changes in the connectome across the life span most rapidly (see [7] for a review of the varying design options), but are commonly confounded by sources of interindividual variation that may be unrelated to age. Although longitudinal designs are best positioned to overcome such confounds, they face a variety of logistical challenges. Most notably, **single-cohort designs** might be optimal in reducing confounds of cross-sectional approaches, but they are inherently impractical for the study of the life span due to time requirements. However, this limitation may not apply in non-human models, in which the life span can be notably less than a decade, depending on the population being studied. Multicohort studies are heralded as an acceptable compromise, but face some of the same challenges as cross-sectional studies – particularly, when not properly structured (see [34]).

Finally, the virtues and challenges of mapping developmental and maturational changes in brain–behavior relationships must be underscored. Such information is crucial to our understanding of the maturation of human brain function, as well as the development of clinically useful biomarkers. Early work has already demonstrated age-related changes in the neural substrates of intelligence [26,124], reading [125], and working memory [126], as well as suggested methodologies for integrating age into brain–behavior analyses [37]. Central challenges that remain for life-span connectomics are the development of phenotyping methodologies optimally suited for integration with brain imaging data (e.g., [127]) and applicable to the life span (see [128,129] for a discussion).

Concluding Remarks

The mapping of brain–behavior relationships across the life span is a defining agenda for the next decade. As highlighted in this review, the success of the research community in meeting such lofty goals will rely on a combination of analytical and technical advancement, as well as increased global collaboration as the field works to piece together the necessary data sets and make reproducible science a reality. The life-span studies to date have worked to track development from early childhood to aging; however, the neurobiological development of the connectome begins prior to birth. Undoubtedly, the window of examination will expand over time as fetal and infant imaging continues to mature [130–132]. Establishment of directional and causal understanding of interactions within the connectome remains an important frontier. Fortunately, increasingly powerful neuromodulation techniques capable of selectively manipulating neural interactions are emerging. Although considerable work remains in pursuing this goal, the potential payoff for neuroscientific and clinical communities would be enormous (see Outstanding Questions).

Outstanding Questions

Can we devise an integrative model of the connectome and its life-span dynamics capable of comprehensively accounting for the broader range of functional and structural indices, especially for common morphological measures? Related to this point will be the challenge of identifying redundant and unique features.

How can we best index changes in neural efficiency associated with the life span? Changes in neural efficiency represent a recurrent theme in the emerging literature, though they are typically inferred or measured indirectly.

How feasible is it for us to generate the big data sets and efficient statistical methodologies to overcome differences in fMRI measurements of the connectome? This will be crucial for effectively linking findings from different phases of the life cycle.

Can we map the dynamical brain–behavior relationships across the life span for the broader range of cognitive and psychiatric variables? And how can we accumulate the data needed to develop predictive models to guide interventions?

Can we identify modifiable connectome-based targets for life-span interventions? And how can we refine neuromodulation techniques sufficiently to impact the trajectory of disorders as they emerge, or even before?

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