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Review article

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Structure–function coupling in macroscale human brain networks

Panagiotis Fotiadis[1,2,3] ✉, Linden Parkes[2], Kathryn A. Davis[4], Theodore D. Satterthwaite[5,6,7,8], Russell T. Shinohara[6,7] & Dani S. Bassett[2,4,5,9,10,11] ✉

Abstract

Precisely how the anatomical structure of the brain gives rise to a repertoire of complex functions remains incompletely understood. A promising manifestation of this mapping from structure to function is the dependency of the functional activity of a brain region on the underlying white matter architecture. Here, we review the literature examining the macroscale coupling between structural and functional connectivity, and we establish how this structure–function coupling (SFC) can provide more information about the underlying workings of the brain than either feature alone. We begin by defining SFC and describing the computational methods used to quantify it. We then review empirical studies that examine the heterogeneous expression of SFC across different brain regions, among individuals, in the context of the cognitive task being performed, and over time, as well as its role in fostering flexible cognition. Last, we investigate how the coupling between structure and function is affected in neurological and psychiatric conditions, and we report how aberrant SFC is associated with disease duration and disease-specific cognitive impairment. By elucidating how the dynamic relationship between the structure and function of the brain is altered in the presence of neurological and psychiatric conditions, we aim to not only further our understanding of their aetiology but also establish SFC as a new and sensitive marker of disease symptomatology and cognitive performance. Overall, this Review collates the current knowledge regarding the regional interdependency between the macroscale structure and function of the human brain in both neurotypical and neuroatypical individuals.

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A full list of affiliations appears at the end of the paper. ✉e-mail: pfotiad@med.umich.edu; dsb@seas.upenn.edu

Introduction

Over the past several decades, scholars have increasingly sought to understand the correspondence between the anatomical wiring of the brain and its functional repertoire[1–3]. Broadly, each brain region can be structurally characterized by its white matter connectivity, that is, the set of neuronal fibres connecting it to other regions of the brain (see Box 1 for complementary definitions of structural connectivity). Such fibres are typically assessed via diffusion weighted imaging. The structural connectivity between two brain regions can then be estimated as the number (or density) of white matter fibres between them (Fig. 1a). In addition, each brain region can be functionally characterized by its neuronal activity. Such activity can be captured directly by, for example, electrocorticography, electroencephalography and magnetoencephalography, or indirectly via the haemodynamic blood oxygen level-dependent (BOLD) signal from functional magnetic resonance imaging (fMRI). The functional connectivity between two brain regions is then typically defined as the statistical similarity between their respective neuronal activity time series (Fig. 1b). In considering how structural and functional connectivity quantify different but biologically related physiological processes, the following is a key question: what is the mechanistic relation between them?

Many neuroimaging studies have attempted to elucidate this relation in humans. Broadly, such studies have found that the anatomical structure of the brain constrains and partially determines its functional connectivity and neuronal activity. In turn, the neuronal activity sculpts structural connectivity via neuromodulation and neuroplasticity processes[1,4–16]. At the resting state, the structural strength of a connection is positively correlated with its functional strength, but that correlation is imperfect and varies according to several factors. For instance, although directly anatomically interconnected brain regions typically also display strong functional connectivity, regions that are indirectly linked via a larger number of polysynaptic connections exhibit a wide range of functional connectivity patterns[6]. For example, homotopic visual cortices with similar retinotopic mappings of the visual field display functional connectivity despite the absence of direct structural connections[17,18]. Similarly, individuals with split-brain[19] or callosal agenesis[20] can display bilateral functional connectivity even in the absence of major commissural fibres connecting both hemispheres[21]. Thus, although on average structure and function tend to track one another, their relationship is not one-to-one but instead varies across brain regions.

Can how the relation between structural and functional connectivity varies be better understood? Mounting evidence indicates that macroscale structure–function relationships differ across brain regions in a manner that depends systematically on their location in the cortical hierarchy[2,3,22–26]. To simplify the communication of the findings of these studies, the field has coined the term structure–function coupling (SFC), which refers to the manner in which a function of the brain region statistically depends on its structure, and vice versa (Fig. 1c). Even though SFC has been assessed using various approaches (Box 1), the most common is correlational: each SFC of the brain region is defined as the correlation coefficient between its vector of structural connectivity values to all other brain regions and its vector of functional connectivity values to all other brain regions (Fig. 1a,b, third row). Higher SFC would then indicate a stronger statistical dependence between functional and structural connectivity vectors of that brain region. For consistency and to allow for a more rigorous comparison of findings, we have mainly focused on studies of macroscale structure–function relationships that use this correlational approach to assess SFC.

In this Review, we synthesize the current state of knowledge regarding this regional interdependency between the macroscale structure and function of the human brain. We begin by collating studies that examine the heterogeneous expression of SFC across the cortical mantle, among individuals and over time, and its role in fostering flexible cognition. We then discuss studies reporting altered SFC in a wide range of neurological and psychiatric conditions, and the potential role of SFC as an effective disease biomarker. In canvassing this literature, we propose SFC as a more informative marker of cognitive resilience and performance than either structural or functional properties alone.

Heterogeneous expression of normative structure–function coupling

To date, most studies examining SFC have focused on four axes of variation: across brain regions, among individuals, as a function of cognitive task, and over time (Fig. 2). As we discuss in this section, these axes of variation have provided notable insight into the organizational principles of the human brain and into how those principles explain individual differences in cognition.

Structure–function coupling differs across brain regions

Over the past few years, the study of structure–function correlations has shifted from a global investigation across the whole brain to a local one in isolated areas. Recent studies have consistently demonstrated that the macroscale coupling of function to structure varies across the cortex and subcortex, with SFC gradually lost along cognitive representational hierarchies[2,3,22–26]. Specifically, primary sensory and motor cortices and unimodal association cortices — unimodal sensory regions — such as the visual, auditory and somatomotor cortices, and subcortical structures (putamen and caudate), display relatively strong SFC[3,23–27]. By contrast, heteromodal association cortices, paralimbic regions and limbic regions — transmodal regions — including the parietal, insular, anterior cingulate and temporal cortices, as well as the limbic and default mode networks, display relatively weak SFC.

Critically, this gradual decoupling between structural and functional connectivity across the cortex has been consistently demonstrated using different — yet complementary — definitions of cortical hierarchy. Such definitions have included coarse parcellations of the cerebral cortex that group brain regions into broader functional networks based on the similarity of their intrinsic functional connectivity patterns (such as functional resting-state systems)[28] or cellular morphological properties (such as cyto-architectonic systems with varying levels of laminar differentiation)[29–31]. More fine-grained gradients have also been used to study the dynamic nature of SFC. Examples include the principal functional gradient of cortical organization, wherein lower assignments within the gradient capture primary sensory and motor regions whereas higher assignments capture regions within the default mode network[32], and profiles of microstructure covariance, wherein primary sensory regions occupy the lower end of the profile whereas limbic regions represent its apex[33,34]. Community detection techniques have also been used to study SFC differences across non-cerebral structures such as those used in a recent study that first partitioned the brain into non-overlapping structural modules and then computed the SFC of each module. Utilizing an unsupervised clustering approach, the authors identified a differential pattern of SFC expression in the cerebellum, with its posterior component exhibiting

Box 1 | Defining structure–function coupling

Several approaches have been used in the literature to define the structure–function coupling (SFC) of a brain region. These approaches mainly differ in how they quantify the relationship between structural and functional organization and can be separated into three broad categories.

Connectivity approach

The most common approach used to assess SFC is a correlational approach wherein the SFC of each brain region is defined as the correlation coefficient (Pearson or Spearman) between its vector of structural connectivity values to other brain regions and its vector of functional connectivity values to other brain regions[22,26,27,96,111].

Structural connectivity. This can be evaluated using the following:

- Diffusion-related metrics such as fractional anisotropy or apparent diffusion coefficient (derived from diffusion weighted imaging)[138]
- Microstructural profile covariance (derived from histological studies)[33,46]
- Covariance among anatomically derived metrics such as grey matter volume or cortical thickness (derived from anatomical sequences such as T1-weighted MRI)[13,56,139]
- Concentration of neuronal tracers mapping axonal projections (derived from retrograde or anterograde neuronal tracing studies)[140–142]

Functional connectivity. This can be evaluated using the following:

- BOLD signal activity time series (derived from resting-state or task-based functional MRI)[143,144]
- Neuronal activity time series (derived from electrocorticography, EEG or magnetoencephalography recordings)[56,69,145,146]

Harmonic analysis approach

Another recently proposed approach is the harmonic analysis approach, wherein the functional brain activity (BOLD signal) of a region is first expressed as a weighted linear combination of the harmonic components of the structural connectome of the whole brain[23,43]. This weighted linear combination is then split into a higher-frequency 'decoupled' component and a lower-frequency 'coupled' component; the structure–function decoupling index is defined as the ratio of the decoupled to coupled signal components' norms. Complementary approaches using the graph spectral properties of structural connectome to map structural to functional connectivity have also been proposed[147–153].

Modelling approach

Studies have also used a linear regression approach to define SFC. For each brain region, the dependent variable of the regression model is the empirically derived resting-state functional connectivity between that brain region and all other regions; independent variables include the Euclidean distance, shortest path length and communicability of the brain region towards all other brain regions (metrics derived using anatomical and diffusion weighted imaging). Using this approach, SFC is then defined as the adjusted goodness-of-fit R^2 value of the model, which represents how well the functional connectivity predicted by the provided structural features corresponds to the empirically derived functional connectivity[3,41,154,155].

Each approach allows the assessment of SFC of the brain region. To assess SFC of a brain network (for example, the limbic network), we can then average (weighted or unweighted) all SFC values corresponding to constituent brain regions of that network. Of course, this is a non-comprehensive list of approaches and cited references, which rather aims to point the interested reader to some relevant work on the field.

substantially higher SFC than its anterior component, which underscored the diverse anatomy and underlying functionality of the cerebellum[35]. Collectively, the hierarchical ordering of brain regions according to various structural and/or functional properties has revealed different canonical axes of spatial organization, such as the sensorimotor association[36,37] and the granular–agranular axes[25,29–31].

The extent to which the spontaneous activity of a brain region is tethered to the underlying white matter may reflect specialization of a region along a cognitive representational hierarchy ranging from a lower (more dedicated) representation to a higher (more flexible) representation of cognitive functions. That is, regions with relatively strong SFC that regulate specific primary processes such as vision, audition and voluntary motion appear to be placed at the lower (specialized) end of this functional hierarchy, whereas regions with weaker SFC that regulate emotion, reward processing, working memory, executive function and social cognition are placed at the higher (less specialized) end[22,23,32]. Rather than specificity, regions at this higher end exhibit a preference for functional diversity and flexibility, which is the capacity to display varying patterns of neural activation in response to different tasks. Indeed, functional flexibility negatively correlated with the strength of SFC across brain regions[38]. Thus, the weaker SFC in transmodal regions may promote functional diversity and cognitive flexibility[22,38–40].

In addition to the aforementioned 'static' SFC assessments, recent work has also investigated how moment-to-moment fluctuations in SFC vary across the cognitive representational hierarchy. As in the case of static SFC studies, this work has quantified temporal fluctuations in SFC using different statistical metrics and has capitalized on complementary definitions of cortical hierarchies[25,41]. When the variance of SFC across time defined temporal SFC fluctuations, transmodal regions across limbic, default mode and fronto-parietal cortices displayed greater fluctuations than unimodal regions across sensory cortices. Interestingly, unimodal regions within the visual cortex displayed a particularly high variance in their SFC coupling[25,41]. By contrast, when the coefficient of variation of SFC across time defined temporal SFC fluctuations, brain regions occupying intermediate positions in the unimodal–transmodal hierarchy displayed the greatest fluctuations[41]. More specifically, brain regions within the ventral and dorsal attention networks, particularly the insular cortex and frontal eye fields, had the most variable SFC across time, whereas unimodal and transmodal regions, including across the visual system and the default mode network, displayed more stable SFC patterns.

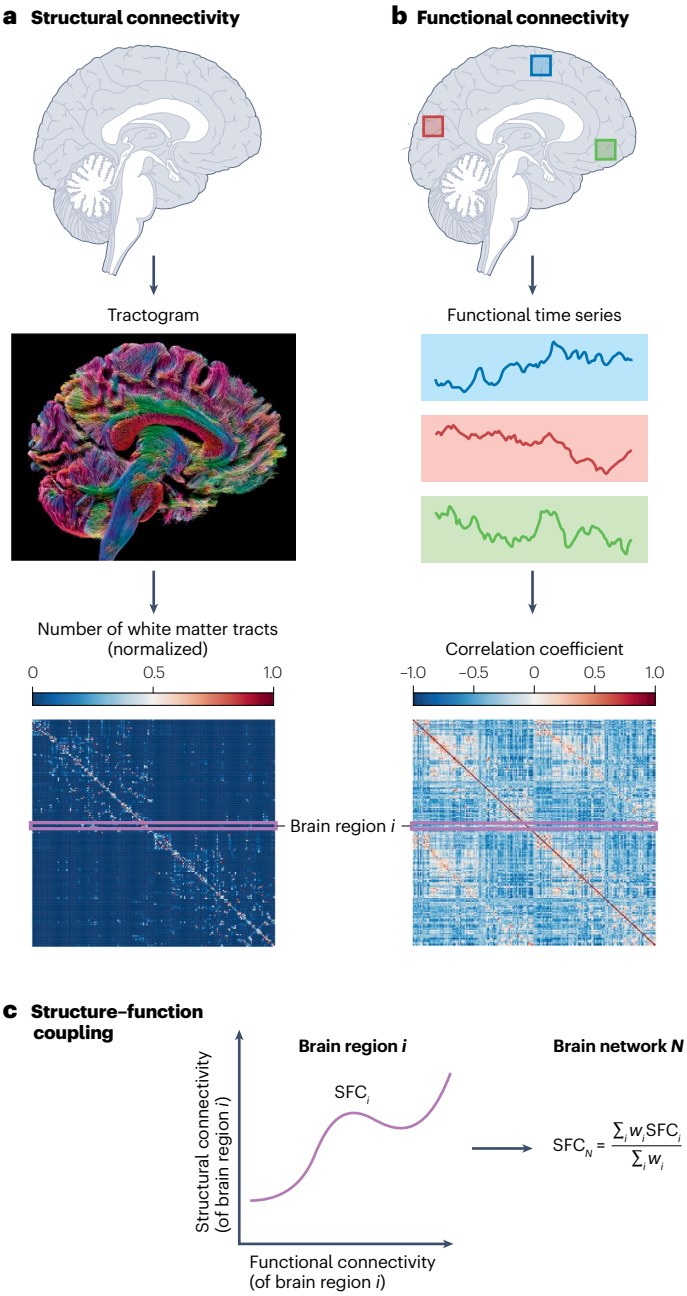

Fig. 1 | Computing the structure–function coupling of a brain region. Structural connectivity and functional connectivity are non-invasively defined from diffusion weighted magnetic resonance imaging and resting-state or task-based functional magnetic resonance imaging, respectively, which are then used to compute structure–function coupling (SFC; see Box 1 for complementary definitions of structure–function coupling to that visualized here). **a**, To determine structural connectivity, the collection of white matter fibres that anatomically connect different parts of the human brain are first reconstructed in its tractogram (middle; colour shades denote different white matter tract primary orientations: red, left–right; green, posterior–anterior; blue, inferior–superior). Next, the structural connectivity matrix of the whole brain is generated (bottom). Each row and each column in that matrix represent a brain region, and the number of white matter tracts (normalized) connecting any two regions is used to capture how strongly structurally connected these two regions are to each other (higher values in the bar indicate stronger structural connectivity). **b**, To determine functional activity, functional signal time series of different brain regions are first assessed (middle). Next, the functional connectivity matrix of the whole brain is generated in which each row and each column again represent a brain region (bottom). The strength of the statistical correlation between the functional signal time series of two brain regions (indicated by the correlation coefficient) captures how functionally connected they are. **c**, To compute the SFC of brain region *i* (SFC_i), its structural connectivity and functional connectivity vectors are first obtained from the respective connectivity matrices. The SFC is then typically set equal to the correlation coefficient between these two vectors (left). Note that, although the resulting shape of the SFC plot should be linear given the definition we used in the text, we chose to plot the SFC using a general curve, to generalize its definition to include linear and nonlinear approaches in computing it (Box 1). To compute the SFC of brain network *N* (SFC_N), all SFC values corresponding to the constituent brain regions of that network can then be averaged (weighted or unweighted). w_i, weight of brain region *i*. Panel **a** tractogram is courtesy of the USC Mark and Mary Stevens Neuroimaging and Informatics Institute (www.ini.usc.edu).

The different results reported between these studies of moment-to-moment fluctuations in SFC could stem from the different mathematical definitions used to define temporal fluctuations in SFC. Variance quantifies the dispersion of SFC values at each network, whereas the coefficient of variation quantifies this dispersion relative to the mean SFC across each network. The overall increased temporal fluctuations in SFC collectively reported in some association areas (such as the limbic and attention networks) compared to other unimodal regions (such as the motor cortex) could reflect an inherently greater variability of their functional connectivity patterns[42]. More broadly, these findings also emphasize how even complementary metrics used to quantify the variables of interest can yield varying results, highlighting the necessity for reproducibility and replicability of results using independent datasets.

Structure–function coupling differs among individuals

From a behavioural standpoint, regional variation in SFC tracks differences in cognitive performance among individuals (Fig. 3a). In a recent working memory study, the task performance of an individual correlated with stronger SFC in transmodal regions of the fronto-parietal and default mode networks (rostrolateral prefrontal cortex, anterior insula, posterior cingulate and medial occipital cortex) and with weaker SFC in the unimodal regions of somatosensory cortex[22]. Another study extracted global cognition scores that reflected the overall cognitive performance of individuals across several cognitive domains[26]. Higher scores associated with weaker SFC within the supplementary motor areas and bilateral middle cingulate and stronger SFC within the right insula[26]. Using a perceptual switching task, a third study found that individual differences in the alignment of BOLD activation signals to the underlying anatomical network explained cognitive switching performance in adults[40]. After decomposing the BOLD signal into coupled and uncoupled components with regards to the underlying anatomical connectivity, the authors showed that increased levels of functional alignment with the underlying anatomy within the uncoupled components associated with faster cognitive switching reaction times. A different study that considered complementary aspects of cognitive flexibility to cognitive switching reported a positive association between stronger SFC and better fluid intelligence and spatial orientation scores in individuals[43]. However, better scores in cognitive

tests that assess executive function (such as sustained attention) and verbal episodic memory correlated with weaker SFC in that study[43].

These cognitive performance findings could provide some insight into how the dynamic interplay between structure and function facilitates different facets of cognition. Faster cognitive switching and enhanced spatial orientation may rely on a more direct correspondence between structural and functional connectivity to quickly and reliably retrieve pertinent information. However, encoding of other cognitive domains such as executive function and memory retrieval could rely on a more relaxed correspondence between structure and function — one that fosters the flexible integration of new information from multiple sensory modalities[40,43]. Indeed, a deeper exploration into why certain task-related functional connectivity patterns are more closely or distantly related to structural connectivity would be insightful.

Notably, SFC could also be used to uniquely identify individuals and predict functional brain states in response to task execution[43]. Functional connectivity patterns decoupled from the underlying structural connectivity — especially the ones found in transmodal regions of higher-order systems such as the fronto-parietal network — accounted for a substantial proportion of interindividual variability in various cognitive traits including sustained attention. Importantly, these patterns could also be used to uniquely identify individuals. Conversely, functional connectivity patterns more tethered to the underlying anatomical paths — such as the ones found in unimodal sensory regions — could be used to differentiate between task-specific functional brain states but not between individuals[43]. Collectively, these studies underscore the relation between SFC and individual differences in cognition, and the potential use of SFC as a 'fingerprint' of the brain organization of an individual[44]. In support of this notion, SFC has been reported to be highly consistent within individuals over time, as well as reproducible across different sample populations[26].

Interindividual differences in SFC are partially explained by biological sex. A recent study in young adults identified greater SFC in males than in females, particularly within the orbito-frontal (right hemispheric), default mode and ventral attention networks[26]. By contrast, young adult females displayed stronger SFC within the right hippocampus. However, findings differed in a study of middle adulthood, which found greater SFC in females compared to males, particularly in association cortices including the left inferior frontal gyrus, left inferior parietal lobe, right superior frontal gyrus and right superior parietal gyrus[45]. However, greater SFC in middle adulthood males localized to hub regions such as the right insula, as well as non-hub regions such as the left hippocampus and the right parahippocampal gyrus[45]. Notably, these regional sex-related differences in SFC associated with cognitive performance: greater SFC in non-hub regions in females associated with poorer working memory, whereas greater SFC of hub regions in males associated with greater reasoning ability[45]. Together, these studies demonstrate that sex is a biological variable of importance in the study of SFC.

The presence of interindividual differences in SFC raises the following question: are the regional patterns of SFC heritable? SFC has been found to be highly heritable within visual, subcortical, cerebellar and brainstem regions, suggesting that spatially patterned SFC is at least partly genetically determined[26]. Critically, some have proposed that the relative decoupling between structure and function in transmodal cortex is a result of the reduced genetic control over both the microstructural architecture and functional activity of its heteromodal component including the fronto-parietal and default mode networks, but not its paralimbic component including the anterior insular and cingulate regions[46]. Nonetheless, there seems to be no marked association between the heritability and magnitude of SFC[26], which indicates that the biological markers that shape SFC across brain regions are potentially regulated by different genetic factors. Interestingly, when averaged across connections emanating from a single region, SFC had similar levels of heritability as functional connectivity strength and substantially higher levels of heritability than structural connectivity strength[26]. However, certain brain regions — especially within the visual, subcortical, cerebellar and brainstem systems — did have more pronounced SFC than functional heritability, suggesting that SFC heritability might be more informative in single regions than either structural or functional heritability alone.

Structure–function coupling changes depending on cognitive task

The task performed or the cognitive context can also markedly alter the relationship between structure and function within the same individual. Using task-based fMRI, one recent study has found an overall decrease in functional connectivity during an attention task but an overall increase in functional connectivity during a memory task, relative to rest[8]. Notably, long intra-hemispheric structural connections linking brain regions that are important for attention and memory displayed substantial changes in their functional connectivity. In particular, these connections exhibited decreased functional connectivity

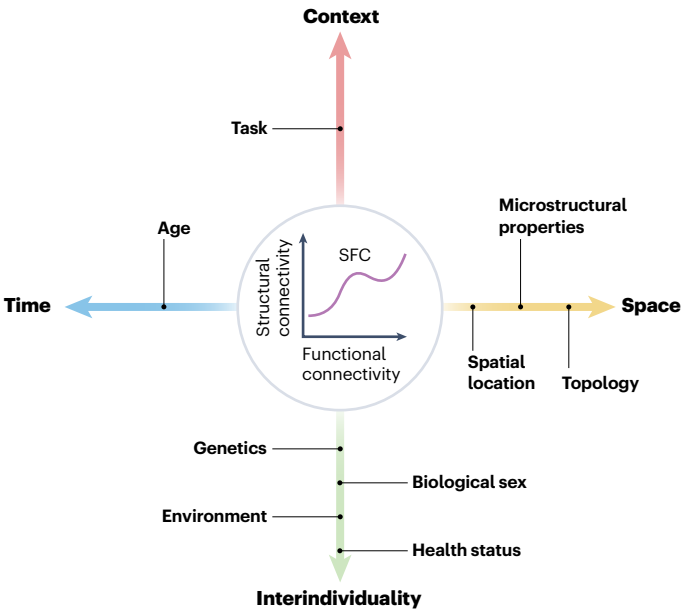

Fig. 2 | Axes of variation in normative structure–function coupling. Four principal axes regulate the normative relationship between structural and functional connectivity in human brains. First, spatial properties, such as location along the cortical or subcortical hierarchy, topology and microstructural architecture (such as laminar differentiation, excitatory and inhibitory cellular constitution), have been reported to determine SFC strength. Second, temporal properties, such as age and particularly neurodevelopment, can also change how functional expression deviates from the underlying anatomical patterns. Third, interindividual differences, such as in genetics, biological sex, health status and environmental influences, affect how strongly tethered the functional expression of a brain region is to the anatomical backbone of the brain. Fourth, SFC magnitude can alter dynamically depending on the demands of a cognitive task as attention, memory and learning differentially change SFC within short timescales. SFC, structure–function coupling.

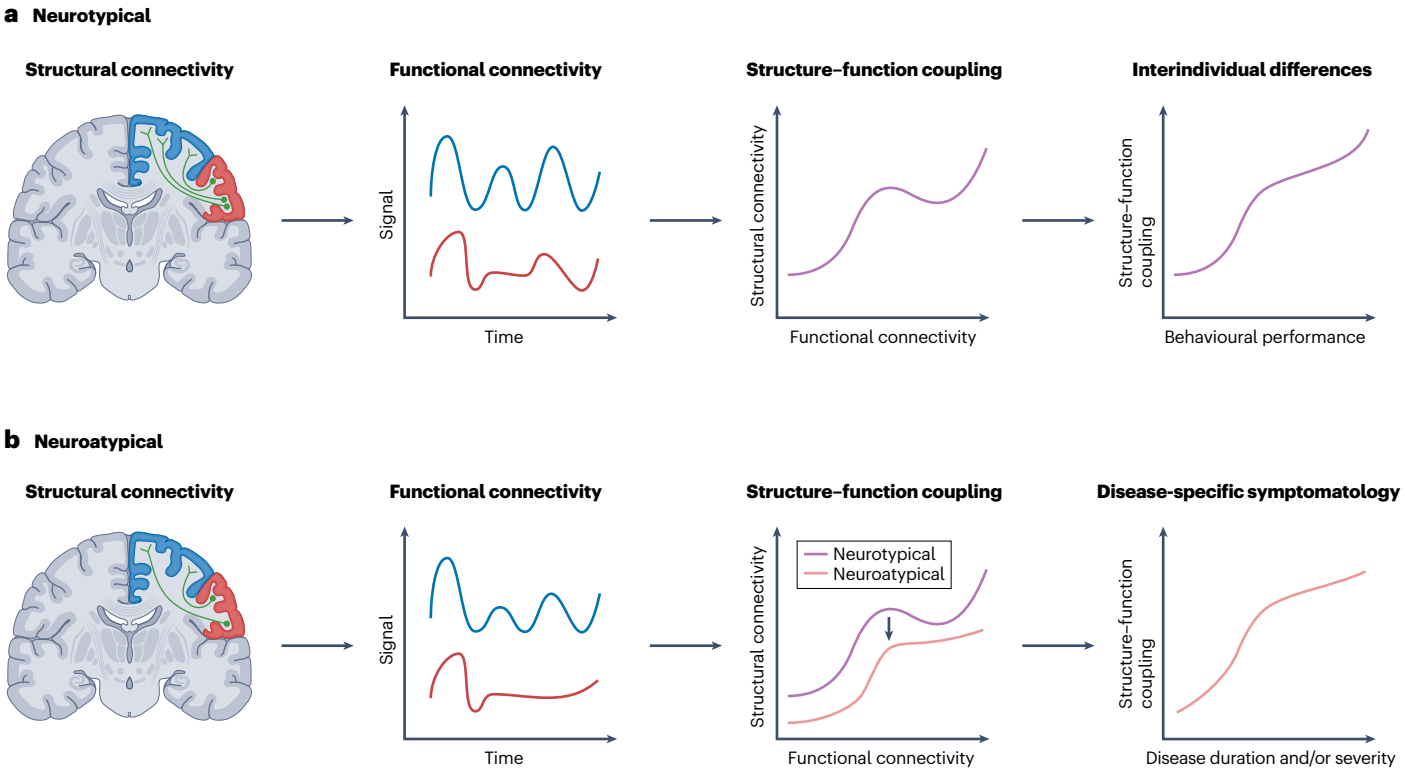

Fig. 3 | Structure–function coupling in neurotypical and neuroatypical individuals. Computing the structure–function coupling (SFC) in neurotypical and neuroatypical individuals can be particularly informative from a clinical perspective and, especially, when studying a specific neurological or psychiatric condition of interest. **a**, After defining the structural and functional connectivity of a neurotypical brain, the SFC of each brain region is determined for that individual. The average SFC of each individual can then be evaluated across all brain regions. Population-based analyses assessing the statistical correlation between SFC and different aspects of cognitive function or behavioural performance can finally be performed using either the average SFC of each individual or the SFC corresponding to a specific brain region or network of interest of that individual. **b**, After similarly defining the brain's structural and functional connectivity in individuals with neurological or psychiatric disorders, the SFC of each brain region is determined for each neuroatypical individual. The average SFC of each individual can then be evaluated across all brain regions. Population-based analyses assessing the statistical correlation between SFC and different aspects of cognitive function or disease-specific symptoms, such as disease duration and severity, can finally be performed using either the average SFC of each neuroatypical individual or the SFC corresponding to a specific brain region or network of interest of that individual. Statistical differences in SFC strength between neuroatypical and neurotypical populations could also be computed, across the regional or individual level.

during the attention task and increased functional connectivity during the memory task[8].

Structurally mediated task-dependent changes in functional connectivity have also been identified during learning[47–51]. One characteristic study has examined the short-term effects of perceptual training on spontaneous BOLD activity[50]. The investigative team used fMRI to extract functional time courses from neurotypical individuals both before and after training on a visual perception task that engaged spatial attention. Anatomically connected[52] areas within the visual cortex and the dorsal attention network (right and left frontal eye field; right superior parietal lobule) that were functionally independent before individuals received training showed anti-correlated time courses after training. The extent of functional anti-correlation between these areas also associated with improved perceptual learning, in the form of faster recognition of familiar (trained on) versus unfamiliar (untrained on) shapes[50]. In a complementary study, researchers performed a similar experiment and recorded spontaneous BOLD signals of individuals before and after a short visuomotor training session[51]. Notably, motor learning increased the BOLD signal variability of brain regions within two neural circuits: the fronto-parietal and bilateral cerebellar systems. Learning-induced modulations of functional activity that spontaneously occurred after visuomotor training reflected the 'off-line' processing of the recently acquired motor skills. It is interesting to note that the two modulated circuits — and particularly the extensive anatomical cortico-cerebellar connections between them — are heavily involved in the consolidation of motor-related memories[51,53].

Collectively, these studies suggest that the functional connectivity of the brain is not simply a reflection of its underlying structural connectivity. Instead, while remaining partially tethered to the structural backbone, functional activity can dynamically shift across multiple timescales to flexibly accommodate task-dependent and context-dependent needs.

Structure–function coupling changes across the lifespan

Thus far, we have examined the ways in which the coupling between structural and functional connectivity differs — at a given time point — across different brain regions, among individuals, and as a function of tasks or cognitive context. Expanding beyond a single time

point, we now ask this question: does the global and regional magnitude of SFC also change over time?

Early work has examined differences in SFC across networks critically involved in higher-level cognition, such as the default mode, salience and fronto-parietal networks, in young children and young adults. One study showed that structural and functional connectivity positively correlated in adults along white matter tracts across the fronto-occipital fasciculus connecting the fronto-insular and dorsolateral prefrontal cortices in the right hemisphere — involved in visuospatial processing and attention — but not in children[54]. Similarly, another study using two definitions of structural connectivity found substantially stronger SFC in adults between posterior cingulate cortex and medial prefrontal cortex — brain regions within the default mode network involved in self-referential and social cognitive processes — but not in children[55]. These complementary results point towards stabilization in the relationship between structural and functional connectivity in white matter tracts involved in higher-order cognition across development.

Recent studies have also identified SFC changes taking place throughout adolescence in a hierarchically constrained way. Primary sensory and motor regions display subtle age-related reductions in SFC, whereas transmodal regions — particularly within the fronto-parietal and default mode networks — display marked age-related increases[4,22]. In addition, increased SFC in right-hemispheric rostrolateral prefrontal cortex, an association region consistently linked with abstract reasoning and goal-oriented behaviour, partially mediated age-related improvements in executive function across adolescence[22]. More generally, overall SFC has been shown to increase throughout childhood and adolescence, plateauing and subsequently decreasing near the onset of adulthood[56].

Broadening out across the lifespan, another study found that the global magnitude of SFC decreased over time[57]. Regionally, age-related reductions in SFC were particularly pronounced within the visual and somatomotor cortices; transmodal regions within higher-order association cortices such as within the default mode and fronto-parietal networks displayed subtle reductions in SFC magnitude, with a few regions even increasing their SFC over time (including the temporal pole and the dorsal and ventral prefrontal cortices)[57]. Thus, brain regions in lower-level unimodal sensory cortices that displayed a strong correlation between their structural and functional connectivity in normative adults tended to be the ones that are more probably going to decrease their SFC over time[57]. This relation is in interesting opposition to the classical 'last-in, first-out'[58] hypothesis typically seen in ageing research, wherein higher-order association regions maturing later during normative development are the first to display accelerated degeneration as humans age. Recent large-scale longitudinal neurodevelopmental cohorts could be leveraged to further decipher changes in SFC across the lifespan[59,60].

Summary

The work reviewed in this section establishes how the statistical similarity between structural connectivity and functional connectivity in humans varies across the cortical hierarchy, and how this heterogeneous expression of SFC tracks differences in flexible cognition and cognitive performance among individuals. Moreover, it collates studies that examine the heritability of SFC patterns, as well as how SFC magnitude changes across the whole brain, across brain regions and over time. In general, the coupling strength between structural and functional connectivity decreases along the sensorimotor-association hierarchy, with primary sensory and motor cortices (unimodal regions) displaying relatively strong SFC, and with higher-order association cortices (transmodal regions) displaying weaker SFC.

Indeed, this heterogeneous relation between structure and function across the brain is thought to facilitate the emergence of a diverse range of functional responses and, in turn, flexible cognition. Notably, regional differences in SFC among different individuals can accurately track differences in their cognitive performance, and studies have underscored the potential of the metric as a fingerprint of the brain organization of an individual. Studies further expanding upon the interindividual differences in SFC have also found that SFC exhibits strong heritability patterns — often surpassing those displayed by functional and structural modalities alone — and that it dynamically adapts to the cognitive task used. Last, SFC changes its magnitude over time, increasing throughout childhood and adolescence, plateauing and subsequently decreasing near the onset of adulthood and across the rest of the lifespan. Increases in SFC magnitude in transmodal association cortices during youth appear to be driving the former phase, whereas decreases in SFC magnitude in sensory and motor cortices occurring after adulthood onset drive the latter phase. Keeping these assessments in mind, we now turn to the question of how the normative relationship between structure and function might deviate in the context of disease.

Structure–function (de)coupling in neurological and psychiatric disorders

The brain is a complex system. How is SFC affected when one of the units of the system is not functioning in a typical manner? The pathological origins of many conditions and disorders can be traced back to such altered function, whether it is a receptor not being typically expressed owing to a genetic mutation, a neurotransmitter not being produced at physiologically typical levels or a neuronal population exhibiting altered morphology. Given the data on how such biological attributes can shape the coupling between the underlying structural connectivity and emerging neuronal activity[61], it would be reasonable to hypothesize that disorders which impact markers such as these would lead to altered macroscale SFC (Fig. 3b).

From a methodological standpoint, a few considerations should generally be accounted for when designing and interpreting studies examining SFC changes in neurological and psychiatric disorders. First, it is important to establish that appropriately sized samples have been used to achieve sufficient power for the statistical analyses to detect true positives[62]. Second, carefully selected control groups should be chosen to properly differentiate findings between the neurological and psychiatric groups of interest and other groups. Third, when acquiring fMRI data from subcortical brain regions that will be used to compute their SFC, special attention needs to be given to the acquired fMRI signal quality. Subcortical regions can display different levels of BOLD sensitivity from cortical regions, mainly because they contain higher levels of iron concentration[63]. Thus, appropriate data acquisition protocols that capture the differences in BOLD sensitivity between cortical and subcortical regions[63,64], and quality control metrics including signal-to-noise, temporal signal-to-noise and contrast-to-noise ratios[65], should be performed for optimal accuracy, transparency and reproducibility of results. Last, careful consideration is necessary when interpreting alterations in SFC. As shown in the neurological and psychiatric studies we discuss, aberrant changes in SFC could signify worsening symptoms and/or secondary compensatory reorganizations, a duality that makes interpretation difficult. To mitigate this

ambiguity, any interpretation in SFC changes should be additionally informed by how its individual components (structural and functional network metrics) also change[66–72].

In this section, we provide a systematic review of research studies that have directly reported alterations in SFC, across a wide range of neurological and psychiatric conditions and disorders (Table 1). We organize our remarks according to three broader categories spanning how SFC changes in neurological disorders typically associated with cognitive decline, motor impairment and paroxysmal (episodic) symptoms, and one category examining how SFC changes in various psychiatric disorders. There are of course overlaps between these four classifications; some of the considered neurological and psychiatric disorders manifest symptoms associated with multiple categories.

Structure–function coupling and cognitive decline

For the first category, we consider SFC changes in neurological disorders typically associated with cognitive decline. We focus on traumatic brain injury, white matter pathology, mild cognitive impairment and Alzheimer disease.

Traumatic brain injury. A particularly disruptive neurological condition and a common cause for loss of consciousness is traumatic brain injury (TBI)[73]. Mild TBI accounts for the majority of all TBIs and is a complex pathophysiological process typically associated with transient neurological, psychological and cognitive deficits that may or may not persist long term[74,75].

Owing to the inherent heterogeneity of a TBI and potentially devastating clinical sequelae, one longitudinal study has examined the relationship between structural and functional connectivity changes in individuals who had sustained a mild TBI, at three time points post-injury: within 2 weeks, at approximately 3 months and after 6–12 months[75]. Even though no substantial differences in SFC existed between individuals with TBI and neurotypical controls at the first time point, progressive decreases in SFC occurred by the second and third time points. A widespread loss of structural connections in response to injury primarily drove this structure–function decoupling, giving rise to structural connectomes characterized by decreased global efficiency and increased path length. Indeed, longitudinal changes in structural connectivity occurring between the 2-week and 6-month time points post-TBI in a separate study correlated with less favourable functional outcomes over time[66]. Moreover, the decoupling between structural and functional connectivity among individuals with TBI increased with time — especially among hub regions — pointing to SFC as a potential proxy for long-term outcomes after TBI[75]. Complementary work in individuals with TBI has also demonstrated that integrated structural and functional information in discriminant function analyses predicted behavioural task performance more accurately than using either modality alone[76].

Overall, these studies suggest that a metric assessing the relationship between structural and functional connectivity could more accurately capture cognitive performance after a TBI than either structural or functional properties alone.

White matter pathology. An important determinant of cognitive impairment following a TBI is the extent and location of white matter damage[77]. Even outside the realm of TBIs, a clinically common marker of white matter pathology is white matter hyperintensities, which are typically thought to indicate demyelination and/or axonal damage among other aspects of underlying pathology[78]. White matter hyperintensities can manifest even among neurotypical — and particularly older — individuals, and their burden has been found to correlate with diminished cognitive function[78].

One study has investigated changes in SFC in the presence of such white matter pathology[79]. More specifically, it assessed SFC differences in older neurotypical adults with low versus high loads of white matter hyperintensity within the default mode network[79]. The authors focused on two brain regions within the default mode network — the posterior cingulate cortex and the medial prefrontal cortex — which are anatomically connected via the cingulum bundle, a prominent white matter tract that has been implicated in the regulation of executive function, episodic memory and emotion, and neurological disorders such as post-traumatic stress disorder, mild cognitive impairment and Alzheimer disease[80]. Older neurotypical adults with high load of white matter pathology displayed weaker SFC between the posterior cingulate cortex and the medial prefrontal cortex compared to adults with low load of white matter pathology[79]. Importantly, the extent of decoupling between the structural and functional connectivity of these two regions in individuals with high loads of white matter hyperintensity positively correlated with worse executive functioning and episodic memory performance. Notably, individual measures of structural and functional connectivity between the posterior cingulate cortex and the medial prefrontal cortex did not predict cognitive decline within the same group of individuals[79]. This latter finding points again towards SFC as a potentially more accurate biomarker of disease status than either structural or functional connectivity alone.

Besides the default mode network, aberrant SFC within the fronto-parietal cognitive control network has also been implicated in individuals with cerebral small vessel disease[81] — a family of cerebrovascular pathologies associated with alterations in white matter microstructure that impact smaller blood vessels in the brain — which constitutes a leading cause of cognitive decline[82,83]. More specifically, decreased SFC in the fronto-parietal network of these individuals has been associated with increased microstructural alterations in the form of higher 'peak width of skeletonized mean diffusivity' scores[81] — an imaging marker sensitive to cerebral small vessel disease progression[81,84,85]. Notably, lower SFC within this network also consistently correlated with reduced general cognitive performance and processing speed, both cross-sectionally and longitudinally[81].

Mild cognitive impairment and Alzheimer disease. Expanding upon the relationship between SFC and cognitive function, we next turn to two neurological diagnoses commonly affiliated with cognitive decline: mild cognitive impairment and Alzheimer's disease.

A recent study has reported individuals with cognitive impairment had an overall increase in SFC[86]. Importantly, the coupling between structure and function progressively increased from neurotypical control individuals according to the severity of cognitive impairment of an individual (from mild to moderate), and the SFC positively correlated with worse cognitive performance in the form of poorer verbal memory, executive function and visuoconstruction[86]. A separate study has corroborated these findings and showcased that individuals with mild cognitive impairment had increased SFC compared to neurotypical control participants[87].

As mild cognitive impairment is a recognized prodromal stage of Alzheimer disease, understanding how the brain reorganizes as it transitions between mild cognitive impairment and Alzheimer disease could help to elucidate potential paths to delay or prevent this transition. SFC progressively increased across neurotypical individuals,

Table 1 | SFC changes in neurological and psychiatric disorders

	Is there a change in SFC (vs neurotypical controls)?		Do SFC changes correlate with disease symptomatology?	Refs.
	Global	Regional		
Neurological disorders				
TBI	No change (2 weeks post-TBI), ↓ (≥3 months post-TBI)	Hub regions: ↓	Yes	66,75
White matter pathology	–	Default mode network (cingulum bundle): ↓	Yes	79
		Fronto-parietal network: ↓	Yes	81
Mild cognitive impairment	↑	Local connections: ↑	Yes	86,87
Alzheimer disease	↑	Local and feeder connections: ↑	–	87
	↓	–		88
	No change	Default mode network: ↑ Rich club structure: ↑ Insula: ↓ Frontal regions (medial prefrontal gyrus, inferior frontal gyrus, rectus): ↓ Temporal regions (middle temporal gyrus, hippocampus): ↓		89
Ischaemic stroke	Basal ganglia: ↓	–	Yes	93
	Internal capsule: ↓ (RH), no change (LH)		Yes	94
	Pons: no change		Yes	94
Parkinson disease	↓	Posterior brain regions: ↓	Yes	96
Clinically isolated syndrome and multiple sclerosis	No change (1-year follow-up after clinically isolated syndrome onset)	Salience, visual and somatomotor networks: ↓	–	67
	↑ (5-year follow-up after clinically isolated syndrome onset)	–	Yes	68
Migraines	↓	Rich club and feeder connections: ↓	Yes	104
Epilepsy	↑ (short term: pre-ictal to ictal periods)	Short-range structural connections: ↑	–	69
	↓ (long term)	Rich club connections: ↓	Yes	106–108
Psychiatric disorders				
Major depressive disorder	–	Within each hemisphere: ↓ Inter-hemispheric connections: no change	Yes	70
Schizophrenia	No change (in offspring with increased familial risk)	Long-distance structural connections: ↑	–	123
	↓	Transmodal networks (posterior cingulate cortex, frontal-striatal, frontal-temporal and frontal-thalamic regions): ↓	–	110–112
	↑	Local connections: ↑	–	113
	–	Default mode network and central modules: ↑ Occipital and subcortical modules: ↓	Yes	112,114, 116
	No change (in first-episode medication-naive individuals with schizophrenia)	Rich club connections: ↓	–	117
Bipolar disorder	No change (in offspring with increased familial risk)	Long-distance structural connections: ↑	–	123
	↓ (in diagnosed adults)	–	–	71
ADHD	↑	–	–	129
	↓ (in medication-naive adults with childhood-onset ADHD without any psychiatric comorbidities)	Feeder connections (fronto-parietal control, visual and somatomotor networks): ↓	Yes	130

This table provides a succinct summary of changes in SFC in individuals with neurological and psychiatric disorders mentioned in the Review and represents a non-comprehensive list of the continuously evolving work currently being done on the field. –, no data available; ↑, SFC increase; ↓, SFC decrease. ADHD, attention-deficit hyperactivity disorder; LH, left hemisphere; RH, right hemisphere; SFC, structure–function coupling; TBI, traumatic brain injury.

individuals with mild cognitive impairment, and then individuals with Alzheimer disease, pointing towards disease progression diminishing the ability of the brain to flexibly deviate its functional expression given the underlying structural connectivity[87]. Additional analyses within the same work have revealed predominant expression of the increased SFC in the two groups with cognitive impairment across connections linking rich club nodes to non-rich club nodes — feeder connections — and across local connections. More notably, the increased SFC in individuals with mild cognitive impairment compared to neurotypical individuals could be attributed to affected local connections, whereas the even stronger SFC in individuals with Alzheimer disease compared to individuals with mild cognitive impairment was owing to disturbed feeder connections[87]. These findings provide overall support for the notion that SFC can offer unique insights into new, and more importantly early, aspects of disease pathophysiology, and potentially act as an early biomarker of disease progression.

However, not all studies have yielded similar results in the directionality of SFC changes in Alzheimer disease. Another study examining how Alzheimer disease disrupts structural and functional brain network topology has reported a more pronounced decrease in SFC in individuals with Alzheimer disease compared to both individuals with amnestic mild cognitive impairment and neurotypical individuals[88]. By contrast, complementary work has demonstrated similar levels of overall SFC across the whole brain between individuals with Alzheimer disease and neurotypical individuals[89]. Instead, regional SFC varied such that individuals with Alzheimer disease displayed increased SFC in the default mode network and the rich club structure, pointing to a more restrictive functional expression in these modules. In addition, several other brain regions directly involved in the pathophysiology of Alzheimer disease, located in the frontal lobe (such as medial prefrontal gyrus, inferior frontal gyrus and rectus), temporal lobe (such as middle temporal gyrus and hippocampus) and insula, exhibited decreased SFC[89]. These results suggest that Alzheimer disease differentially impacts neuronal circuits that regulate distinct aspects of higher-level cognition. By increasing the SFC within the default mode network and rich club connections, modules involved in optimizing global brain communication are impacted, whereas by decreasing the SFC of regions within the frontal, temporal and insular cortices, regions regulating episodic memory, attention and audiovisual integration — hallmark cognitive deficiencies of Alzheimer disease — are impacted.

These differences observed in the directionality of whole-brain SFC occurring in individuals with Alzheimer disease could also point towards its heterogeneous nature as a neurodegenerative disorder. Each work included individuals of varying levels of clinical severity, as established by cognitive rating scales such as the clinical dementia rating scale, the mini-mental state examination scale and the Montreal cognitive assessment scale. Thus, the directionality of overall SFC of the brain could also be used to distinguish between different levels of cognitive impairment associated with Alzheimer disease.

Structure–function coupling and motor impairment

For the second category, we consider SFC changes in neurological disorders typically associated with motor impairment. We focus on stroke, Parkinson disease, clinically isolated syndrome and multiple sclerosis.

Stroke. Higher-level cognition can also be severely impacted after a stroke; indeed, strokes are considered the second most common cause of dementia, after Alzheimer disease[90]. Much like real estate, the structural and functional price of a stroke depends primarily on its location. For instance, ischaemic strokes represent the vast majority (~87%) of all strokes and tend to occur in the territory defined by the middle cerebral artery[91,92]. The middle cerebral artery is a major paired artery that irrigates many parts of the cerebrum, including the frontal, parietal and temporal lobes, as well as the basal ganglia, via small perforating arteries called lenticulostriate arteries.

Owing to their clinical importance, ischaemic strokes have been the subject of ongoing neuroimaging investigations, particularly within the context of structural and functional network reorganization post-stroke. One such study examined individuals with ischaemic strokes within their basal ganglia and reported an overall decreased SFC when compared to controls[93]. Notably, the study reported a positive correlation between the degree of SFC and performance on a motor assessment scale, indicating how individuals with ischaemic stroke with increased structure–function decoupling also exhibited more pronounced motor deficits[93].

However, is SFC similarly impacted across different subtypes of ischaemic stroke? To further address this question, another study examined individuals with capsular and pontine strokes (characterized by lesions to the internal capsule and pons, respectively)[94]. Individuals with right-hemisphere lesions from capsular stroke displayed decreased SFC when compared to both individuals with right-hemisphere lesions from pontine stroke and neurotypical control individuals[94]. Curiously, there were no substantial differences in SFC between the three groups when individuals with equivalent lesions on their left hemispheres were considered instead, which could potentially be attributed to the limited sample size. Furthermore, no SFC differences existed between individuals with pontine stroke and neurotypical individuals; however, network disruptions in both structural and functional connectivity in individuals with either capsular or pontine stroke did exist. The aforementioned findings could point towards global functional reorganization occurring in response to the underlying stroke-induced structural damage in such a way as to initially preserve the whole-brain SFC. However, when the structural damage exceeds a certain threshold — as in the case of individuals with capsular stroke — the SFC becomes aberrant. Behaviourally, stronger SFC in individuals with capsular or pontine stroke correlated with better performance on a motor assessment scale (similarly to the ischaemic stroke study[93] described above)[94].

Overall, these complementary works demonstrate that in individuals with ischaemic strokes, the amount of decoupling between structure and function in subcortical brain regions involved in motor function (basal ganglia, internal capsule and pons) correlates with the extent of motor impairment. Collectively, these results point to the capacity of SFC to act as a potential biomarker of disease progression and as a metric monitoring post-stroke recovery.

Parkinson disease. Motor impairment is perhaps most typically recognized as a hallmark sequela of Parkinson disease. Nonetheless, individuals with Parkinson disease are also at a high risk for non-motor symptoms, such as cognitive decline; cognitive impairment is common in these individuals and can often progress into dementia towards more advanced stages of the disease[95].

Clinically, visual hallucinations and illusions have been found to precede (and increase the risk of) dementia in individuals with Parkinson disease[95,96]. Owing to these cognitive changes and the well-known motor deficits affiliated with Parkinson disease, one study has hypothesized that loss of SFC might also be expected in individuals

with Parkinson disease and especially in those individuals with visual deficits[96]. That study found widespread structure–function decoupling associated with disease severity across neurotypical control individuals, individuals with Parkinson disease and high visual performance, and individuals with Parkinson disease and low visual performance[96]. Compared to neurotypical individuals, individuals with Parkinson disease (irrespective of visual capability) displayed globally reduced SFC, and especially within posterior brain regions previously associated with disease-induced hypometabolism[96–98]. Even though whole-brain SFC between the two groups of individuals with Parkinson disease did not differ, individuals with low visual performance exhibited substantial structure–function decoupling within the bilateral insula and right calcarine gyrus[96]. Indeed, the extent of decoupling within the right calcarine gyrus — a region critically involved in visual processing — in individuals with Parkinson disease also correlated with worse cognitive performance, as assessed by the Montreal cognitive assessment test evaluating general cognition.

Furthermore, because Parkinson disease has been linked to altered neuromodulatory transmission, the authors also investigated the relationship between neurotransmitter receptor gene expression and disease-related structure–function decoupling. Notably, the extent of decoupling between structural and functional connectivity in individuals with Parkinson disease (compared to neurotypical individuals) associated with reduced dopaminergic (*DRD2*) and serotonergic (*HTR2A*, *HTR2C* and *HTR4*) receptor expression and increased cholinergic (*CHRNA4*) and serotonergic (*HTR1E*) receptor expression[96]. In addition, structure–function decoupling in individuals with Parkinson disease and low visual performance correlated with reduced cholinergic (*CHRNA3*) and adrenergic (*ADRA2A*) receptor expression and increased cholinergic (*CHRNA2* and *CHRNA4*) and serotonergic (*HTR1E* and *HTR5A*) receptor expression[96].

Collectively, these results point to the potential importance of regional patterns of SFC or structure–function decoupling in distinguishing between different Parkinson disease subtypes. They also suggest that SFC can track neuromodulatory changes that occur in individuals with Parkinson disease and the extent of their cognitive decline, thereby serving as a viable biomarker of disease progression.

Clinically isolated syndrome and multiple sclerosis. Further considering how SFC changes in neurological disorders typically associated with motor impairment, we discuss studies in two other disorders — besides Parkinson disease — commonly associated with impaired mobility: clinically isolated syndrome and multiple sclerosis.

One recent study that assessed the longitudinal evolution of SFC in individuals with clinically isolated syndrome — a condition that is typically considered to be a prodromal stage of multiple sclerosis — reported after only 1 year of follow-up overall preserved whole-brain SFC in these individuals compared to neurotypical controls[67]. However, the authors did notice regional structure–function decoupling in salience, visual and somatomotor systems across that time period. In the absence of cognitive decline being reported, this indicated that structural and functional reorganization in individuals with clinically isolated syndrome takes place before cognitive impairment sets in. To further investigate the structural and functional reconfiguration in the early stages of multiple sclerosis, the same authors also examined the evolution of SFC 5 years after clinically isolated syndrome onset[68]. Notably, they found stronger SFC in individuals with clinically isolated syndrome at the 5-year follow-up; this increased SFC also associated with lower cognitive scores and level of clinical disability.

Overall, the altered SFC in select regional networks — yet preserved cognitive performance — after 1 year of disease onset could indicate compensatory functional reorganization taking place during that period in response to disease-induced structural insult, leading to relatively conserved whole-brain SFC[68]. Consistent with this possibility, feeder and local connections are targeted at the early stages of clinically isolated syndrome; however, as the disease progresses, structural damage extends into the rich club connections (connections which have a key role in the efficient communication and global integration of information across the brain)[99–101]. Once a critical threshold of structural damage is surpassed, the capacity of the brain to accordingly reconfigure its functional expression diminishes, increasing its overall SFC and leading to the subsequent cognitive deterioration and neurological disability that characterize the later stages of the disease[68,102].

Altogether, these complementary studies on the early stages of multiple sclerosis highlight the clinical importance of SFC as a potential early biomarker for disease severity and clinical trial outcome, which could help inform cognitive rehabilitation programmes[68].

Structure–function coupling and episodic symptoms

For the third category, we consider SFC changes in neurological disorders that are typically associated with paroxysmal (episodic) symptoms. We focus on migraines and epilepsy.

Migraines. In addition to disorders associated with chronic progressive deterioration of the nervous system, SFC has also been implicated in neurological disorders whose symptoms are more commonly episodic in nature. A characteristic example of such a disorder is migraine, a common neurological disorder characterized by recurrent and often debilitating headaches that can last up to 72 hours[103].

Chronic exposure to migraines could alter brain circuits that regulate pain. Accordingly, one study has examined potential alterations in SFC between individuals with migraines without aura (the most common type of migraines)[103] and individuals without migraines[104]. Overall, individuals with migraines exhibited reduced SFC compared to those without them, with this reduction particularly expressed in rich club and feeder connections, including pathways between the basal ganglia and orbitofrontal cortex that have been known to regulate pain processing[104]. Moreover, SFC strength negatively correlated with the number of feeder connections in individuals with migraines but not within neurotypical individuals. Aberrantly increased feeder connections have been proposed to reflect over-integration of information between brain regions participating in pain regulation, thus, enhancing their neuronal excitability while decreasing their inhibitory capacity in modulating migraine-induced pain[104]. Interestingly, the number of feeder connections also substantially predicted headache duration.

These findings collectively point towards decoupling between structural and functional connectivity as a clinically relevant proxy of an aberrantly increased number of feeder connections in individuals with migraines.

Epilepsy. Imbalances in excitatory and inhibitory control of neuronal circuits are also thought to be implicated in epileptic seizure pathogenesis[105]. The aberrant electrical activity commonly associated with epilepsy could, thus, be expected to alter the relationship between structural and functional connectivity.

Complementary studies examining SFC in individuals with epilepsy have reported decoupling between structural and functional connectivity compared to neurotypical control individuals, and

especially among rich club connections; these studies focused on individuals with idiopathic generalized epilepsy and individuals with temporal lobe epilepsy[106–108]. Critically, there was a negative correlation between SFC strength and disease duration in individuals with both types of epilepsy[106–108]. In addition to long-term changes in SFC throughout the duration of the disease, short-term changes over the course of seizure evolution have also been reported. SFC consistently increased as individuals with epilepsy transitioned from the pre-ictal to ictal periods, and short-range structural connections primarily drove this increase[69]. This highlights how seizures may rely on the anatomical scaffolding of the brain, especially its short-range anatomical projections, to spread during their initial stages[69]. Furthermore, the authors of the same study reported that, for several of the individuals examined, the rise in SFC occurred even before seizure onset (initiation of the ictal period), pointing to the potential capacity of SFC to predict it[69].

Collectively, these findings underscore the clinical relevance of SFC as a potential biomarker in monitoring long-term and short-term epileptic seizure pathogenesis, especially considering how structural or functional network properties alone did not correlate with disease duration in individuals with epilepsy[69,106,107].

Structure–function coupling and psychiatric disorders

In this section, we turn to the literature on SFC in psychiatric disorders. We specifically consider major depressive disorder, schizophrenia, bipolar disorder and attention-deficit hyperactivity disorder.

Major depressive disorder. First, we examine whether SFC is altered in individuals with major depressive disorder, a condition predominantly characterized by persistently low or depressed mood, among other symptoms, as persistent disturbances in mood can be theorized to associate with structural and functional network alterations.

One study has reported overall decreased SFC between structural and functional connections within each hemisphere in individuals with major depressive disorder, when compared to neurotypical control individuals[70]. However, in the same study, inter-hemispheric connections did not differ in their SFCs between the two groups[70]. Critically, the degree of coupling between structure and function within each hemisphere in individuals with major depressive disorder positively correlated with higher scores on a depression scale; structural or functional network measures alone did not correlate with clinical measures of disease severity[70].

We again notice this motif of SFC — but not structural or functional properties — in largely tracking individuals' performance on a pathology-related behavioural scale, indicating the use of SFC as a potentially pertinent marker of disease severity.

Schizophrenia. A different psychiatric disorder that is often accompanied by depressive — but more characteristically psychotic — symptoms is schizophrenia[109]. Psychotic symptoms typically include hallucinations, delusions and disrupted thoughts.

Three complementary studies examining disruptions of the structural and functional connectome in individuals with schizophrenia have found overall weaker coupling between structure and function in those individuals compared to neurotypical control participants, particularly in transmodal regions of networks involving the posterior cingulate cortex, frontal-striatal, frontal-temporal and frontal-thalamic regions[110–112]. These results suggest a reduction in the constraint that the underlying white matter architecture exerts on emerging brain dynamics, and particularly in networks consistently associated with phenotypes observed in psychotic disorders. By contrast, another study that examined differences in rich club organization reported an overall increase in SFC between individuals with schizophrenia and neurotypical individuals; local connections — connections linking non-rich club nodes to non-rich club nodes — mainly drove this increase[113]. Interestingly, the other two types of connection studied (the rich club type defined as rich club nodes connected to rich club nodes, and the feeder type defined as rich club nodes connected to non-rich club nodes) did not display decreased SFC[113].

In addition to global SFC disturbances in the brain, individuals with schizophrenia also exhibit alterations in SFC at the regional level. Characteristically, individuals with schizophrenia showed increased SFC within default mode and central modules when compared to neurotypical control participants[114]. This finding is indicative of more restrictive functional dynamics within those regions, which could be thought to underlie the deficits in attention, working memory and language commonly associated with the disorder[114,115]. Furthermore, decreased SFC found within the occipital and subcortical modules among individuals with schizophrenia could explicate impairments in early-stage visual processing they often experience; of clinical importance, this structure–function decoupling within these networks correlated with longer illness duration and more severe symptoms[112,114,116]. Researchers have also examined first-episode medication-naive individuals with schizophrenia to mitigate the potential effects that medication history might have had on these findings[117]. Even though whole-brain SFC was similar, substantial structure–function decoupling along the rich club connections occurred in the individuals with schizophrenia compared to neurotypical individuals; however, SFC in feeder and local connections did not differ between the two groups.

Broadly, the heterogeneous results across these studies could be due to differences in sample characteristics and brain regions included in the analyses or could reflect the confounding effects of medication and clinical history. However, these studies overall have found differences in SFC within brain networks consistently associated with schizophrenia.

Bipolar disorder. Much like schizophrenia, bipolar disorder also shares depressive and psychotic symptoms. Bipolar disorder is characterized by recurrent episodes of depression and (hypo)mania; individuals with bipolar disorder also often exhibit psychotic symptoms, such as hallucinations or delusions, during either a manic or depressive episode[118,119]. Moreover, similar to schizophrenia, bipolar disorder is a highly heritable disorder[120,121]; indeed, both disorders share common genetic markers[122]. However, do the offspring of parents with schizophrenia display different SFC levels than those of parents with bipolar disorder?

To address this query, a study examined structural and functional connectivity in children and adolescents with increased familial risk for these two disorders (who had not yet experienced psychotic symptoms)[123]. Overall, whole-brain SFC did not substantially differ across the three groups examined (offspring of an individual with schizophrenia, offspring of an individual with bipolar disorder, and neurotypical control individuals)[123]. However, both offspring groups showcased stronger coupling between structural and functional connectivity of long-distance structural connections compared to the neurotypical controls[123]. Such connections spanning long distances have been found to efficiently integrate information between different brain areas and substantially enhance the functional diversity of the brain regions involved, and thus to have a pivotal role in the emergence

Glossary

Coefficient of variation
A statistical metric quantifying the dispersion of a set of data points in relation to their mean value and defined as the ratio between the standard deviation and mean value of the data points.

Discriminant function analyses
Statistical analyses used in classification problems to determine the discriminant functions — weighted combinations of the provided independent variables — that maximize separability among two or more categories within the outcome (dependent) variable; accuracy of classification is also evaluated.

Global efficiency
The average of the inverse shortest-path distances from one node to all other nodes, capturing network efficiency in transferring information.

Heteromodal association cortices
Regions receiving convergent inputs from unimodal areas from more than one sensory modality.

Hub regions
Brain regions characterized by a relatively large number of connections to other regions (more commonly referred to as high-degree nodes).

Ictal periods
The periods between seizure onset and seizure termination, as defined electrographically.

Laminar differentiation
Brain regions with high levels of laminar differentiation (also referred to as granularization) are characterized by well-defined, highly developed cortical layers II and IV.

Limbic regions
Cortices including the hippocampal complex, the amygdaloid complex, the prepiriform olfactory cortex, the septal area and the substantia innominata.

Local connections
Connections linking non-rich club nodes to other non-rich club nodes.

Modules
A group of densely interconnected brain regions that are sparsely connected to the rest of the brain (also known as a community).

Paralimbic regions
Cortices including the caudal orbitofrontal cortex, the insula, the temporal pole, the parahippocampal gyrus and the retrosplenial–cingulate–parolfactory complex.

Path length
The minimum number of edges (the shortest path) required to traverse from one node to another.

Primary sensory and motor cortices
The cortical regions wherein sensory information from the external environment is first projected into the brain; the primary motor cortex relays motor programmes into spinal motor neurons to initiate further action.

Rich club
A subset of high-degree brain regions (nodes) that are densely interconnected; connections between rich club nodes are referred to as rich club connections.

Transmodal regions
The combined set of heteromodal association cortices and paralimbic and limbic regions; transmodal areas receive and integrate input from multiple sensory modalities to give rise to complex conscious perception and flexible cognition, and often exert a 'top–down' influence on unimodal association cortices.

Unimodal association cortices
Regions receiving projections from primary sensory areas and other unimodal association areas from the same sensory modality.

Unimodal sensory regions
The combined set of primary sensory and unimodal association cortical regions.

Variance
A statistical metric quantifying the dispersion of a set of data points around their mean.

of higher-order cognition[1,124,125]. Critically, aberrant long-distance connectivity in children with increased familial risk for psychosis is thought to precede the age at which psychotic phenotypes typically manifest. Altered SFC within these long-range structural connections could, thus, serve as an early mechanism of action underlying affective psychiatric disorders[123].

In addition to at-risk children and adolescents, is SFC affected in young adults with bipolar disorder? To address this question, a complementary study assessed the coupling between structural and functional connectivity across a group of adolescents and young adults with bipolar disorder in euthymic state – a period of remission from clinically significant depressive or (hypo)manic symptoms[71]. This group of individuals displayed an overall decreased SFC compared to neurotypical individuals. More importantly, SFC had higher predictive power in distinguishing individuals with bipolar disorder from neurotypical individuals than structural or functional modalities alone.

Collectively, local alterations in SFC could already be detected in children and adolescents at risk of developing bipolar disorder; changes in SFC across the whole brain became evident in young adults diagnosed with bipolar disorder compared to neurotypical controls. The progression of SFC changes between at-risk youth and diagnosed adults and the observation that SFC could be used to more accurately distinguish individuals with bipolar disorder from controls compared to structural or functional connectivity alone could point towards the potential use of SFC in tracking disease-specific symptoms.

Attention-deficit hyperactivity disorder. Another psychiatric disorder that is typically first diagnosed during childhood and adolescence is attention-deficit hyperactivity disorder (ADHD)[126–128]. ADHD is a common neurodevelopmental disorder characterized by hyperactivity, inattention and impulsive behaviours, whose symptoms can often persist into adulthood[128]. Thus, adults with ADHD could be expected to display deviations in their SFC.

One study that examined potential abnormalities in the organization of the rich club connectome in adults with ADHD found an overall increase in SFC compared to neurotypical adults[129]. Moreover, a negative correlation existed only between SFC strength and the number of rich club connections in the individuals with ADHD[129], which did not extend to their feeder or local connections[129]. These findings support the notion that ADHD specifically targets the structural organization and functional flexibility of nodes within the rich club connectome.

To address any potential confounding effects that medication or psychiatric history could have had on these results, another study recruited a large cohort of medication-naive adults with

childhood-onset ADHD without any psychiatric comorbidities[130]. In contrast to the above study[129], individuals with ADHD displayed an overall reduction in SFC relative to neurotypical individuals[130]. This structure–function decoupling localized within feeder connections and specifically impacted connections linking the fronto-parietal control and sensory (visual and somatomotor) networks — key networks in regulating sustained attention and inhibitory control. Not surprisingly, the extent of structure–function decoupling in individuals with ADHD also associated with more severe symptomatology. The conflicting results between these two studies could be due to not only differences in cohort size, medication history and psychiatric comorbidity but also the use of different brain parcellation schemes and their corresponding classifications of connection types (rich club, feeder and local).

Because structural connectivity did not differ between the individuals with ADHD and neurotypical individuals in the latter study, the authors used computational modelling to pinpoint the neural source underlying the decoupling between structural and functional connectivity observed in individuals with ADHD[130]. Notably, they found that the SFC reduction along the feeder connections linking fronto-parietal control with sensory networks captures and is most probably driven by increased neural noise heterogeneity across the connected brain regions; critically, SFC reductions in feeder connections positively correlated with ADHD symptom severity. This computational finding is consistent with prior work that has reported increased brain signal variability in individuals with ADHD within fronto-parietal networks as a marker of ADHD symptom severity[131,132]. Notably, pharmacological attempts to reduce signal variability within those regions have been fruitful[130].

Collectively, these observations once again establish SFC or structure–function decoupling as an important network measure linked to psychopathology.

Summary

SFC captures the relative relationship between its two connectivity constituents, and in that regard has been shown to capture more than the sum of its parts. As a metric, it integrates information from both structural and functional modalities and in that capacity may allow for a more representative assessment of cognitive faculties than either modality alone. This is perhaps no better illustrated than by studies investigating the structural, functional and cognitive changes occurring in individuals with neurological and psychiatric disorders. Even though various structural and functional connectivity changes often occur long before cognitive deficits manifest in these individuals, SFC could be critical in identifying the point of transition from cognitive resilience to cognitive impairment. Relatively preserved SFC in the acute stages of disease progression characterized by minimal to no cognitive impairment clearly demonstrated this role in some of the aforementioned neurological and psychiatric disorders. However, after surpassing a critical threshold of structural damage via the evolving disease progression, the capacity of the brain to accordingly reconfigure its functional expression with respect to the underlying anatomical backbone went awry, and aberrant SFC and cognitive dysfunction ensued. Furthermore, the high predictive power of SFC in distinguishing individuals with varying disorders from neurotypical individuals and its ability to accurately monitor disease-specific duration, disability and cognitive impairment — often much more precisely than structural or functional network properties alone — point to its promise for translational applications.

Conclusion

The anatomical architecture of the brain shapes and constrains its functional activity; it places operational boundaries on how functional signals propagate to deter uncontrolled behaviour. However, this dependence of functional expression on the underlying structural connectivity is not homogeneous across the cortical mantle. Unimodal regions, and specifically the primary sensory and motor cortices, display strong statistical correlations between their structural and functional connectivities; this property could presumably facilitate real-time detection and swift transmission of external environmental stimuli up the cortical hierarchy. Conversely, transmodal association regions display a weaker coupling between structure and function, which could enable the generation of a diverse repertoire of functional responses that interpret these stimuli, giving rise to conscious perception and flexible cognition. The heterogeneous expression of SFC extends beyond the regional level, to the individual level as well. Indeed, regional differences in SFC across individuals can accurately track differences in their cognitive performance while serving as a fingerprint of the brain organization of an individual. The heterogeneous patterns of SFC also appear to exhibit strong heritability patterns, as well as dynamically change over the course of the lifespan.

Further insight on the dynamic relationship between structural and functional connectivity across different brain regions can be drawn from neurological and psychiatric disorders, wherein the dynamic interplay between structure and function is impacted. Critically, aberrant SFC has recently started being established as a potentially important marker of disease-related cognitive impairment — in some cases, tracking disease duration and symptomatology more accurately than either structural or functional connectivity alone. The efficacy of SFC as a metric of clinical significance should be further examined by clinical studies focusing on different neurological and psychiatric disorders.

Citation diversity statement

Recent work in several fields of science has identified a bias in citation practices such that papers from women and other minority scholars are under-cited relative to the number of such papers in the field[133–137]. We obtained the predicted gender of the first and last author of each reference by using databases that store the probability of a first name being carried by a woman[137]. By this measure (and excluding self-citations to the first and last authors of our current paper), our references contain 8.9% woman(first)/woman(last), 9.6% man/woman, 35.6% woman/man, and 45.9% man/man. This method is limited in that (1) names, pronouns, and social media profiles used to construct the databases may not, in every case, be indicative of gender identity and (2) it cannot account for intersex, nonbinary, or transgender people. We look forward to future work that could help us better understand how to support equitable practices in science.

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