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Brain network analyses in clinical neuroscience

The goal of brain network analyses is to explain function and behaviour through measures of connectivity

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Summary

Network analyses are now considered fundamental for understanding brain function. Nonetheless neuroimaging characterisations of connectivity are just emerging in clinical neuroscience. Here, we briefly outline the concepts underlying structural, functional and effective connectivity, and discuss some cutting-edge approaches to the quantitative assessment of brain architecture and dynamics. As illustrated by recent evidence, comprehensive and integrative network analyses offer the potential for refining pathophysiological concepts and therapeutic strategies in neurological and psychiatric conditions across the lifespan.

Keywords: *anatomical connectivity*, *functional connectivity*, *effective connectivity*, *diffusion MRI*, *functional MRI*

Introduction

Over the past two decades, the focus of neuroscience and brain imaging research has increasingly shifted from region-specific analyses to network models [1–3] or – in the language of systems neuroscience – from functional segregation to integration. Nonetheless, the uptake of connectivity analyses remains rather limited in clinical neuroscience. This article outlines the different types of brain connectivity that can be assessed with contemporary brain imaging (fig. 1).

Brain connectomics has developed as an attempt to non-invasively map brain connectivity at the macro-scale. According to Sporns' definition [4], the word "connectomics" describes "macroscopic brain connectivity as a pattern of anatomical links (anatomical connectivity), of statistical dependencies (functional connectivity) or of causal interactions (effective connectivity) between distinct units within a nervous system." These pairwise relationships can be summarised by a connection matrix (with each cell representing a measure of connectivity between two regions of interest) or equivalently by a graph or network, which provides a schematic description of the neural connections [5]. The connectome refers to this full wiring diagram of the brain. As such, connectomes allow the comprehensive reconstruction of fundamental motifs of human brain architecture that underwrite brain function. Connectomics also enable the study of aberrant causality and brain remodelling in pathological conditions, such as in the recent-

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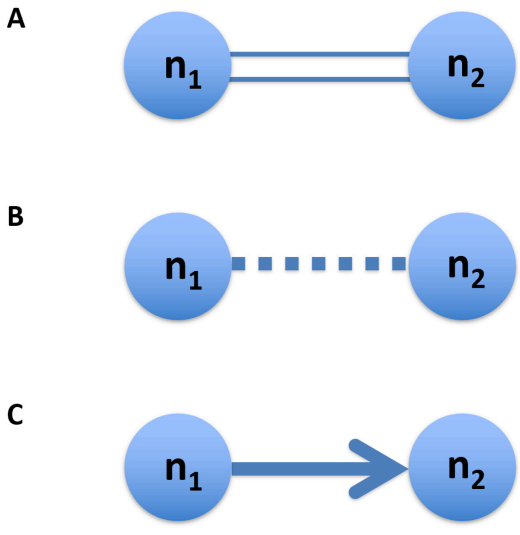
Figure 1: Different types of brain connectivity. (A) Anatomical or structural connectivity represents the white-matter pathways (double line) between two brain regions (network nodes) n_1 and n_2. (B) Functional connectivity can be derived from correlations (dashed line) between functional activities in two regions. (C) Effective connectivity is the directed and causal influence (arrow) that activity in region n_1 exerts over the activity in region n_2.



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ly introduced connectome-based lesion-symptom mapping [6].

Here, we discuss some promising network analyses in patients with neurological and psychiatric disorders. Furthermore, we highlight recently developed approaches that allow one to infer brain architecture and dynamics through multimodal integration and advanced signal processing. These approaches bear a significant potential for improving models of disease and, ultimately, treatment strategies and outcomes.

Anatomical connectivity

In brain imaging, anatomical (structural) connectivity is afforded by tractography algorithms that infer axonal pathways within the white matter of the brain from diffusion-weighted magnetic resonance imaging (dMRI) data (fig. 2). Empirically, dMRI is sensitive to the density, orientation and permeability (e.g., myelin) of axons and microtubules in the white matter [8], as well as the presence of cell bodies or dendrites. Even if the characteristic length scales in neural tissue are in the order of microns and the typical resolution of an MR image is in the order of millimetres, dMRI has the potential to detect microstructural white matter changes related to (de)myelination, pruning or axonal loss [9]. Due to its simplicity, diffusion tensor imaging [10] is the preferred reconstruction scheme in clinical studies. However, diffusion tensor imaging is based on Gaussian assumptions about water molecule diffusion inside the white matter. As such, it often fails to properly resolve the complex fibre configurations (such as "crossing and kissing tracts" [11, 12]) present in 60-90% of the voxels comprising a brain magnetic resonance image. For a more complete and accurate approximation, sophisticated acquisition techniques, such as diffusion spectrum imaging [13], high angular resolution diffusion imaging [14, 15] and others are often suggested.

Tractography algorithms use the information provided by dMRI at the voxel level to noninvasively map white matter cortico-cortical and cortico-subcortical connections. Tractography algorithms can be divided roughly into deterministic versus probabilistic and local versus global. Deterministic tractography methods assume a unique fibre estimate in each imaging voxel, assigning a single pathway starting from each seed point [16]. Probabilistic tractography, on the contrary, generates a distribution of possible trajectories from each seed point, resulting in a measure of "probability of connection" between two brain regions [17]. Local methods use small successive integration steps by following the local fibre orientations to draw tracks between brain regions, whereas global methods [18] attempt to reconstruct all tracts simultaneously by finding the configuration that best explains the acquired dMRI signal (see [19] for a comprehensive review of different algorithms, their technical considerations, strengths and weaknesses).

Interestingly, once the tracts are estimated, their properties and the implicit characteristics of the underlying anatomical connectivity can be measured in different ways. These approaches encompass fibre trajectory-linked metrics (e.g., tract number, volume, density), diffusion metrics along the fibre trajectories (e.g., fractional anisotropy, parallel or transversal diffusivity) and other metrics derived from dMRI (e.g., axonal density, axonal orientation dispersion) or complementary contrasts (such as T1/T2 relaxometry or magnetisation transfer [20]). By correlation of the properties of changes in specific white matter tracts (e.g., limbic circuitry, uncinate fascicle, arcuate fascicle) to behavioural measures, white matter tractography also enables the characterisation of structural alterations underlying abnormal brain function [21].

Connectivity matrices summarise the anatomical connectivity information provided by tractography reconstructions at the macroscopic level (structural connectomes). They are built by storing the characteristics of anatomical pairwise relationships (such as tract density, fractional anisotropy or other diffusion-derived scalars) between cortical regions in each cell of the matrix (fig. 2). Comparison of connectomes between two groups of subjects generally consists of performing a statistical test between matrix cells. A correction for multiplicity has to be considered as multiple tests, involving different null hypotheses, are performed on a single data set [21]. Even if structural connectomes are unable to resolve the directionality of white matter fibres (i.e., differentiate between afferent of efferent fibres) [22], they deliver insights into the large-scale architecture of the brain [23]. For instance, the human brain can be considered a small-world network, organised according to a hierarchical modular architecture. This architecture is composed of communities of nodes that are highly interconnected (called "hubs" and predominantly located in heteromodal association cortex), but sparsely connected with other modules [23]. However, some hub regions (mainly frontal and parietal cortex, precuneus, cingulate and the insula, as well as the hippocampus, thalamus, and putamen) tend to be overly connected to each other, forming a so-called "rich club". This rich-club organisation is thought to be crucial for brain evolution and development [7]. Adult-like structural network organisation (topology), with both small-world characteristics [24] and rich-club organisation [25] is already present at birth, although white matter tracts are in an immature state, supporting only limited functional interactions [7]. From toddler to late teenage years, white matter maturation promotes network refinement with increasing network integrity [26].

Structural connectomes allow quantification of the heterogeneity of the connectivity structure in a given population or between groups, and association of localised or diffuse structural connectivity alterations with neurological and psychiatric diseases in a noninvasive manner. Disruption in brain network refinement has been related to specific neurocognitive deficits; such as anatomical frontal network alteration and socio-cognitive impairments in children born preterm and/or with intra-uterine growth restriction [27, 28]. Lower long-range connectivity has been linked to autism spectrum disorder (ASD) in a cohort of young adults [29]. However, affection of short-range connectivity remains controversial. ASD has been generally linked to a short-range overconnectivity, but a recent study on a population with high-functioning ASD reported decreased short-range connectivity [30]. Moreover, the authors point out the role of short-range anatomical connectivity in development of functional brain integrity, suggesting that its reduction is a key substrate for social deficits in ASD. In adult populations, structural connectomics have been applied to study a broad spectrum of brain disorders in-

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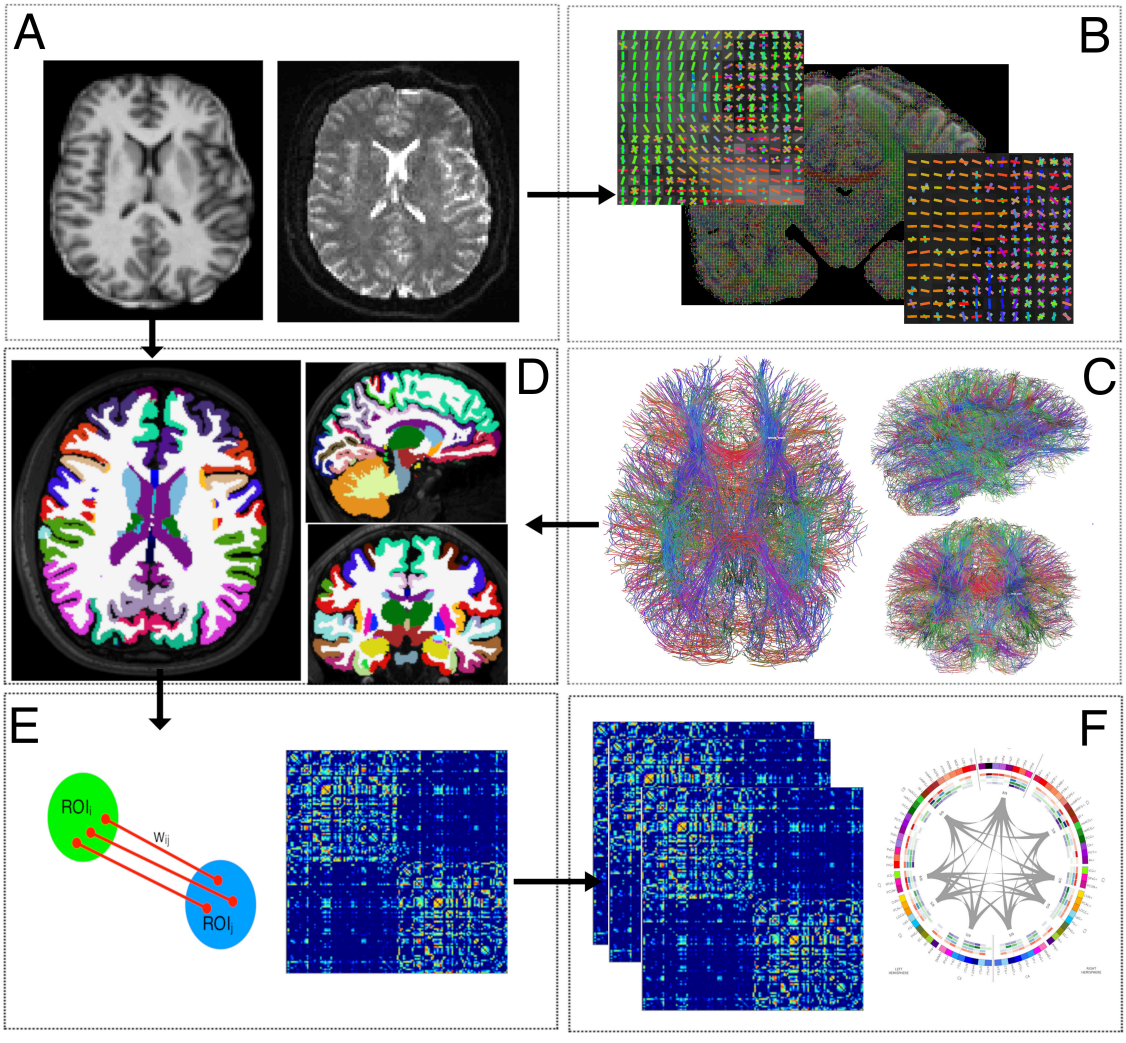
cluding Alzheimer's disease, schizophrenia, epilepsy and Parkinson's disease. A recent study of patients with amnestic mild cognitive impairment (MCI) revealed altered network topology prior to conversion to Alzheimer's disease, and offers hypotheses about how connectivity underwrites the spread of Alzheimer's disease through the brain [31]. Schizophrenia has also been characterised by a selective disruption of anatomical connectivity, mainly among central hub regions of the brain, potentially leading to reduced communication capacity and altered functional connectivity [32, 33]. Patients with temporal lobe epilepsy exhibit alterations in hub architecture, and both global and regional connectivity patterns [34]. Interestingly, several studies have shown that left temporal lobe epilepsy changes are largely ipsilateral, whereas right temporal lobe epilepsy tends to be more bilateral and affect the limbic system more frequently [34, 35]. Recent work suggests widespread structural dysconnectivity in patients with Parkinson's disease [36], with lower network clustering capability (presence of highly interconnected groups of nodes) and reduced hippocampal efficiency (lower network resilience to a failure on a small scale, such as when one node is removed). Both measures reflect network segregation, the ability for specialised processing to occur within densely interconnected groups of brain regions. Despite the widespread white matter affection, only three structural connectomics studies have been performed so far in in multiple sclerosis (MS) [37–39]. Two of them applied diffusion tensor imaging and showed widespread reductions of network integrity in MS patients as compared with controls [37], which negatively correlated with expanded disability status scale scores, disease duration and total white matter lesion load [38]. The most recent study has evaluated the connectome in a small group of MS patients and controls using connectivity strengths based on the g-ratio, which represents the relation between the inner and the

Figure 2: Structural connectome construction pipeline: A) Preprocessing: The main preprocessing steps include registration of T1-weigthed images to the diffusion space as well as motion, distortions, Gibbs ringing and eddy current artifact's correction over the diffusion weighted imaging data; B) Diffusion weighted images reconstruction: The simplest reconstruction model is the diffusion tensor imaging (DTI) model; C) Cortical parcellation: WM/GM surfaces as well as cortical and subcortical regions are extracted from the registered T1; D) Tractography: Deterministic or probabilistic tractography is computed over the reconstructed diffusion data; E) Weights estimation and matrix construction: The ratio between the sum of all virtual streamlines connecting each pair of regions of interest and their individual length is generally used as a measure of connection density. Other weights include streamline volume, count as well as mean fractional anisotropy values along the streamlines, among others. These weights are stored in a matrix; F) Analysis: Connectivity matrices are generally compared using cell-by-cell statistical tests. Other analyses include graph-based comparisons as the connectivity matrix can be considered a graph. (Figure 2.F is adapted with permission from [7].)



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outer myelinated axon diameter [39]. This work showed that g-ratio connectomics could reveal both connectivity reductions and increases in patients with MS, which correlated with measures of disease severity. Lastly, a multi-contrast connectomics approach (connectometry) has also been applied to early-stage multiple sclerosis patients. This study showed that, although cerebellar network properties were preserved, local connectivity among different cerebellar lobules was disrupted, showing lower axonal and myelin integrity than the equivalent connections in healthy controls [40].

Several software packages are commonly used to perform connectomics in human subjects including the FMRIB's Diffusion Toolbox within the FMRIB Software Library (Oxford Centre for Functional MRI of the Brain, UK), the MRtrix toolbox , DSI studio , the Brain Connectivity Toolbox and the Connectome Mapper. However, connectomics analysis has not made its way into clinical practice, mainly because of the lack of integrated software solutions and standardised analysis pipelines. Future applications and developments should aim at overcoming this limitation since the information related to changes in anatomical connectivity that underlie specific cognitive of behavioural dysfunctions, may extend and refine clinical care.

Functional connectivity

Functional connectivity reflects statistical dependencies between the activity in different brain regions, typically by computing Pearson linear correlations between time courses [41]. In functional magnetic resonance imaging (fMRI), the blood oxygenation level dependent (BOLD) signal provides a proxy for neural activity; reflecting both evoked and spontaneous brain activity. In the latter case, resting-state functional connectivity represents an attractive way to characterise spontaneous network dynamics [42]. In consequence, the presence of large-scale functional networks has been established in terms of distributed brain regions that share similar spontaneous activity, also called intrinsic or resting-state networks (RSNs) [43–46]. These RSNs also often play in unison when specific tasks are performed and are interesting from the clinical point of view as they have been found to be altered in several neuropsychiatric conditions such as dementia, MS, schizophrenia and bipolar disorder (e.g., [47]). At the same time, RSNs are easier to retrieve as compared with protocols including tasks that might be arduous to perform for patients.

Resting-state functional connectivity analyses can be conducted using several approaches, including voxel-wise or atlas-based methods. Voxel-based RSNs have been mainly recovered through multivariate voxel-wise projection techniques such as principal component analysis [48] or especially independent component analysis [49–52]. Seed-based functional connectivity reflects the correlation between a preselected region of interest (seed) and all other voxels in the brain [45], and is useful in clinical contexts with prior knowledge of focal brain aberrations. Atlas-based methods, in contrast, have been adopted to build functional brain connectomes (fig. 3A). In these approaches, a given brain parcellation [55] is applied and functional connectivity between all pairs of regions is evaluated [56]. The ensuing functional connectomes can be treated as adjacency matrices or graphs, that can be used to study network properties [57–59] and for classification of clinical populations [60].

However, these approaches are essentially summarising data over the entire acquisition time, generally spanning several minutes. The observation that functional connectivity between brain regions at rest may change over shorter periods of time [54] incited the development of time-resolved analyses. Since then, a multitude of methods have been introduced to explore dynamic functional connectivity (dFC; see [61–64] for detailed reviews). In its simplest form, a dFC analysis can be performed by computing correlations between different brain areas within successive sliding windows [65] spanning the entire scan duration (fig. 3B). This approach allows one to summarise the temporal evolution of specific functional connectivity properties [66–68], and can afford the so-called connectivity states characterising a population. These states can be obtained from dFC data by applying decomposition techniques, such as k-means clustering [69], principal component analysis [70], dictionary learning [71, 72], independent vector analysis [73], as well as temporal, spatial or group information guided independent component analysis [74–77]. For dFC analyses, several toolboxes are available (e.g., https://miplab.epfl.ch/index.php/software/dynFC).

By allowing the observation of connectivity changes over time, dFC approaches appear crucial to unravelling key information for a truthful description of pathological neural processes, particularly in diseases accompanied by highly dynamic neural activity abnormalities. Sliding-window approaches have revealed pathological dFC changes and achieved higher accuracy in diagnostic classification with respect to conventional static functional connectivity [78] in schizophrenia [79–83], epilepsy [84], ASD [85–87], attention deficit hyperactivity disorder (ADHD) [88] and Alzheimer's disease / MCI [89–92]. In fact, dynamic approaches have been shown to be the optimal tools to assess the "profound disruption of thought" [93] also defined as a "disconnection syndrome" [94] in schizophrenia. Condition-specific brain states are characterised by reduced and less defined functional connectivity and more frequent recurrence [74, 95–101]. A higher temporal variability of dFC time-courses, was reported in schizophrenic patients in several attention, perceptual and emotion regulation RSNs [102–106], and related to a disruption in perceptual functions [105, 107]. In contrast, lower temporal variability was reported for the default mode and fronto-parietal networks [105, 107]. Furthermore, weaker and less variable dFC among speech and auditory areas was related to hallucinations [101]. The flexible least squares-based time-varying parameter regression strategy [108], a frame-wise equivalent of the sliding-window approach that estimates BOLD signal changes by taking into account the previous time point, also pointed to a dysfunction of the salience network in terms of increased intra-network dFC instability in schizophrenia [104].

In epilepsy, a dFC analysis appears particularly relevant, as the pathology is characterised by transitory, dynamical neural events (seizures), causing substantial changes in network properties during the acquisition. The simultaneous recording of electroencephalography (EEG) with fMRI and the integration with dFC analysis provided key insights on network dynamics beyond those accessible by

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conventional fMRI or static functional connectivity [109–111]. For instance, the retrieved epilepsy-related dFC states allowed analysis of otherwise hidden dynamics of epileptic networks, which were found to be concordant with the clinical profile of each patient [110].

As another example, dFC allowed explanation of long-distance functional hypoconnectivity in ASD (mirroring the structural one mentioned in the previous paragraph) in terms of higher intra-individual variance of these functional connections over time [112, 113] rather than overall lower connectivity values. Flexible least squares parameter regression also showed greater intra-individual dFC variance in long-range connections in this pathology [114]. Therefore, long-range connections in ASD may not be weaker *per se* but rather more variable. This higher variance has been recently linked to symptom severity [113, 115].

Despite bringing new insights in the characterisation of several pathologies, sliding-window approaches are not exempt from methodological caveats, such as limited statistical power and potential noise from low frequency components [116], as well as the relatively arbitrary choice of window parameters [64]. A considerable effort in the dFC field has been dedicated to overcoming these limitations. One line of research introduced data-driven window selection through algorithms for detecting changes in fMRI time courses [55, 117, 118]. Ou and colleagues [118] tested their method in individuals with ADHD, highlighting abnormal dFC patterns that allowed disease classification.

Time-resolved analysis of instantaneous activity patterns represents an alternative to sliding windows [53]. A few key fMRI frames have been shown to yield already sufficient information to reconstruct known RSNs [119] or seed-based functional connectivity maps [120]. With this discovery in mind, an approach applying temporal clustering to selected frames was introduced, yielding representative brain states (fig. 3C) called coactivation patterns (CAPs) [120]. CAPs analysis identified brain networks linked to tremor pathology, and tracked functional recovery following thalamotomy [121].

Innovation-driven CAPs (fig. 3D) revisits CAPs but focuses on fMRI frames containing transient activity [63]. A recent application of this technique probed functional signatures of prodromal psychotic symptoms and anxiety in subjects with 22q11.2 deletion syndrome, revealing shorter activation in cognitive brain networks and longer activation in emotion processing networks [122].

Alternative methods explore recurring spatiotemporal patterns [123] and quasi-periodic patterns [124], an indicator of infra-slow electrical activity (i.e., slower than what is considered in conventional clinical EEG) in the default mode and task-positive networks. In ADHD, where default mode network and task-positive network connectivity are disrupted, quasi-periodic patterns were shown to contribute less to overall functional connectivity and revealed more differences than static functional connectivity, thus representing a potentially useful biomarker [50]. Overall, resting-state functional connectivity analyses may represent useful, readily available and efficient tools for clinical neuroscience.

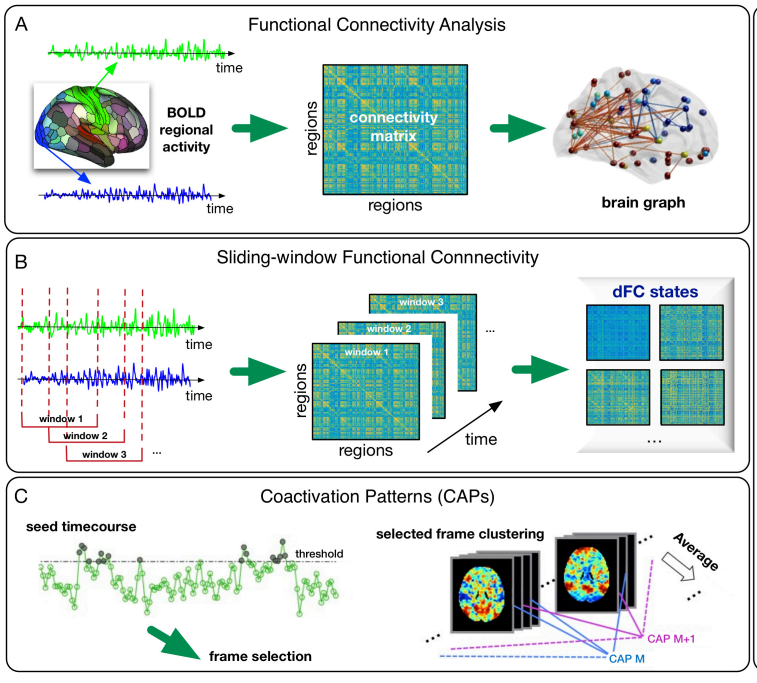

Figure 3: A. Atlas-based functional connectivity computes the pairwise correlations between regional fMRI timecourses. Functional connectomes can be easily translated into graphs or adjacency matrices where regions are nodes and pairwise correlations are edges. B. Sliding-window functional connectivity approaches allow one to appreciate the temporal evolution of the functional connectome over time. Decomposition techniques can be applied to retrieve so-called dFC states. C. Coactivation Patterns (CAPs) are obtained by clustering fMRI frames selected when a specific region (seed) is active (readapted with permission from [53]). D. Innovation-driven CAPs (iCAPs) capture instead transients (moments of change) in the fMRI signal, and represent spatially and temporally overlapping networks (readapted with permission from [54]).

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Effective connectivity

However, as a measure of statistical dependency between measurements, functional connectivity is a statement about the data, not the underlying neuronal coupling. To go beyond descriptive anatomical and functional connectivity measures, one has to turn to (models of) effective connectivity. Effective connectivity refers to causal functional interactions between brain regions; namely, the directed effect that one brain region exerts over another. Effective connectivity can be inferred by manipulating the neuronal activity in one part of the brain and measuring responses in remote regions with fMRI or EEG. These manipulations may be achieved through the delivery of carefully controlled stimuli or by procedures like transcranial magnetic stimulation, under some assumptions about their effects [125]. Transcranial magnetic stimulation and high-resolution EEG measures of effective connectivity have been found useful in discriminating between patients with vegetative and minimal conscious state [126]. Moreover, effective connectivity can also be inferred from task-related and resting-state neuroimaging data acquired using EEG, magnetoencephalography (MEG) or fMRI.

Psychophysiological interaction (PPI) and dynamic causal modelling (DCM) [127, 128] are the most widely used approaches for assessing task-related effective connectivity. These methods also allow one to study changes in effective connectivity related to a specific condition (e.g., different stimuli, attentional set or clinical diagnosis). PPI and DCM are closely related in that they both have an explicit model of neuronal activity and haemodynamic responses. However, PPI is a much simpler procedure because it is based upon a linear (convolution) model. This allows PPI to be applied in a voxel-wise fashion, but its simplicity precludes an unambiguous interpretation of changes in directed connectivity. In contrast, DCM estimates both the directionality of causal interactions and modulatory effects (condition-specific changes). DCM integrates a neuronal and an observational model, and aims at explaining network dynamics in the most accurate yet simple way [128]. The optimal trade-off between model accuracy and complexity is ensured by means of Bayesian analyses that maximise the model evidence. The ability to evaluate the evidence for a particular architecture (or condition-specific effects) is important because it enables comparing different hypotheses.

Recent statistical advances in Bayesian model comparison have dramatically increased the efficiency of comparing alternative models of group differences, such as between patients and controls [129]. Instead of specifying and estimating every alternative model in conventional DCM, the automated analytical search provided by Bayesian model reduction only requires specification and estimation of a full model that contains all the parameters one intends to assess. DCM, as implemented in Statistical Parametric Mapping (SPM12; Wellcome Centre for Human Neuroimaging, Institute of Neurology, University College London, UK), is relatively straightforward to use and not only available for task-related, but also resting-state data [130].

Granger causality [131] and structural equation modelling [132] represent related approaches to inferring directed connectivity. However, strictly speaking, Granger causality is a measure of (directed) functional connectivity because it is based on temporal dependences in the measured data: Granger causality infers a “Granger causal” interaction between two time series if the information contained in the first is useful for predicting the second. Application of Granger causality analyses to fMRI data is confounded by the latency between neuronal activity and the subsequent haemodynamic response, which can lag by several seconds. However, Granger causality has a utility for spectral or frequency based analyses of electrophysiological data. The exquisite temporal resolution afforded by scalp and intracranial EEG as well as MEG is of fundamental value for concepts of brain function and connectivity in normalcy and pathology [133]. For instance, Granger causality analyses on resting-state EEG data can disentangle the major interactions driving spontaneous brain activity in normal individuals [134], and approximate seizure onset and propagation in patients with epilepsy [135]. Structural equation modelling assesses the covariances among regional responses, without a model on temporal dynamics [136]. In general, it is more apt for cross-sectional data. In contrast to DCM, Granger causality and structural equation modelling do not model neuronal states or haemodynamics. However, as outlined above, they have facilitated analyses of larger network sizes and resting-state data, whereas conventional DCM has been restricted to task-related data and networks with a rather circumscribed number of nodes. Recent advances in DCM also allow the analysis of large graphs and resting-state time series [129, 130], enabling the complementary use of DCM and Granger causality [137].

In typically developing individuals, effective connectivity analyses have revealed mechanisms and pathways underwriting a wide array of functions, including visual pursuit [138], attention [139], reading [140], cerebro-cerebellar visual processing of body motion [141, 142], mental imagery [143] and memory retrieval [144]. Analyses of how directed connectivity relates to clinical deficits may not only provide mechanistic insights into the links between brain function and behaviour, but also elucidate pathophysiology and how specific connections mediate therapeutic effects. Assessment of effective connectivity has only recently been employed in patients with neuropsychiatric conditions, but has already yielded useful insights.

For instance, in subcortical stroke, reduced coupling between the ipsilesional supplementary motor area (SMA) and primary motor cortex (M1) was related to impairment of the paretic hand [145]. As compared with placebo, a single dose of the noradrenergic reboxetine substantially improved paretic hand function and yielded significant neural effects including improved coupling between ipsilesional SMA and M1 [146]. However, these neural effects were not directly associated with clinical improvement. In patients with Parkinson’s disease, decreased coupling between SMA, premotor and parietal areas was also linked to micrographia [147]. Dopaminergic medication increased endogenous connectivity from the prefrontal cortex to SMA, paralleling improved bradykinesia of finger movements [148]. Furthermore, antipsychotic medication appeared to normalise otherwise reduced fronto-temporal effective connectivity in patients with schizophrenia [149].

The value of effective connectivity in assessing brain plasticity is not limited to pharmacological treatment. A greater

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number of connections in patients with MS [150] and stronger effective connections in stroke patients with motor deficits [151, 152] and aphasia [153, 154] as compared with healthy controls have been interpreted as compensatory mechanisms. PPI data revealed that cerebellar reorganisation after neurosurgery drives plasticity in the communicating temporal cortex [155]. Post-stroke motor and language neurorehabilitation were shown to specifically enhance effective connectivity of the premotor [156] and left inferior frontal cortices [157], respectively. Taken together, analyses of effective connectivity could help better understand brain plasticity, and contribute to planning and monitoring neurorehabilitation.

Directed connectivity may also be of interest as a prognostic biomarker of disease progression. Granger causality on MEG data suggested global decreases in beta band effective connectivity in MCI patients as compared with controls [158]. During a go/no-go task with emotional faces, altered modulation of the connection from the dorsolateral prefrontal cortex to the inferior frontal gyrus by the anterior cingulate cortex was found in first-degree relatives of patients with bipolar disorder [159], interpreted as an aberrant influence of fear-related mechanisms on cognitive control. In Huntington's disease, in the absence of differences in fMRI whole-brain activation during a verbal working memory task between mutation carriers and controls, a DCM analysis revealed reduced input to the right dorsolateral prefrontal cortex in asymptomatic mutation carriers, and even more so in individuals with early-stage symptoms [160].

Finally, effective connectivity may also inform interdisciplinary and multimodal research on pathophysiology. Concurrent electromyography-fMRI data pointed to the internal globus pallidus and not the cerebello-thalamo-cortical loop as the primary mediator of resting tremor onsets in Parkinson's disease [161], whereas the cerebello-thalamic pathway was related to essential tremor variation during a motor task [162]. DCM has also been used to model the propagation [163, 164] as well as dynamic characteristics of epileptic seizures [165].

Multimodal integration

The value of neuroimaging for neurobiological constructs and models depends on how much information can be extracted and processed from the available signal. Each of the connectivity analyses described above usually rely on a single brain imaging modality. The modalities differ fundamentally with respect to spatiotemporal precision, imaging technologies and analytic methods. Both resting-state and task-related functional connectivity can inform the analysis of effective connectivity, by providing inferences about causality and directionality in functional brain architectures – and their pathologies [136, 141]. More important, white matter pathways underwrite long-range communication in the brain [2] and, as illustrated for ASD above [30, 112–114], different perspectives on brain connectivity provide complementary insights and consilience. As another example, sweetness perception has been associated with aberrant anatomical and effective connectivity in the pathways connecting the prefrontal cortex, striatum and hypothalamus in patients with anorexia and bulimia nervosa [166].

Nonetheless, formal computational integration of these measures remains challenging. The earliest integrative approaches that correlated anatomical and functional connectomes [167–169] showed that anatomical pathways explain only about 55% of functional connectivity, instead of a one-to-one mapping. Apart from methodological limitations, this is due to the fact that functional and effective connectivity change over time, whereas anatomical connectivity does not. However, the absence of an anatomical pathway can be used to infer the absence of a direct functional or effective connection. Indeed, informing the prior probability for an effective connection in DCM according to the strength of the corresponding white matter pathway yields models with greater evidence, as compared to uninformed unimodal DCM, both at individual and group levels [170, 171]. While anatomical and effective connectivity have not yet been formally integrated in clinical populations, the classification of participants in absent, single-domain or multi-domain cognitive decline based on MEG resting-state functional connectivity was significantly improved when using anatomical connectivity priors derived from dMRI [172]. In amyotrophic lateral sclerosis, a dual-regression analysis showed that altered white matter connections were associated with greater resting-state fMRI functional connectivity [173]. Given their differences in temporal and spatial resolution, multimodal integration between M/EEG, dMRI and/or fMRI data is of particular interest. For instance, when anatomical white matter connectivity is reconstructed from resting-state functional connectivity, functional data from simultaneous EEG and fMRI provide better estimates than fMRI data alone [174].

Anatomical connectivity not only constrains and optimises functional and effective connectivity analyses, but is also fundamental for synthetic models of brain dynamics. Simulation approaches have aimed at describing how anatomy shapes function by combining structural connectomes with neural models of local dynamics [175–179]. These approaches, such as The Virtual Brain, may help predict the behavioural effects of a lesion in a given brain region, and point towards patient-specific modelling and treatment in epilepsy [180, 181] or a better understanding of post-stroke recovery [182].

More recently, the emerging framework of graph signal processing has also been applied to brain imaging to integrate functional and structural information [183–186]. In this context, functional activity recorded in each brain region is considered as a functional signal in a structural graph. This method detected altered brain dynamics during a psychedelic state and might provide useful insights into other mental traits and states [184].

Perspectives for clinical neuroscience

The ultimate goal of brain network analyses is to explain function and behaviour through measures of connectivity. The higher variability in patients as compared with the general population may afford useful insights, not only for clinical but also fundamental neuroscience. As opposed to correlations between single connection properties and behavioural measures, recent efforts have focused on multivariate analyses [1, 142]. These approaches can help understand how a combination (e.g., linear mixture) of network connections and dynamics may shape a behav-

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ioural phenotype. Furthermore, they allow the incorporation of information from genomics or clinical assessments. Larger-scale network models enriched and refined in such ways will not only increase the plausibility and value of connectivity analyses, but also establish the roles of regions, connections and subgraphs in distributed neuronal networks.

Crucially, these methods may pave the way towards insights into brain-function relationships. For instance, connectome-based lesion-symptom mapping [6] not only related behavioural deficits to remote network alterations due to circumscribed lesions, but also pointed to the roles of specific regions and their connectivity, such as the temporo-parietal junction and its interactions with different components of the language network in patients with chronic post-stroke aphasia [187]. Longitudinal studies of connectivity during development or recovery can also shed light on causality [188, 189]. Generative models validated by their diagnostic, therapeutic or prognostic implications in clinical care provide the currently highest available level of causality and mechanistic understanding [179, 181].

Interdisciplinary, translational and interventional network analyses offer the potential for significant breakthroughs in clinical neuroscience. Recent work on schizophrenia and ASD linked behavioural deficits to aberrant functional and anatomical connectivity in both patients and rodent models. Subsequently, pharmacological or stimulation treatment improved both connectivity and behavioural measures [190, 191]. Overall, the value of network analyses for clinical neuroscience will depend on replication and extension with other modalities and methods. Modelling of concurrently recorded intracranial and extracranial imaging data is a promising avenue for validation and improved conceptualisation of brain networks [192]. Methods such as DCM can also be applied to intracranial electrophysiological data in animals [193] and humans [194]. Furthermore, ongoing efforts towards atlases of conduction velocities and other properties of white matter pathways based on intracranial recording will contribute to further refining generative models of brain architecture and function [195–197].

Finally, as the functional dynamics arising from a rather static brain architecture may vary substantially over the course of a few seconds to minutes in any given individual [64], the assessment of these transient states and their behavioural correlates appears crucial for understanding brain function and dysfunction.

Taken together, analyses of the different types of currently available measures of brain connectivity can drive substantial progress in clinical neuroscience. However, each approach to brain connectivity has its benefits and pitfalls, reflecting the different biophysical substrates, imaging and analysis techniques. Integrative and multimodal brain connectivity analyses can help overcome these limitations and afford complementary information, validating and extending pathophysiological concepts – potentially leading to improved therapeutic and prognostic approaches. The choice of the connectivity type to be analysed and the use of integrative methods depends on the study population, brain function and research hypotheses. Clear-cut and clinically relevant objectives and hypotheses are indispensable to harness the true potential of brain connectivity analyses within an interdisciplinary framework involving behavioural, causal and dynamic assessments.

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Potential competing interests

No potential conflict of interest relevant to this article was reported.

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